EVALUATION OF THE RELATIONSHIP BETWEEN MEDICATIONS AND FALLS AMONG URBAN COMMUNITY DWELLERS IN MALAYSIA

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FACULTY OF MEDICINE
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ABSTRACT

Malaysia is labelled as an aging nation because of its rapidly expanding older population. Falls are the commonest cause of accidents, injuries, disability and death among the geriatric population. While older people are the highest users of medications; polypharmacy and "fall risk increasing drugs"(FRID) are widely related to falls. The falls prevention guidelines recommend medication reviews and FRID withdrawal among older fallers. We aimed to evaluate the association between medications and falls among older Malaysian urban community dwellers.This study was performed and analysed in 2sections; case control comparisons and prospective intervention study. The fallers were recruited as the participants aged ≥65years with ≥2falls or 1 injurious fall in the previous year who visited the primary care clinics, geriatric medicine clinics and the emergency department of a hospital. The non-fallers were the volunteers aged≥65 years with no falls over the past year. Case-control-comparisons were performed between fallers and non-fallers to assess the association between falls and FRID, possible mechanisms and mediators of FRID and the appropriateness of prescription drugs using STOPP2 criteria. A prospective study was performed to assess the feasibility and effectiveness of medication review as an intervention for fall prevention.We found that use of multiple FRID was associated with falls rather than polypharmacy or single FRID. Contrary to the previous preconceptions that antihypertensives are associated with falls through the mechanism of orthostatic hypotension; we found that antihypertensives were not associated with orthostatic hypotension or falls. Rather fallers had significantly lower standing systolic blood pressure obtained 2-3 minutes after standing. We observed that anticholinergic burden of drugs is associated with falls due to reduced physical performance exhibited by the deterioration in timed up and go and functional reach scores. We found that prescribing of potentially inappropriate

drugs to older adults was significantly associated with falls; while polypharmacy, orthostatic hypotension and poorer timed-up-and-go scores were associated with potentially inappropriate prescriptions. In prospective study, out of 205 fallers with FRID, 98(47.8%) were randomized to intervention, and 107(52.2%) to conventional care, the medications were changed in 19(9.3%) participants of the intervention group. There was no significant difference in falls outcomes among the fallers with FRID regardless of whether they received medication review. While our study is the first assessment of the role of medications in falls in Malaysia, it uniquely found that the presence of multiple FRID, anticholinergic burden even with the lowest score and potentially inappropriate prescriptions instead of single FRID or polypharmacy are associated with falls. Furthermore, instead of antihypertensives or orthostatic hypotension, a lower standing systolic blood pressure is associated with falls. The positive association between anticholinergic score and falls is mediated by gait and balance impairment. An attempt to reduce FRID burden via medication review remains unsuccessful as it is not feasible to withdraw FRID without affecting patient's disease management. While future research is needed to consolidate our findings, our prospective study may serve as a pilot of a larger randomized controlled study evaluating the usefulness and longer term effects of medication reviews in addressing falls.

ABSTRAK

Penduduk yang lebih tua di Malaysia dijangka meningkat 210 % antara 1990-2020 . Falls adalah punca yang paling biasa kemalangan, kecederaan, hilang upaya dan kematian di kalangan penduduk yang berkembang pesat yang lebih tua. Polypharmacy dan penggunaan ubat-ubatan yang dikenali sebagai " risiko jatuh dadah semakin meningkat " (Frid) secara meluas yang berkaitan dengan jatuh ; jatuh garis panduan pencegahan mengesyorkan ulasan ubat -hati di kalangan fallers berisiko tinggi. Kami bertujuan untuk menilai hubungan antara ubat-ubatan dan jatuh di kalangan masyarakat bandar Malaysia kediaman orang dewasa yang lebih tua.Kita diambil fallers berisiko tinggi sebagai peserta berumur ≥65years dengan ≥2falls atau 1 kejatuhan mendatangkan bencana pada tahun sebelumnya yang melawat klinik penjagaan utama , klinik perubatan geriatrik dan jabatan kecemasan hospital. Bukan fallers adalah sukarelawan aged≥65 tahun yang tidak mempunyai sejarah jatuh sepanjang tahun lalu . Perbandingan kes-kawalan telah dijalankan antara fallers dan bukan fallers untuk menilai persatuan antara jatuh dan Frid , mekanisme yang mungkin jatuh Frid berkaitan dan kesesuaian ubat-ubatan preskripsi menggunakan kriteria STOPP2 . Kajian rintis campur tangan bakal ulasan ubat juga telah dijalankan untuk menilai sama ada ia boleh dilaksanakan dan berkesan untuk melaksanakan jatuh tradisional disyorkan ulasan ubat pencegahan. Kami mendapati bahawa penggunaan pelbagai Frid dengan luka kira ≥2FRID dikaitkan dengan jatuh bukannya polypharmacy atau penggunaan tunggal Frid. Lebih-lebih lagi, bertentangan dengan prasangka sebelum ini bahawa antihypertensives dikaitkan dengan jatuh melalui mekanisme yang dianggap mendorong atau semakin teruk hypotension orthostatic kami mendapati bahawa antihipertensi tidak dikaitkan dengan hypotension orthostatic atau jatuh. Sebaliknya fallers mempunyai jauh lebih rendah tekanan darah sistolik berdiri diperolehi 2-3 minit selepas memegang postur yang tegak tetapi hypotension orthostatic tidak berkaitan dengan jatuh berulang atau memudaratkan.

Kami juga mendapati bahawa beban kognitif antikolinergik dadah dikaitkan dengan jatuh disebabkan oleh prestasi fizikal dikurangkan dipamerkan oleh kemerosotan dalam masa yang ditetapkan dan pergi dan berfungsi skor jangkauan. Kami diperiksa yang menetapkan berpotensi tidak sesuai oleh pakar-pakar perubatan telah ketara yang berkaitan dengan jatuh; manakala polypharmacy, hypotension orthostatic dan miskin ditetapkan masa-up-dan-pergi skor dikaitkan dengan preskripsi yang berpotensi tidak sesuai. Dalam bakal kajian, daripada 205 fallers dengan Frid, 98 (47.8%) secara rambang untuk campur tangan, dan 107 (52.2%) kepada penjagaan biasa, ubat-ubatan telah berubah di 19 (9.3%) daripada kumpulan campur tangan. Tidak ada perbezaan yang signifikan dalam hasil jatuh di fallers dengan Frid tanpa mengira sama ada mereka menerima kajian ubat. Walaupun kajian kami adalah penilaian yang komprehensif pertama peranan ubat-ubatan dalam jatuh di Malaysia, ia unik mendapati bahawa ≥2FRID bukannya Frid tunggal dikaitkan dengan terjatuh. Tambahan pula, bukan antihipertensi atau hypotension orthostatic, kedudukan tekanan darah sistolik yang lebih rendah dikaitkan dengan peningkatan risiko berulang atau jatuh memudaratkan. Terdapat juga persatuan yang positif antara skor antikolinergik dengan jatuh yang diselesaikan oleh gaya berjalan dan kemerosotan nilai-kira. Manakala penggunaan Frid tidak dapat dielakkan untuk pengurusan penyakit berkesan, penggunaan STOPP2 mungkin membuktikan berguna semasa pencegahan jatuh ulasan ubat. Kajian rintis bakal kami boleh berkhidmat sebagai asas rawak yang lebih besar dikawal, mungkin kajian pelbagai pusat menilai kegunaan dan jangka panjang kesan ulasan ubat dalam menangani jatuh dalam suasana budaya kita.

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Anam Zia,
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LIST OF ABBREVIATIONS

FRID	:	Fall Risk Increasing Drugs
A2RA	:	Angiotensin II receptor antagonists
ACE-I	:	Angiotensin converting enzyme-Inhibitors
CCB	:	Calcium channel blockers
β-blockers	:	Beta receptor blockers
α-blockers	:	Alpha receptor antagonists
CNS	:	Central nervous system
SSRI	:	Selective serotonin reuptake inhibitor
TCA	:	Tricyclic antidepressants
NSAID	:	Non-steroidal anti-inflammatory drugs
PPI	:	Proton pump inhibitors
H2RA	:	Histamine 2 receptor antagonists
PIP	:	Potentially inappropriate prescribing
STOPP	:	Screening tool for older person's potentially inappropriate prescriptions
OH	:	Orthostatic Hypotension
BP	:	Blood Pressure
SBP	:	Systolic blood pressure
DBP	:	Diastolic blood pressure
ACB	:	Anticholinergic cognitive burden
TUG	:	Timed up and go
FR	:	Functional Reach
GS	:	Grip Strength

LIST OF APPENDICES

CHAPTER 1: INTRODUCTION

With the increase in life expectancy, older people are making up a large and rapidly growing percentage of the world population. According to United Nations, the population of adults aged 60 years and older is expected to increase from 507.95 million (11.6% of the population) in 2015 to 1,293.7 million (24.6% of the total population) by 2050 (UnitedNations, 2015). The majority of older people live in middle to low income countries (Ebrahim, 2002). The population of Malaysia is also expanding rapidly and is expected to increase by 80% between 1990 to 2020, however the aged population is expected to exponentially increase by 210% during this time span (Mafauzy, 2000). Among the total Malaysian population of approximately 26 million, 6.5% of people are of age above 65 years, with a projected population growth of 2% annually, this percentage of older population is expected to reach 9.5%. In the year 2035, the country is expected to have a population of about 46 million, of which 6.9 million (15%) will be above 65 years (Azhar et al., 2013). Due to this ticking of demographic time bomb and its associated chaos, the issues associated with population aging need to be dealt urgently and efficiently.

The physical and social changes associated with the aging are pooled with the debilitating effects of multiple pathologies. The physiological process of aging is related to a marked decline in health, including for example reduced muscle and bone strength, gait and balance problems, visual deficits, multiple comorbidities, multiple medication usage and frailty, all of which increase the risk for falling and falls associated complications. Therefore, as the number of older adults increases, so does the incidence of falls and falls related injuries with one in every third adult experiencing a fall per annum (Azhar et al., 2013). Falls are the most common cause of accidents among the older population leading to both fatal and nonfatal injuries often ending up in prolonged

hospitalizations or early institutionalizations (CDC, 2013). Aside from physical effects, the psychological fear of falling results in the restriction of physical and social activity with subsequent physical deconditioning, depression, poor quality of life and increased frailty. Falling, therefore, is a major health challenge among countries with rapidly growing older populations.

Due to an increased number of comorbidities, the use of medications also increases with increasing age. More than one-half of all prescription medications are dispensed to individuals older than 60 years (Tangiisuran et al., 2014). Therefore, this segment of the population accounts for about 25% of the total drug expenditures, this figure is predicted to reach 40% by 2030 (Williams et al., 1992). Although medication has helped to cure and control disease, it has also led to serious iatrogenic illnesses and adverse drug events. Almost 41% of patients admitted to the hospital are 65 years or older and are involved in 41% of the adverse drug reaction reports, 60% of these are related to medication-related falls (de Jong et al., 2013). In spite of all this evidence, older people with falls are exposed to polypharmacy and the studies on medication withdrawal among fallers are scarce, the handful of studies performed either yielded negative results or have low clinical implications (Costello et al., 2008). Only the studies on psychotropic medication withdrawal yielded positive results but suggested that it is difficult to achieve permanent drug withdrawal (Campbell et al., 1999).

Therefore, the problems of multiple comorbidities, multiple medication usage and falls are closely linked among older individuals. While falls have serious consequences and should be prevented at all cost if possible, medications are also necessary for the secondary prevention of non-communicable diseases which become more prevalent in older age and can lead to disability and death if left untreated. Hence, every medication cannot be “avoided” or “omitted/ deprescribed” merely for the purpose of falls prevention. While the studies on the association of medication

associated falls, their mechanisms or medication review interventions among older individuals are scarcely done in middle to low income countries, none of the study has been conducted in Malaysia. This critical issue of medication involvement with falls needs to be thoroughly explored to provide a significant evidence for benefit versus risk ratio for the consumption of drugs against falls among the older adults in this region.

This thesis is presented in article style as due to the nature of the study, the analysis were conducted from different aspects at different phases of recruitment culminating in different sample sizes. Chapter 2 will first of all comprise the literature review, much of the contents of literature review were published as two clinical reviews in Postgraduate Medicine (ISI listed Q2) (A. Zia et al., 2015a, 2015b). The chapter 3 presents the overall methodology of the study; the specific details of methods are mentioned in the relevant chapters. Chapter 4 addresses the association between FRID, polypharmacy and falls; the results of this chapter were published as an article in Geriatrics and Gerontology International (ISI listed Q3) (Anam Zia et al., 2016). Chapter 5 illustrates the complex association between antihypertensives, postural blood pressure changes and falls, the article is published in European Journal of Clinical Investigations (ISI listed Q1) (Anam Zia et al., 2015). Chapter 6 addresses the mediators behind the positive association between anticholinergic burden and falls, the results are published in Maturitas (ISI listed Q2) (A. Zia et al., 2016). Chapter 7 explains the association of PIP with falls among community dwelling older adults, the article is submitted to Age and Aging. Chapter 8 is the longitudinal assessment of the medication review intervention on the risk of falls while chapter 9 concludes the finding of this whole study.

1.1. Research question, Hypothesis and Objectives

1.1.1. Research questions

The related research questions for this study were: What is the role of FRID count in the association between polypharmacy and falls? (i) Are antihypertensives associated with falls through the mechanism of postural drop in blood pressure? (ii) What are the possible mediators of anticholinergic burden associated falls? (iii) Is PIP associated with falls and what are the factors associated with PIP? (iv) Can medication review actually be feasible and effective in reducing falls among high risk older fallers?

1.1.2. Hypothesis

Hypothesis 1: There is a positive association between polypharmacy, FRID count and falls among the community-dwelling older adults.

Hypothesis 2: There is a positive association between antihypertensives, postural blood pressure drop and falls.

Hypothesis 3: Functional performance is the mediator of anticholinergic burden associated falls.

Hypothesis 4: Potentially inappropriate prescriptions are significantly associated with falls.

Hypothesis 5: The intervention of medication review is feasible and beneficial to reduce falls among high risk older fallers.

1.1.3 Objectives of the study

1.1.3.1. General Objective

To evaluate the relationship between medications and falls among urban community-dwelling older adults in a middle-income developing country.

1.1.3.2. Specific Objective

I. To assess the association between polypharmacy, FRID count and falls among the community-dwelling older adults in a case control manner.

II. To evaluate the relationship between antihypertensives, postural blood pressure drop and falls in case control fashion.

III. To determine the association of anticholinergic burden and its mediators with the risk of falls in a case control analysis.

IV. To determine the association between potentially inappropriate prescribing and falls in case control comparisons.

V. To determine the effect of medication review as an intervention on falls reduction in a prospective manner.

1.2. Definition of terms

1.2.1. Falls

"An unexpected event in which the person comes to rest on the ground, floor or lower level" (Lamb et al., 2005).

1.2.2. Community-dwelling

This term is used when referring to elderly persons who are not in assisted living (including nursing homes, residential care homes, hospitals and other types of institutional accommodations).

1.2.3. Medications

Medications were grouped according to the British National Formulary, 67th Edition [14].

Cardiovascular medicines: Antihypertensives (A2RA, ACE-I, thiazide diuretics, CCBs and β-blockers), vasodilators (α-blockers and nitrates) and antiarrhythmics.

Antidiabetics: Biguanides, sulphonylureas, other oral antidiabetics and insulin.

Central nervous system medications: All classes of psychotropic drugs (TCA, SSRI, antipsychotics, anxiolytics and antidepressants) and antiparkinsonian medications.

Analgesics: NSAIDs, cyclooxygenase-2 inhibitors and narcotic analgesics.

Other drug classes: PPI, H2RA, thyroid drugs, steroids and cholesterol lowering drugs (dyslipidaemics).

1.2.4. Polypharmacy

"Regular use of five or more medicines" (Gnjidic et al., 2012; T. Kojima et al., 2012).

1.2.5. Fall risk increasing drugs

Fall risk increasing drugs were identified according to the available metaanalysis by Bloch et al and Woollcott at al (Bloch et al updated the meta-analysis of Leipzig et al) (Bloch et al., 2013; Leipzig et al., 1999a, 1999b; Woolcott et al., 2009)). These included cardiovascular agents (α-blockers, β-blockers, CCB, diuretics and nitrates), CNS drugs (antipsychotics, sedative hypnotics, benzodiazepines, antidepressants and antiparkinsonians), analgesics (NSAIDs), thyroid drugs and antidiabetics.

1.2.6. Potentially Inappropriate prescriptions:

"Prescription of a drug where the potential harm outweighs the benefit" (O'Mahony et al., 2015).

1.2.7. Orthostatic Hypotension:

A sustained reduction in SBP of 20mmHg or DBP of 10 mmHg within 3 minutes of standing or head up tilt of at least 60^0 on a tilt table with reference to supine blood pressure (Freeman et al., 2011).

1.2.8. Physical Performance Scores

The cut off point for poorer TUG was defined as ≥13.5seconds, (Shumway-Cook et al., 2000) poorer FR as ≤18cm (Duncan et al., 1990) and reduced GS as <20kg for women while <30kg for men (Peters et al., 2011; Sallinen et al., 2010).

1.2.9. Multiple FRID

Multiple FRID was defined as "the consumption of two or more FRID (≥2 FRID)". Should the participant be on two medications which fall within the same category but different class, for instance CCB and ACE-I, they would be considered to be on two FRID.

1.2.10. Multiple Antihypertensives

Multiple antihypertensives use was defined as the consumption of two or more antihypertensives (≥2antihypertensives) (Benetos et al., 2015).

CHAPTER 2: LITERATURE REVIEW

2.1. Epidemiology of Falls in the Elderly

Though fall accidents may occur at all ages, the incidence, severity, associated injuries and complications increase exponentially with the advancing age (Berry et al., 2008). This seems rational because falls are generally considered to be a marker of frailty and decreased mobility, both of which intensify with increasing age (Soriano et al., 2007). The syndrome of falls occurs because of the interplay between multiple intrinsic and extrinsic factors occurring within an aging individual. The risk of recurrent falls multiplies after the first fall leading to recurrent and injurious falls, and in turn a marked decline in functional health, independence (Ambrose et al., 2013; Smee et al., 2012; Ward et al., 2015) as well as markedly increased mortality only at 1 and 3 years after a fall (M. P. Tan et al., 2015). The fear of falling, which occurs in older adults both with and without history of falls, further decreases functional independence, social participation as well as quality of life thereby starting a vicious spiral of serious and recurrent falls (Scheffer et al., 2008). This section, "epidemiology of falls", deals with the literature on incidence, risk factors and consequences of falls among older adults.

2.1.1. Incidence and consequences of falls in community

Among community-dwelling older adults, 28-35% of older individuals aged over 64 years and 32-42% of those aged over 70 years (WHOGlobalreport, 2007) and 50% of those over 80 years (Soriano et al., 2007) fall each year while 10-20% of those fall recurrently (Tinetti et al., 1988). Every tenth older individual sustains a serious injury after a fall. Falls accompanied by injuries e.g. fractures, soft tissue injuries, traumatic brain injuries etc. account for 85% of all the injury-related hospital admissions, more than 40% of the nursing home admissions (Woolcott et al., 2009) and 40% of injury related deaths among the older population (WHOGlobalreport, 2007).

Therefore, falls make up the leading cause of death in older individuals and these fall related death rates have risen sharply over the past two decades (CDC, 2013). Even with these figures, the under-reporting of falls is also a problem with evidence that 75–80% of all falls without injury are not being reported at all (Fleming et al., 2008).

Among the older adults who fall, approximately one-half are unable to get up and remain on the ground. These "long-lies" lead to dehydration, rhabdomyolysis, pressure sores, and pneumonia (Fleming et al., 2008). In addition, 25%–55% older adults who fall develop a marked fear of falling, up to 40% restricting their activities of daily living (Soriano et al., 2007). This further increases the risk of falls by a decline in physical fitness and increase in functional dependence, social isolation and depression. Aside from their effects on mobility, independence and quality of life of older adults they is also an increase in the burden on hospitals and residential care facilities (Alexander et al., 1992).

Among Asian countries, the incidence of falls in Malaysia appears to be higher, one survey study in a primary care clinic in Kualalumpur, Malaysia reported the prevalence of falls to be 47%, recurrent falls to be 57% while injurious falls to be 61% (Sazlina et al., 2008). The prevalence of falls is 16.9% in males and 24.3% in females according to the Korean study (Choi et al., 2014) and 21% in a Taiwanese study (Wu, Chie, Yang, Liu, et al., 2013). Falls made up 51.3% of all injury related admissions according to one Singaporean study (Wui et al., 2014). According to a systematic review the fall rates in China ranged between 14.7% and 34% per annum, while 60% to 75% of those reported injurious falls with fractures constituting 6% to 8% of all injuries (Kwan et al., 2011).

Falls along with their consequences are responsible for a large part of preventable health care costs, the annual costs attributable to falls and fall-related

complications have been estimated to be billions of dollars worldwide (Scuffham et al., 2003). National fall related costs of prevalence-based studies are 0.85–1.5% of total healthcare expenditure (Heinrich et al., 2010). Although this data does not take into account the long term consequences of falls such as admission to care facilities or longer term need for home care, as falls are a strong predictor of placement in a skilled-nursing facility among older people living in the community (Tinetti et al., 1998). Therefore, falls are the primary reason for death and disability, an overall decrease in quality of life, increase in hospitalisations and early admissions to nursing homes; the burden of falls and their sequel on individuals, society and health care system is substantial.

2.1.2. Risk Factors

The risk factors associated with falls are categorised into extrinsic and intrinsic factors. The intrinsic and hence non-modifiable risk factors include age, gender (Kwan et al., 2011; Lehtola et al., 2006; Wu, Chie, Yang, Liu, et al., 2013), history of falls (Vieira et al., 2011; Wu, Chie, Yang, Kuo, et al., 2013), gait and balance impairment, mobility restriction and multiple comorbidities (Lee et al., 2006). The likelihood of falling and being seriously injured after a fall increases with age due to both physiological and pathological changes. Women are 58% more likely than men to suffer a nonfatal fall injury (Ambrose et al., 2013).The extrinsic factors considered modifiable include environmental hazards i.e. community hazards, home hazards and footwear problems. These include poor lightning, slippery floors, loose carpets, and lack of bathroom safety equipment etc. (Vieira et al., 2011). Medications are strongly associated with falls both through their direct effects and through indirect mediating factors (Kwan et al., 2011; Wu, Chie, Yang, Liu, et al., 2013). Medication intake, although generally considered modifiable, could be non-modifiable because certain medications are necessary for the optimal management of otherwise fatal diseases. A

study identified that unlike most other studies, the major causes of falls in Malaysia were the intrinsic factors with comorbidities as the major factor followed by mobility limitation, sensory deficits and age (Azhar et al., 2013). Most falls are multifactorial, it is therefore important to be aware of interactions and synergism between the risk factors. The risk of falls increases linearly with the increase in number of risk factors, it increased from 8% to 78% with none to four or more risk factors in one year prospective study on community dwelling adults aged 75 years and above (Tinetti et al., 1988).

Multifactorial falls prevention interventions, which include exercise, vision correction, medication review and home hazard management, are considered beneficial among fallers residing in the community with history of previous falls (J. T. Chang et al., 2004; Costello et al., 2008; M. Tinetti et al., 2010). In addition, studies have also highlighted the benefits of single interventions on falls reduction among elderly. Campbell et al and Velde et al showed that medication withdrawal may prove successful as a single intervention in reducing falls (Campbell et al., 1999; van der Velde, Stricker, et al., 2007). Other studies have shown that cardiac pacing among fallers with cardioinhibitory carotid sinus hypersensitivity (Kenny, 1999) and cataract surgery (Harwood et al., 2005) significantly reduce falls as a single intervention. Some studies also suggested that single intervention of comprehensive exercise alone is successful in reducing falls (Costello et al., 2008; M. Tinetti et al., 2010). A meta-analysis of randomised controlled trials amongst community dwelling older persons determined that multifactorial fall prevention interventions are more effective for individual patients, while for community programmes involving high risk populations, targeted single interventions may be beneficial as they are easier with better compliance and cost effectiveness (Campbell et al., 2007).

2.2. Medication use in older adults

Older people use more medications due to the age-related increase in prevalence of multiple pathologies. This, combined with the physiological changes in drug metabolism makes the older people two to three times more likely to experience adverse effects of drugs than younger people (Turnheim, 2004). Falls is the commonest adverse drug event, accounting for up to 25% of the hospitalizations in elderly patients (Nickel et al., 2013). Gurwitz et al evaluated the records of 30,397 Medicare enrolees aged ≥65 years and reported the incidence of adverse drug events as 50.1 per 1000 person years (Gurwitz et al., 2003). Viktil et al found 47% of their older patient sample used five or more drugs which was associated with a linear increase in adverse drug events due to "drug interactions" (Viktil et al., 2007). In spite of the higher prevalence of adverse drug events, the use of medicines among the elderly is increasing with time, a Swedish study analysed the number of drugs dispensed for the entire country during 2005-2008 and found that the prevalence of polypharmacy (≥5 drugs) and excessive polypharmacy (≥10drugs) increased by 8.2% and 15.7% respectively during this time span. Moreover, the prevalence of excessive polypharmacy displayed a clear age trend, with the largest increase for the group of 70 years and above (Hovstadius et al., 2010). A population-based study of older adults reported that the use of common cardiovascular medications increased dramatically with age and the use of at least three cardiovascular medicines increased from 39% to 54% during their five year follow-up period (P. K. Hiitola et al., 2007). Not only cardiovascular medications but the prescription of psychotropic drugs is also increasing, with a 22.2% increase in the prescription of three or more psychotropic medications in the past three decades (Rittmannsberger, 2002).

The age associated changes in physiological mechanisms which alter the pharmacodynamics and pharmacokinetics of drugs. The pharmacokinetic changes associated with ageing occur as a result of reduction in the renal or hepatic clearance

leading to increased serum drug levels and consequent drug toxicity even with the prescription of normal recommended adult doses (McLachlan et al., 2012). Nutritional status and body composition also affect drug metabolism. As lean body mass may decrease by 12-19%, body water content may reduce by 10-15% and total body fat may increase by 14-35% in an older person, the plasma levels of drugs primarily absorbed by the muscles increase thereby resulting in an increased plasma concentration of those hydrophilic drugs (Noble, 2003). The pharmacodynamic changes associated with increasing age include decreased responsiveness to β-adrenergic receptor agonists (β-agonists) and decreased α-adrenergic receptor activity. Moreover, the brain may be exposed to higher drug levels due to reduced effectiveness of the blood brain barrier in the elderly (Turnheim, 2004). In addition, the changes in drug handling abilities due to the various deficits arising with age e.g. the presence of dementia, may lead to medication errors especially among those with complex medication regimens (Nickel et al., 2013). With the increase in number of comorbidities and consequently polypharmacy, drug-drug interactions and drug-disease interactions also add up to the risk of adverse events in older people.

2.3. Medications and Falls: Fall risk increasing drugs

The studies performed on the risk assessment of falls have reported use of certain medications to be the significant risk factor for falls. These medications are termed as "fall risk increasing drugs" (FRID) in the falls literature. Particularly in older community dwellers, the drugs related to CNS are ten times more likely to increase falls risk through their direct effects of sedation, drowsiness and dizziness (French et al., 2006). The association of cardiovascular drugs with falls is complex as they are considered to mediate via blood pressure changes, orthostatic hypotension and syncope, which themselves are independent factors for falls and may or may not co-exist with

cardiovascular drugs (Milos et al., 2014; Poon et al., 2005). Hypoglycaemia caused by antidiabetic agents is a significant risk factor for falls in the older population (Berlie et al., 2010). Recent studies have reported that not only anticholinergic drugs themselves but other drugs with anticholinergic activity are also associated with falls through their effects on CNS as well as peripheral effects (Kersten et al., 2014). One Singaporean study found that elderly hospitalized patients on hypnotic drugs, cough preparations and anti-platelets are more likely to fall (Mamun et al., 2009). The systematic review by Hartikainen et al including 29 studies stated that the main group of drugs associated with an increased risk of falling was psychotropics: benzodiazepines, antidepressants, and antipsychotics while antiepileptics and blood pressure lowering drugs were weakly associated with falls (Hartikainen et al., 2007). Not only individual drug classes but an increased FRID count may also be a potent predictor of falls. Studies have stated that older adults with severe falls have increased FRID count which in turn is related with the increased number of medications, comorbidities and frailty (Bennett et al., 2014; Milos et al., 2014). This increase in FRID count is associated with an increased risk of fall injury in a dose response fashion (Laflamme et al., 2015). However, FRID count increases with the increase in total number of medications, therefore the reports have suggested that in an older person receiving multiple medications, polypharmacy itself or polypharmacy with at least one other FRID may be a strong predictor for falls (Richardson et al., 2015; Ziere et al., 2006). Table 2.1 provides a list of available meta-analysis on the association of individual FRID classes and falls among older adults.

2.3.1. Antihypertensives

The drugs used to treat high blood pressure encompass a controversial relationship with falls. While 25% of clinicians tend to prescribe less antihypertensives to older people as they believe it would do more harm than good (Fisher et al., 2003), a meta-analysis by Zang, involving 42 studies concluded that there is no clear evidence

for the association between blood pressure lowering medications and serious injurious falls (Zang, 2013). Since untreated cardiovascular pathologies can lead to devastating outcomes, some studies have actually found cardiovascular medications to be protective against falls (Kuschel et al., 2014). The angiotensin system blocking medications are considered the safest amongst others for blood pressure lowering therapy and recent prospective studies have even found them to be protective against falls among older adults (Romero-Ortuno et al., 2013; Wong et al., 2013).

On the contrary of the above evidence, a meta-analysis on the risk factors of falls found antihypertensives to be among the major risk factors for falls (Vieira et al., 2011). One study found that among all the antihypertensive agents, their older participants on diuretics and β-blockers were more likely to experience a fall (Costa-Dias et al., 2014). However, even the positive association between antihypertensives and falls is not simpler and the factors of dosage increment or initiation of a new antihypertensive drug may be more of a culprit in increasing the falls risk. According to Gribbin et al, although there was no association between antihypertensive medications and falls at baseline, fall risk increased with in the first three weeks of prescription of a diuretic (Gribbin et al., 2010) while Butt et al found the initiation of antihypertensive therapy to be associated with a 43% increased risk of hip fracture (Butt et al., 2012). The history of previous falls may be another factor in the complex association between antihypertensives and falls. The longitudinal studies by Callisaya et al. and Tinetti et al. involving older participants concluded that among those who had recurrent falls at baseline a higher intensity antihypertensive treatment was independently associated with future serious falls (Callisaya et al., 2014; Tinetti et al., 2014).

Table 2.1: Risk of falls and drugs usage among older people: results from published meta-analyses.

Drug Class	Examples	Odds ratio (95% confidence interval)		
		Bloch et al;2013(Bloch et al., 2013)	**Woollcott et al;2009(Woolcott et al., 2009)**	**Leipzig al;1999(Leipzig et al., 1999a, 1999b)**
Taking drugs(yes/no)	Consuming any medication	4.24 (3.06–5.88)*	-	-
Polypharmacy		1.71 (1.50–1.96)*	-	-
Cardiovascular drugs		0.78 (0.67–0.90)	-	-
Any Antihypertensives		1.10 (1.05–1.16)*	1.24(1.01-1.50)*	-
ACE inhibitors	Captopril, Lisinopril, Perindopril	-	-	1.20 (0.92, 1.58)
β-blockers	Propanolol, Atenolol, Metoprolol,	1.12 (1.04–1.21)*	1.14(0.97-1.33)	0.93 (0.94, 1.14)
Calcium channel blockers	Nifedipine, Amlodipine, Felodipine	1.21 (1.15–1.28)*	-	0.94 (0.77, 1.11)
Diuretics	Furosemide, Spironolactone, Amiloride	-	-	1.08 (1.02, 1.16)*
Digoxin	-	1.48 (1.11–1.99)*	-	1.22(1.05, 1.42)*
Type1a antiarrhythmics	Quinidine, procainamide	-	1.07(1.01-1.14)*	1.59(1.02, 2.48)
Vasodilators				
	α-blockers (Prazosin, Doxazosin)	1.12(1.04-1.21)*		1.13 (0.95, 1.36)
	Nitrates (Glyceryl Trinitrate, Isosorbide)			

Table 2.1 continued

Psychotropics	*Typical* (Chlorpromazine, haloperidol)	1.74 (1.56–1.95)*	1.59(1.37-1.83)*	1.73(1.52-1.97)*
Antipsychotics	*Atypical* (Clozapine, Olanzapine)	1.37 (1.16–1.61)*		1.50(1.25-1.79)*
	Barbiturate, Methaqualone, Thalidomide		1.47(1.35-1.62)*	
Sedative hypnotics		1.53 (1.40–1.68)*	1.57(1.43-1.72)*	1.54 (1.40, 1.70)*
Benzodiazepines	Lorazepam, Alprazolam	1.61 (1.35–1.93)*	-	1.48 (1.23, 1.77)*
Short acting	Diazepam, Clonazepam	-	-	1.44 (1.09, 1.90)*
Long acting	*Selective Serotonin Reuptake Inhibitors*	-	1.68(1.47-1.91)*	1.32 (1.09, 1.90)*
Antidepressants	(Fluoxetine, citalopram), *Selective Norepinephrine Reuptake inhibitors* (Venlafaxine, Duloxetine), *Tricyclic Antidepressants* (Imipramine, Desipramine), *Non-Tricyclic Antidepressants*(Mirtazapine, Trazodone)	1.59 (1.43–1.75)*		1.66 (1.41, 1.95)*
Anti-epileptics	Acetazolamide, Carbamazepine, Gabapentin, Lamotrigine			
	Dopa and Dopa derivative dopaminergic		-	
Antiparkinsonians	*agents*, *Dopamine receptor antagonists*	1.56 (1.28–1.90)*		-
	(Bromocriptine, Pergolide, Pramiprexole)		-	
		1.55 (1.21–1.97)*		-
Analgesics		1.33 (1.07–1.65)*	-	-
Opioids	Oxycodone, Hydrocodone, Morphine	1.43 (1.27–1.61)*	0.96(0.78-1.18)	0.97 (0.78, 1.12)
NSAIDs	Diclofenac sodium, Ibuprofen, Indomethacin, Naproxen	1.25 (1.11–1.42)*	1.21(1.01-1.44)*	1.16 (0.97, 1.38)
Others				
Metabolic and endocrine drugs	*Sulfonylureas* (Gliclazide), *Biguanides* (Metformin), *Thiazolidinediones*, *Insulin* Thyroid drugs (levothyroxine)	1.39 (1.20–1.62)*	-	-
Laxatives	Lactulose, Bisacodyl	2.03 (1.52–2.72)*	-	-

2.3.1.1. Does OH explain the possible mechanism of antihypertensives associated falls?

a. Falls and OH

The possible mechanism by which antihypertensives may be associated with falls remains unclear. The Swedish National Board of Health & Welfare classified the drugs associated with falls into two categories; the category FRID consisted of opioids, and all classes of psychotropics while the category of drugs indirectly related to falls by causing or worsening orthostatism consisted mainly of antihypertensives i.e. diuretics, β-blockers, CCB, ACE-I, A2RA, α-blockers and vasodilators (Milos et al., 2014). The commonest reason for physicians' reluctance in prescribing effective antihypertensive therapy is the belief that antihypertensives lead to OH (Choulerton et al., 2010). It has often been assumed that the relationship between antihypertensives and falls may be explained by the increased risk of OH in individuals treated with the antihypertensives, as the mechanisms of lowering blood pressure through decreased intravascular volume (diuretics), reduced cardiac output (β-blockers), vasodilatation (CCB, centrally acting agents) are responsible for causing OH as well (Schiffrin, 2010). To date, there has been no published study which evaluated the association of medication induced OH with falls among older patients (Bradley et al., 2003). However, Vischer reviewed the benefits and limitations of hypertension treatment among very old persons and concluded that hypertension being a bigger problem for fallers, should be treated efficiently and antihypertensive induced OH should not be a reason to not treat hypertension (Vischer, 2012). Similarly, it remains to be established whether withdrawal or dose adjustment of antihypertensive medications alone may be associated with a prospective reductions in falls. Such a study, when conducted, should take into account the potential increased risk of cardiovascular endpoints which may be associated with the higher or uncontrolled in blood pressure levels.

Orthostatic hypotension is not a disease in itself, but a physical finding resulting from the complex interplay of multiple contributory factors e.g. impairment of the autonomic nervous system, decreased intravascular volume, reduced cardiac contractility or decreased venous return. Among older adults, in addition, baroreflex-mediated cardio-acceleration and vasoconstriction declines in efficiency with age and when superimposed with hypertension or medications, these effects are exaggerated (Bradley et al., 2003). Amongst community dwelling older people, the prevalence of OH is 18.2% (Rutan et al., 1992) while among hospitalized older patients it is 44% (Coutaz et al., 2012). The prevalence of OH increases with increasing age, ranging from 31% in patients aged 75-79 years, 35% in individuals aged 80-84 years to 40% in those aged 85 years or more (P. Hiitola et al., 2009).

Orthostatic hypotension may present as light-headedness, dizziness, blurred vision, and shakiness immediately after standing and may result in falls by causing loss of consciousness or postural instability as a result of cerebral hypoperfusion (M. P. Tan et al., 2006). However, the exact reproduction of symptoms of falls or loss of consciousness is rarely demonstrated in older fallers. Several studies have found strong association between OH and frequent falls with medication induced OH being responsible for 33% of these falls (Craig, 1994; Rubenstein et al., 1990; Rutan et al., 1992). In contrast, a later study by Kario et al found no association between OH and falls despite demonstrating a significant relationship between lower standing SBP and falls (Kario et al., 2001). However, the presence of symptomatic OH may be distinctively related to falls instead of the physical finding of OH. In a study by Shibao et al, 34% of patients with OH were symptomatic and 83% of these individuals with symptomatic OH experienced falls (Shibao et al., 2007).

b. Antihypertensives and OH

Orthostatic hypotension is widely attributed to diseases like hypertension, diabetes and parkinsonism (Perez-Lloret et al., 2012) and is also considered to be a side-effect of medications prescribed for these conditions. Therefore, OH may occur as a consequence of medication or an underlying illness or due to combination of both. However studies have shown that intensely prescribed antihypertensive therapy to older adults could increase the risk of OH. Intensive hypertensive treatment could be determined by higher doses of antihypertensive medications, increased number of antihypertensive drugs or lowering blood pressure below the recommended target of 140/90mmHg (Aronow et al., 2011). It has been suggested that the total number of blood pressure lowering medications (Verwoert et al., 2008) or the use of at least three antihypertensive drugs is a significant predictor of OH (Kamaruzzaman et al., 2010). The study by Hiitola et al, reported that OH was only associated with the total number of medicines consumed but not with any particular antihypertensive medications or the number of cardiac medications (P. Hiitola et al., 2009). However, in Hiitola's study the use of medicines was very high with participants taking up to 23 medications which suggest higher number of comorbidities and more likely the comorbidities associated with OH. To date, there have been no studies linking the dosage of antihypertensives with OH.

To determine the association of antihypertensives with OH, the effects of antihypertensive withdrawal on OH has been evaluated in a handful of limited studies. Fotherby et al. withdrew antihypertensive therapy from 47 subjects with a blood pressure of 175/100mmHg or less and reported a decrease in prevalence of OH in the antihypertensive withdrawal group while the prevalence of OH remained unchanged in the group which continued their antihypertensive therapy but only after re-exclusion of those with a blood pressure of greater than 175/100mmHg (Fotherby et al., 1994). This

suggests that although antihypertensive withdrawal may be beneficial in reducing OH, it is not possible in patients with higher blood pressure readings. The antihypertensive therapy evaluated in this study consisted mainly of diuretics, CCB and β-blockers, as newer antihypertensive agents such as ARB were not yet available at the time of study.

In another study where all cardiovascular medications (antihypertensives, anti-arrhythmic and anti-anginal medications) were withdrawn, 78% of subjects reported improvements in symptoms of syncope and falls and the physical finding of OH. Furthermore, the renewal of medications was not necessary in 70% of the group (Alsop et al., 2001). However the criterion for antihypertensive withdrawal was that if the patient on antihypertensive therapy had a blood pressure of 120/80mmHg or lower suggesting that withdrawal only occurred in individuals with intensive antihypertensive therapy.

Van der Velde et al also found the withdrawal of these culprit drugs to be effective in the resolution of OH. In addition, the withdrawal of cardiovascular drugs produced significantly larger reductions in OH than psychotropic medications and other drugs (van der Velde, van den Meiracker, et al., 2007). The authors mentioned that the drugs were only withdrawn if they were duplicative or if withdrawal was considered safe, but no clear cut-off values for blood pressure or duplicative classes on antihypertensives were mentioned. The above studies citing the reduction in OH with the withdrawal of antihypertensive agents did not include longitudinal follow up data on cardiovascular end-points or all-cause mortality. We are therefore unable to define the benefits of withdrawing antihypertensive agents and to the extent these drugs could safely be withdrawn.

The association of antihypertensives with OH differs according to individual classes of blood pressure lowering medications. Angiotensin converting enzyme

inhibitors, ARBs and CCB are less likely to be associated with OH as compared to β-blockers and thiazide diuretics. The "Predictive Values of Blood Pressure and Arterial Stiffness in Institutionalized Very Aged Population" (PARTAGE) study reported that β-blockers had significantly higher impact on OH due to their increased sympathomimetic activity, while OH was less common among ARB users (Valbusa et al., 2012). Supporting this evidence, the TILDA study reported an association of OH with β-blockers and α-blockers, while CCB were shown to be protective against OH. Except one study in which thiazides were found to be protective (Fisher et al., 2003), studies suggest that thiazides are associated with OH (Kamaruzzaman et al., 2010). A randomized, double blind trial comparing the use of an ARB and a thiazide diuretic with an ARB and a calcium channel blocker found that both combinations were equally effective in controlling high blood pressure, but the ARB and thiazide combination group was more likely to develop OH (Fogari et al., 2009).

The evidence from older studies linking blood pressure lowering drugs to postural hypotension can be considered relatively out-dated as they were mostly performed while patients were on older hypertensive medications such as methyldopa, prazosin, thiazide diuretics or propranolol which had more side-effects and a higher propensity to cause OH. The newer antihypertensive agents such as ACE-I or ARB which have been developed in response to the unsatisfactory side-effects of older antihypertensive medications, now have fewer side-effects and better compliance profiles (Fogari et al., 2009). There is an urgent need for well-designed studies to measure the risk of adverse cardiovascular and mortality outcomes of withdrawal of blood pressure lowering therapy on falls and OH.

The available studies on the association between antihypertensives, OH and falls are listed in table 2.2.

c. Antihypertensives, Orthostatic hypotension and Hypertension

While antihypertensives are used for the treatment of high blood pressure/hypertension, a highly prevalent pathology amongst older adults, the literature review could not be completed without taking this factor into account. An English study involving 3515 older individuals aged ≥64 years found that 81% of their nationally representative population fulfilled their criteria for hypertension during at least one time point, with 76% of those with untreated hypertension presenting with isolated systolic hypertension (Beckett et al., 2008). Isolated systolic hypertension in turn, has been found to be strongly associated with OH (Rutan et al., 1992). The increased pulse pressure and isolated systolic hypertension which is unique to hypertension in older people is presumed to add to the challenges of achieving blood pressure targets in older people, as lowering of systolic blood pressure could then lead to unacceptably low diastolic blood pressure with the increased potential of adverse events.

Table 2.2: Summary of Studies Evaluating the Relationship between Antihypertensive Medications with Falls and Orthostatic Hypotension.

Reference	Participants	Study Design	Findings
Fotherby et al. 1997 (Fotherby et al., 1997)	N=74, ≥ 60 yrs Hospital patients	Cross-Sectional study	Orthostatic hypotension was not associated with antihypertensive treatment in elderly
Ooi et al. 2000 (Ooi et al., 2000)	844 people ≥ 65 yrs from nursing homes	Prospective cohort study	OH was not associated with first fall but among subjects with history of falls, those with orthostatic hypotension had an increased risk of recurrent falls [RR=2.1; 95%CI (1.4-3.1)].
Kario et al. 2001 (Kario et al., 2001)	N=266, ≥ 65 yrs community dwelling	Prospective study	Lower SBP on standing is associated with falls independently but OH is not associated with falls. Antihypertensive therapy does not increase the falls risk [RR=0.58; 95%CI (0.29–1.2)].

Table 2.2 continued

Heitterachi et al. 2002 (Heitterachi et al., 2002)	N=70, age =60-92yrs community dwelling	Prospective study	OH was significantly associated with falls [RR=1.71, 95%CI (1.14-2.59)]. Antihypertensives were strongly associated with OH but not with falls [RR=0.91, 95%CI (0.60-1.51)]. Other causes of OH need to be evaluated as antihypertensives are not related with falls.
Fisher et al. 2003 (Fisher et al., 2003)	N=119, >80 yrs Residential care facilities	Case control study	There was no significant association between antihypertensives and OH [OR=0.8 CI (0.3–1.7)] and antihypertensives and falls [OR=0.8; 95%CI (0.4–1.6)].
Poon et al. 2005 (Poon et al., 2005)	N=342, ≥ 75yrs, geriatric clinic	Retrospective study	Prevalence of OH increased with the increase in number of culprit medicines including antihypertensives prescribed [X^2=15.18; p=0.002] and was predictor of falls. Study is about the whole culprit medication group but among antihypertensives thiazides were the most frequent used by patients having OH.
Kamaruzaman et al. 2010 (Kamaruzzaman et al., 2010)	N=4286 women, age= 60-80 years; community dwelling	Cross-sectional sub study of a large prospective study	OH was associated with three or more hypertensives [OR=2.24, 95% CI 1.47–3.40, P < 0.001]. No other antihypertensives were associated with OH except beta blockers [OR=1.58; 95%CI (1.19-2.09); p < 0.01]. This medication induced OH was not associated with falls.
Gribbin et al. 2010 (Gribbin et al., 2010)	N=968, >65years primary care	Prospective Case control study	Thiazide diuretics were found to increase the risk of first fall significantly [OR=1.25; 95%CI (1.15–1.36)], no other antihypertensive showed any significant association with falls.
Shuto et al. 2010 (Shuto et al., 2010)	N=349, , >65years hospital	Case-Control study	Antihypertensives were strongly associated with falls risk [OR=8.42; 95%CI (3.12-22.72)]. As the patients are hospitalized, use of antihypertensive with another risk factor like frailty may lead to falls.
Coutaz et al. 2012 (Coutaz et al., 2012)	N=388, >65years hospital	Cross- Sectional study	Antihypertensive therapy does not increase the risk of falls even in the presence of OH.
Wong et al. 2013 (Wong et al., 2013)	N=520, >65years community dwelling	Prospective cohort study	Antihypertensive medications were not associated with falls [OR=1.05; CI (0.37–2.93)]. Angiotensin system blocking medicines showed protective effects against falls [OR= 0.68; 95%CI (0.48–0.97)]
Butt et al. 2013 (Butt et al., 2013)	N=543,572 , >65yrs, population based	Prospective study	New antihypertensive users have 69% increased risk of having a fall [RR=1.94; 95%CI (1.75-2.16)]. This finding was consistent for Thiazide diuretics, Angiotensin converting enzyme in inhibitors, Calcium channel blockers, β-blockers but not for Angiotensin receptor blockers.

Table 2.2 continued

Callisaya et al. 2014 (Callisaya et al., 2014)	N=409, age= 60-86 years, community dwelling	Prospective population-based cohort study	Antihypertensives as a group were not associated with falls however higher dose of antihypertensives was independently associated with greater fall risk [RR = 1.07; 95%CI (1.02–1.11); p = .004). The risk was 48% higher in those with more than 3 times the daily defined dose [RR=1.48; CI (1.06–2.08); p=.02)].
Tinetti et al. 2014 (Tinetti et al., 2014)	N=4961, age ≥70years, community-living	Prospective population-based cohort study	Antihypertensive medications by number or class were not associated with serious fall injuries but in participants with previous falls or injurious falls use of high intensity daily defined doses of antihypertensives were associated with serious fall injuries [HR=2.31; 95%CI (1.01-5.29)].
Kuschel et al. 2014 (Kuschel et al., 2014)	N=64399, ≥ 65 years community living	Case control study	Twenty commonly prescribed medicines were tested and antihypertensives showed a protective effect against falls. The protective effect was highest for ACE-Inhibitors and Calcium channel blockers

Risks are presented as odds ratio (OR), risk ratio (RR) and hazard ratio (HR) with 95% confidence interval (CI). OH=orthostatic hypotension

While randomized-controlled studies such as the "Hypertension in the Very Elderly Trial" (HYVET) have clearly demonstrated significant survival benefits in blood pressure treatment even among the very old participants (Beckett et al., 2008), opinions between clinicians do differ with respect to the how aggressively hypertension should be treated among older patients. Many geriatricians remain sceptical as participants of the HYVET study consisted of physically healthy older individuals who did not necessarily represent the average older person attending a geriatric service. The larger studies on OH and blood pressure control have reported uncontrolled hypertension to be markedly associated with OH more than the use of antihypertensive therapy. The British women heart and health study (BWHHS) involving 3775 women aged 60-80 years, related OH with uncontrolled hypertension by reporting the prevalence of OH to be 24% higher among hypertensive women with a SBP >140mmHg than normotensive women (Kamaruzzaman et al., 2010). The observational cohort "Predictive Values of Blood Pressure and Arterial Stiffness in Institutionalized Very Aged Population" (PARTAGE) study involving 994 participants aged ≥80 years

also demonstrated the close association of OH with uncontrolled blood pressure by concluding that elderly with OH had significantly higher SBP and DBP than those without OH. On the other hand, both normotensive older individuals and those with well-controlled blood pressure (SBP≤ 140mmHg) had a lower prevalence of OH than those with SBP exceeding 140mmHg. The MOBILIZE Boston (Maintenance of Balance, Independent Living, Intellect and Zest in the Elderly of Boston) study involving 722 community dwelling adults aged 70 years and above showed that both OH and the risk of falls is 2.5 times higher in individuals with uncontrolled hypertension (≥140/90mmHg) compared to those with controlled hypertension (Gangavati et al., 2011).

The Irish Longitudinal Study on Ageing (TILDA) research group classified orthostatic hypotension into three groups; small drop with fast recovery, medium drop with slow recovery and large drop with no recovery. They found that severe OH with slow or no recovery was associated with uncontrolled systolic hypertension (Romero-Ortuno et al., 2013). As previous studies had not evaluated the patterns of blood pressure drop in their OH subjects, the significance of the three classifications remains unclear. However, the study clearly showed the association of higher blood pressure readings with the severity of OH. The mechanism of association between uncontrolled hypertension and OH may be that the normotensive individuals and those with controlled hypertension have less arterial stiffness, improved baroreflex sensitivity and subsequently less OH as compared to individuals with uncontrolled blood pressure levels (Berni et al., 2011; Protogerou et al., 2008).

While the above studies have demonstrated a significant association between uncontrolled hypertension and OH, the Austrian Vorarlberg Health Monitoring and Prevention Programme involving 3544 community living seniors aged 60 years

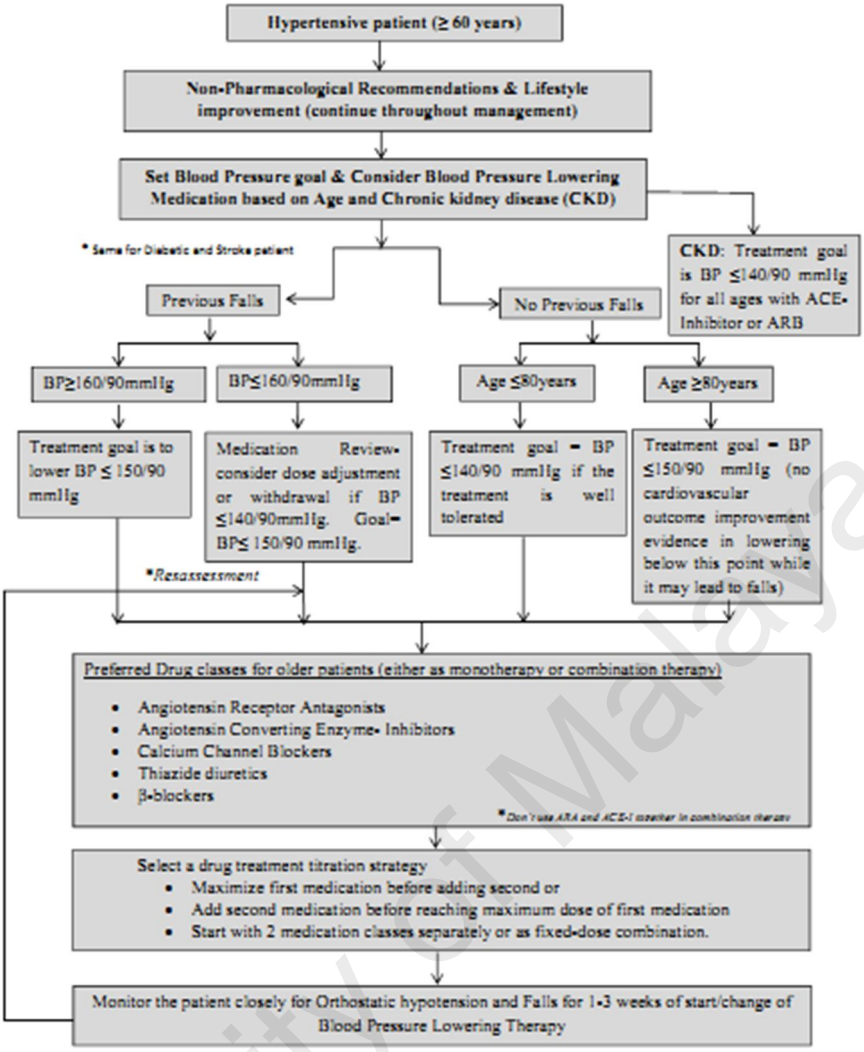
suggested the lower blood pressure readings or tightly controlled hypertension to be associated with falls by showing that the individuals with blood pressure >120/80 mmHg had a significantly lower risk of falls compared to those with lower blood pressures. They reported that an increase in SBP of 10mmHg and DBP of 5mmHg is associated with a 9% reduction in falls risk (Klein et al., 2013). The values cited were lower than the recommended treatment targets for hypertension (>140/90mmHg) and sitting blood pressure was measured without considering postural blood pressure changes, suggesting that while controlled hypertension may be necessary to avoid OH and falls, a tighter blood pressure control may not be the best option for older adults.

While, the above body of evidence suggests that OH is more prevalent among individuals with uncontrolled or untreated hypertension, there has been no published intervention study to date, determining whether effective treatment of hypertension can reduce the severity of OH. Among the frail elderly, even a slight drop in postural blood pressure may increase the propensity to fall due to the increase in postural instability as the result of cerebral hypoperfusion (P. Hiitola et al., 2009). The available evidence therefore suggests that in robust older individuals, aggressive blood pressure lowering therapy is beneficial while in individuals with predilection to falls, blood pressure lowering therapy may increase the risk of falls in a dose dependent fashion. In frail individuals with a history of falls, blood pressure lowering therapy should be initiated and monitored cautiously, the withdrawal of antihypertensives among those with blood pressure of <140/90mmHg may reduce the risk of falls in this particular group of older adults.

d. Use of Antihypertensives to Manage Hypertension in Older Patients

With conflicting evidence on the association between antihypertensives, OH and falls, the treatment of hypertension among older adults with history of falls warrants

careful attention. Figure 1 consists of a flow diagram on management of hypertension in older people based on current guidelines and available evidence. Prior to prescribing any blood pressure lowering treatment, the physician should take into account the factors of age, presence of other drugs, other existing pathologies and previous history of falls. Intensive blood pressure treatment should be prescribed among robust older individuals aged less than 80 years. In individuals aged 80 years and over, it is currently not advisable to treat high blood pressure aggressively. In individuals with established risk factors for falls, aggressive blood pressure lowering treatment should be avoided and in individuals previously on antihypertensive treatment with a treatment target of less than 140/90mmHg, their treatment targets should be revised to less than 150/90, and medication withdrawal considered. Close monitoring is required for the potential onset or exacerbation of OH in these individuals, particularly in the first month of initiation of therapy. The blood pressure lowering agents ARB, ACE-I and CCB should be used preferentially, especially among the high falls risk group, as diuretics and β-blockers have been found to be associated with OH and falls and should be avoided in individuals at the risk of falls. Should any older individual on antihypertensive treatment sustain a fall, their blood pressure management should be revised, and treatment targets adjusted accordingly.



2.3.2. Anticholinergics

Several drugs prescribed to older adults for their common medical conditions have anticholinergic properties; many drugs not usually denoted as anticholinergics as well as many over the counter drugs have shown strong anticholinergic activity. The prevalence of anticholinergics among the elderly is quite high, prospective epidemiological studies among community dwelling older adults have reported the prevalence of medications with anticholinergic properties to be 48% in Europe (Fox et al., 2011) 50% in America (Carriere et al., 2009) and 52.66 % in New Zealand (Narayan et al., 2013). According to prospective studies on nursing homes, 24% of the French

while 46.1% of the Italian participants were on atleast one medication with anticholinergic activity (Beuscart et al., 2014; Landi et al., 2014). Amitriptyline, nortriptyline, oxybutynin (Narayan et al., 2013) and hydroxyzine (Beuscart et al., 2014) are the commonly prescribed drugs among the elderly with significant anticholinergic potency.

Anticholinergic drugs are the most widely used inappropriate drugs by older population. A cross-sectional study identified that approximately one in ten older adults used anticholinergic medications considered as inappropriate, the most frequently used inappropriate anticholinergics were cyclobenzaprine, promethazine, amitriptyline, hydroxyzine and dicyclomine according to Beers' criteria (Kachru et al., 2015). Anticholinergic burden is associated with poor mobility, functional decline, psychomotor slowing, and cognitive impairment and falls (Cao et al., 2008; Landi et al., 2014; Nebes et al., 2007). Newer studies have related anticholinergic drugs with increased hospitalisations (Salahudeen et al., 2014) cardiovascular diseases and mortality (Fox et al., 2011; Myint et al., 2015).

2.3.2.1 Anticholinergic burden and falls

Several studies have linked the anticholinergic activity of drugs to falls among older adults (Aizenberg et al., 2002; Dauphinot et al., 2014; Wilson et al., 2011). The meta-analysis of eighteen studies determined that a greater use of drugs with anticholinergic activity was significantly associated with falls, in particular, olanzapine and trazodone were associated with the highest risk of falls (Ruxton et al., 2015). However, it may be the cumulative damage from multiple small dose anticholinergics rather than single high dose drugs which markedly increased the risk of falls (Parkinson et al., 2015). While prescribing a new drug or providing medication reviews the collective anticholinergic burden might be overlooked because these drugs belong to

different chemical classes or the patient might be taking over the counter drugs that may increase the risk of falls extensively. Although studies on the association of anticholinergics and falls are performed in different settings using different tools to measure anticholinergic effect, they depict a positive association between anticholinergics and falls. Table 2.3 gives a summary of studies showing the association of anticholinergics with falls using different tools.

2.3.2.2. Possible mechanisms of anticholinergic associated falls: Gait and Balance

While substantial evidence exists for anticholinergics to be strongly associated with falls, there are more than one plausible mechanism behind the association between anticholinergics and falls. Anticholinergics are well known for their cognitive impairment effects on older adults (Cao et al., 2008; Carriere et al., 2009; Fox et al., 2011; Landi et al., 2014; Salahudeen et al., 2014) which itself is an independent predictor for falls (Harlein et al., 2011; Vieira et al., 2011). They may also lead to falls through their immediate effects i.e. mydriasis (leading to blurred vision), dizziness, urinary hesitancy, confusion, sedation, and inability to concentrate (Feinberg, 1993). A substantial number of studies have shown higher anticholinergic burden of drugs to be associated with the negative impact on gait and balance, poor physical performance and general functional decline (Cao et al., 2008; L. Han et al., 2008; Landi et al., 2014; Nebes et al., 2007; Pasina et al., 2013). Reduced muscle strength and gait and balance impairment is a major independent predictor of falls (M. E. Tinetti et al., 2010), most of the falls studies have employed TUG and FR as sensitive and specific measures for identifying functional performance including dynamic balance and gait disturbances among community dwelling adults (Desai et al., 2010; Shumway-Cook et al., 2000).

Table 2.3: Association of anticholinergic load of drugs with falls.

Reference	Study Design	Participants (n)	Scale Used	Association with Falls
Aizenberg et al(Aizenberg et al., 2002)	Case-Control Study	n=482, age≥65 yrs Hospital Setting	ABS	ABS score was significantly associated with falls (p <0.05).
Rudolph et al(Rudolph et al., 2008)	Cross sectional	N=117 age≥65 yrs Primary care	ARS	Higher ARS score wad significantly associated with falls (1.5; 95% CI, 1.3-1.8 p<0.001)
Wislon et al(Wilson et al., 2011)	Longitudinal	N=602 age≥70 yrs Residential Care	DBI	Incidence rate ratios of falls were 1.69 (95% CI, 51.22–2.34) for low DBI (<1) and 2.11 (95% CI, 51.47–3.04) for high DBI (≥1).
Dauphinot et al(Dauphinot et al., 2014)	Longitudinal	N=337 age≥65 yrs Hospital Setting	DBI	Increased DBI during hospital stay was associated with falls with a hazard ratio, 2.9; 95%CI, 1.14–7.12 ;p =0.03).
Landi et al(Landi et al., 2014)	Prospective	N=1490 age≥65 yrs Nursing Homes	ARS	Higher score on ARS was associated with falls with odd ratio 1.26; 95%CI, 1.13-1.41; p<0.05
Salahuddin et al(Salahudeen et al., 2014)	Pharmacoepidemiological study.	N= 537,387 age≥65 yrs Population based	9 published scales	Anticholinergic burden scores according to all nine scales were significantly associated with falls related hospitalizations.
Yayla et al(Yayla et al., 2015)	Cross Sectional	N=563, age≥65 yrs Primary Care patients	ARS	Mean number of falls among anticholinergic drug users for a mean duration of 3.17 years were 1.14±1.17.

ABS=Anticholinergic burden scale, ARS=Anticholinergic Risk scale, Drug Burden Index

Gait and balance is an outcome coordinated by the central nervous system involving various systems of the body. The blockade of acetylcholine transmission in the CNS has been related to widespread undesired adverse effects, including reduced executive and motor functions (Kersten et al., 2014) and overall reduced performance on general daily activities (Chew et al., 2008). Another physiological explanation behind the association of anticholinergics with impaired physical function is the high sedative load of anticholinergics, generally defined as the cumulative effect of taking multiple drugs with sedative properties, leading to both acute and chronic decline in mobility and function. In addition, Taipei et al suggested that a higher sedative load was associated with significantly impaired balance as well as a longer time required to

perform the TUG test (Taipale et al., 2011). Moreover, Buchner his review article stated that anticholinergics have an effect on physical performance and activity due to their sedative effects leading to weak muscle strength due to disuse atrophy of muscles and subsequently causing falls (Buchner, 1997). Even when diverse measurement methods are employed, the anticholinergic burden is significantly associated with deterioration in physical function as well as gait and balance. Table 2.4 shows the list of studies showing the association between anticholinergics and poor functional scores which subsequently leads to falls.

2.3.3. Others: Central Nervous system (CNS) drugs, Analgesics, Antidiabetics

Drugs affecting the CNS are the medications most commonly associated with adverse drug events. Older adults on CNS drugs are almost 10 times more likely to fall (Costa-Dias et al., 2014), sustain recurrent falls (van Strien et al., 2013) and fall injuries (Kuschel et al., 2014). Among all the CNS drugs, psychotropics are independent risk factors for in falls (Lawlor et al., 2003; Souchet et al., 2005) and injurious falls (Stenbacka et al., 2002) in a dose dependent manner (C. H. Chan et al., 2013). Different studies have identified antianxiety (Shuto et al., 2010; Sterke et al., 2008; Tanaka et al., 2008; van Strien et al., 2013) antidepressants (Costa-Dias et al., 2014; Kallin et al., 2002; Lawlor et al., 2003; Sterke et al., 2008; van Strien et al., 2013) and sedatives/ hypnotics (Lawlor et al., 2003; Shuto et al., 2010; van Strien et al., 2013; Wu, Chie, Yang, Kuo, et al., 2013) to be strongly associated with falls. Psychotropic drugs contribute to falls through their cardiac side-effects (Mehta et al., 2011) and central nervous system effects of sedation, dizziness, drowsiness and orthostatic hypotension (C. H. Chan et al., 2013; Wilson et al., 2011), as they act on receptors both centrally and peripherally. Rodriguez et al found that the increase in the serum levels of antidepressants is a significant contributor of OH (Rodriguez de la Torre et al., 2001),

while in another study 75% of patients reported OH after treatment with antipsychotic drugs (Mackin, 2008). Moreover, there is a significant association of psychotropic medications and sensorimotor functioning leading to postural instability resulting in falls (Lord et al., 1995).

Table 2.4: Studies showing the effect of anticholinergic load on poor physical performance.

Reference	Study Design	Participants (n)	Scale Used	Findings on the association of ACB with physical function, gait and balance
Taipale et al(Taipale et al., 2012)	Cross Sectional	n=700 age≥75 yrs Community dwelling	TUG, Berg Balance scale, Walking speed	Timed Up and Go test (P = 0.005), slower walking speed (P = 0.0003), longer time to perform and lower scores on Berg Balance Scale (P =0.005) were associated with anticholinergic burden.
Pasina et al (Pasina et al., 2013)	Prospective	N=1380 age≥65 yrs Hospital Setting	Barthal Index	Anticholinergic burden by ARS was associated with poor functional performance scores for activities of daily living.
Han et al (L. Han et al., 2008)	Prospective	N=544 men age≥65 yrs Community dwelling	IADL scale	Cumulative anticholinergic exposure across multiple medications over 1 year may negatively affect executive function in older men causing deterioration of activities of daily living.
Landi et al(Landi et al., 2014)	Prospective	N=1490 age≥65 yrs Nursing Homes	IADL scale	A higher score of anticholinergic burden in the ARS scale was associated with a greater likelihood of functional decline (described as the loss of ≥1ADL point)
Nebes et al(Nebes et al., 2007)	Cross-sectional	N=90 Mean age= 72 yrs	simple response-time task, Walking speed	Higher serum anticholinergic activity (SAA) was associated with a significant slowing in both gait speed and simple response time.
Cao et al(Cao et al., 2008)	Cross-sectional	N=932 women age≥65 yrs Nursing Homes	ADL scale, chair stands, mobility and balance, gait speed, grip strength	Anticholinergic drug burden was independently associated with greater difficulty in four physical function domains for balance & mobility difficulty; slow gait; chair stands difficulty; weak grip strength; upper extremity limitations; and difficulty in activities of daily living.
Bostock et al(Bostock et al., 2013)	Prospective	N=271 Mean age= 83 yrs Hospital setting	BI	The use of anticholinergic drugs showed independent associations with lower BI, shoeing a decreased performance in activities of daily living
Lowry et al(Lowry et al., 2012)	Prospective	N=362 age≥65 yrs Hospital setting	BI	Higher score of anticholinergics and sedatives were associated with lower score of BI, indicating a decrease in activities of daily living
Lampela et al(Lampela et al., 2013)	Cross-sectional	N=621 age≥65 yrs population-based	SAA	Anticholinergic drug burden was inversely associated with activities of daily living and instrumental activities of daily living.

TUG=Timed up and Go, ADL=Activities of daily living, BI=Barthal Index, SAA= Serum Anticholinergic Activity

While the persistent use of psychotropics leads to falls and fractures in the elderly (Vitry et al., 2010), the start of a new drug (C. H. Chan et al., 2013) or the dose increment of an old psychotropic drug may be associated with 3.4 fold increase risk of falls (Sorock et al., 2009). Echt et al. supported these findings by demonstrating that the start or dose titration of any new psychotropic was significantly associated with falls within the first seven days (C. H. Chan et al., 2013; Echt et al., 2013). While SSRI are considered safer compared to TCA because of fewer cardiovascular side effects, they pose the same increase in the risk of falling in the elderly (Wilcock et al., 2005). In one study where 54.7% of participants were using SSRI and 31.6% were taking TCA, SSRI were found to be associated with falls instead of TCA, while trazodone, venlafaxine, mirtazapine were associated with most adverse outcomes (Coupland et al., 2011). Benzodiazepines are considered the culprit medicines for falls, fracture associated falls (Formiga et al., 2008; Wahab et al., 2012). The short acting benzodiazepines are considered to counter the side effects of the older long acting drugs but the safety profile of these newer agents against falls have yet to be firmly established. One study showed that short acting benzodiazepines pose the same risk falls as are long acting benzodiazepines (van Strien et al., 2013) while another showed that short acting benzodiazepines are more likely to cause falls than long acting benzodiazepines when taken in same dosages (Shuto et al., 2010; van Strien et al., 2013).

Drugs prescribed for Parkinson's disease are also considered to be strongly associated with falls by the mechanism of OH and mental confusion (Shuto et al., 2010; Tanaka et al., 2008). Muscle relaxants are associated serious falls in elderly patients by causing weakness and drowsiness (Coutinho et al., 2008). Narcotic analgesics (Costa-Dias et al., 2014) and anticonvulsants (Vieira et al., 2011) are also among the drugs significantly associated with falls through their CNS effects.

Diabetes is one of the commonest pathologies among older adults; antidiabetics have shown to increase the risk of falls and their recurrence in some studies (Costa-Dias et al., 2014). While a tight glycaemic control is vital in reducing all the diabetes related complications as well as falls adults (Schwartz et al., 2008), hypoglycaemia is also related to fracture associated falls, the association of antidiabetics with falls may be attributed to hypoglycaemia (Johnston et al., 2012). Among oral antidiabetics, metformin is indirectly associated with falls by causing vitamin B12 deficiency while thiazolidinediones are associated with fracture associated falls due to their effects on bone (Wu, Chie, Yang, Kuo, et al., 2013) tissue (Mayne et al., 2010). Insulin therapy also significantly increases the risk of falls in older adults (Schwartz et al., 2008).

2.4. Polypharmacy

There is an extensive body of evidence linking increasing age and adverse drug events with polypharmacy. In the absence of consensus definition various authors have termed polypharmacy as the total number of medications or use of multiple medications (Bushardt et al., 2008); published papers have used varying cut-offs for polypharmacy ranging from 2 to 9 medications (Hajjar et al., 2007), with the definition of "use of four or five drugs by the patient" most frequently employed in the falls literature (Bushardt et al., 2008; Wyles et al., 2005). Existing definitions may or may not include over the counter and complementary treatments. Table 2.5 lists the published definitions used to define polypharmacy among older adults.

Polypharmacy in a patient can occur for the treatment of one disease or several diseases. Polypharmacy, however, may be necessary in the older population with multiple pathologies in view of clear substantiation on improved clinical endpoint for diseases effecting mainly older people like ischaemic heart disease, stroke, diabetes and

hypertension (Bushardt et al., 2008). In addition, the use of combination therapy is considered essential for the standard treatment for conditions like diabetes, tuberculosis and AIDS (Aronson, 2006). However, the risk of cumulative side effects and drug interactions with multiple medications and multiple pathologies persists, even if an older individual is prescribed polypharmacy for clinically justified reasons.

Table 2.5: List of Previously Published Definitions for Polypharmacy.

Reference	Definitions of polypharmacy
Veehof et al. (Veehof et al., 2000)	A long-term (240 days a year) simultaneous use of two or more drugs. They classified polypharmacy as minor (2-3drugs), moderate (4-5 drugs) and major (>5drugs).
Brager et al. (Brager et al., 2005)	The use of two or more medications to treat the same condition or the use of two or more drugs of the same chemical class; or the use of two or more agents with the same or similar pharmacologic actions to treat different conditions.
Ziere et al. (Ziere et al., 2006)	Use of four or more medications with at least one inappropriate/ fall risk increasing medication.
Slabaugh et al. (Slabaugh et al., 2010)	Simultaneous use of five or more medications occurring for at least one day.
Hovstadius et al. (Hovstadius et al., 2010)	The use of multiple drugs with ≥5 drugs was termed as polypharmacy while the use of ≥ 10 drugs was termed as excessive polypharmacy occurring within a period of three months.
Kamaruzzaman et al. (Kamaruzzaman et al., 2010)	The intake of more medications by a patient than is clinically justified.

The term polypharmacy has also been used interchangeably with inappropriate polypharmacy due to prescribing of drugs considered inappropriate for older individuals (Bushardt et al., 2008). The presence of polypharmacy leads to an increased risk of inappropriate prescribing and inappropriate omission of medications and vice versa (Taro Kojima et al., 2012; Steinman et al., 2006). Therefore, some authors have employed terms of appropriate or "rational" and inappropriate or "irrational" polypharmacy with rational polypharmacy being justified among older people because of the existence of multiple pathologies (Brager et al., 2005; Hammond et al., 2013). With the advent of evidence-based prescribing for long-term pathologies, however,

physicians caring for older individuals often find it impossible to prescribe less than four or five medications (Hammond et al., 2013). There is currently inadequate evidence on the ratios of the risk of prescribing multiple medications versus the potential benefits of prophylactic treatments to inform the determination of a standard "cut-off" for polypharmacy among older adults.

2.4.1. Prevalence, Risk factors and Consequences

Polypharmacy is prevalent among the geriatric population, one Italian study on older adults reported that 39.4% of their sample was exposed to at least one episode of polypharmacy which substantially increased with age and with higher number of chronic conditions (Slabaugh et al., 2010). The prevalence was even higher in an Austrian study where 58% of their older participants fulfilled the criterion for polypharmacy (Schuler et al., 2008). The trend towards polypharmacy is increasing with time, the prevalence of polypharmacy and excessive polypharmacy increased by 8.2% and 15.7% respectively during 2005-2008 in Sweden (Hovstadius et al., 2010) while it increased by 17.8% to 60.4% respectively during 1997 to 2012 according to an Irish study (Moriarty et al., 2015). A study from New Zealand analyzing the pharmaceutical collections maintained by the Ministry of Health from 2005 to 2013, found a significant increase in polypharmacy (29.5 vs. 23.4%) and excessive polypharmacy (2.1 vs. 1.3%) during this time period (Nishtala & Salahudeen, 2014).

Old age, female gender and increased number of comorbidities increase the risk for polypharmacy (Jokanovic et al., 2015; Nishtala & Salahudeen, 2014; Pan et al., 2014). Polypharmacy in older people is often viewed in a negative light due to the increased risk of adverse events including generalised worsened physical and psychological health leading to increased hospital visits (Nguyen et al., 2006; Swanenburg et al., 2010). The consequences of polypharmacy are increased risk of

inappropriate prescriptions as well as inappropriate omissions of drugs, drug interactions and non-adherence with drugs in older adults with complicated medication regimens, cognitive impairment, functional decline, falls, urinary incontinence, malnourishment and mortality (Fried et al., 2014; Hajjar et al., 2007; Jyrkka et al., 2009; Maher et al., 2014). Polypharmacy, especially inappropriate polypharmacy is also associated with increased costs due to drug-related morbidity, dependence and mortality (Tamura et al., 2012).

2.4.2. Polypharmacy and Falls

Polypharmacy has been considered as a significant risk factor for falls among the older population (Wu, Chie, Yang, Liu, et al., 2013) fractures associated with falls (S. W. Lai et al., 2010; Pan et al., 2014) and injuries (Baranzini et al., 2009). The falls studies have suggested that multiple number of drugs or the cut-off of ≥4 or ≥5 medications are independently associated with falls, while the falls risk intensely increases with the use of 5 or more medications (Baranzini et al., 2009; Buatois et al., 2010; Freeland et al., 2012; Tromp et al., 2001). Hammond et al. stated that there appears to be a stronger link between falls and the type of medications taken e.g. FRID, rather than polypharmacy on its own (Hammond et al., 2013).The reason that the risk of falls increases linearly with the increase in the number of medicines is the increase in FRID associated with polypharmacy which predisposes an older person to falls (Swanenburg et al., 2010).

Different tools have been developed by the researchers to assess adverse events due to polypharmacy among older people. The “GerontoNet Score” can predict the increased risk of adverse drug events with the increase in score which includes number of comorbidities, number of drugs, heart failure, renal failure, liver disease and previous adverse drug reactions (Onder et al., 2010). Similarly, the Medication Regimen

Complexity Index (MRCI) can assess the complexity of medication regimen depending on dosage of drugs (McDonald et al., 2013). However, FRID differ from those drugs associated with adverse drug events among older people, there being no published tool to assess the risk of falls by taking into account the presence of polypharmacy, FRID, other risk factors for falls and concomitant illness.

The published studies uniformly demonstrate significantly increased risk of falls with polypharmacy despite the variable definitions used. In a longitudinal survey of diabetic people, the users of four or more prescription medications were twice as likely to fall than those who consumed one or two prescription medications (E. S. Huang et al., 2010). The longitudinal study Concord Healthy and Ageing in Men Project (CHAMP) study suggested the use of five or more medications to be associated with the increased risk of falls (Gnjidic et al., 2013). One hospital based study including patients ≥60 years explained the pathway of polypharmacy associated falls by reporting that polypharmacy increases the prevalence of drug-drug interactions and FRID, both of which are strongly associated with falls and this association is stronger in case of frail than robust older adults (Bennett et al., 2014). Table 2.6 summarises the findings of available studies relating polypharmacy with falls.

2.5. Potentially Inappropriate Prescriptions (PIP)

The increase in number of medicines is not only associated with adverse drug reactions, but also increases the risk of inappropriate prescribing by the physicians (Mamun et al., 2004). However, studies have established that the number of medications is not as important as the number of potentially inappropriate drugs (Schuler et al., 2008; Tamura et al., 2012). A systematic review of 19 studies concluded that one in five prescriptions issued to elderly persons in primary care is inappropriate. Medications with largest rate of PIP were propoxyphene, doxazosin, diphenhydramine

and amitriptyline (Opondo et al., 2012). Among older adults, medicines are considered "inappropriate" if they are prescribed at inappropriately higher doses or for longer time periods than recommended and if the choice of drugs is inappropriate i.e. when the risk of treatment potentially outweighs the benefits or when it can potentially interact with any existing pathology or drug, if prescribed while contraindicated, or if duplication therapy exists (O'Mahony et al., 2008; Wyles et al., 2005). It also includes non-compliance or the omission of medications in the presence of a valid indication (M. Chan et al., 2001).

In one study on inappropriate prescribing, unnecessary drugs were found to be prescribed in 36.3% of all patients, drugs to avoid (Beers criteria) in 30.1%, duplication in 7.6%, wrong dosage in 23.4% and possible drug-drug interactions in 65.8% (Schuler et al., 2008). In another study involving community dwelling seniors aged ≥ 65years who consumed five or more medications daily, 65% were using one or more inappropriate medications, 57% were taking medicines which were ineffective, not indicated or therapeutically duplicative while 37% were on drugs considered inappropriate according to the Beers' criteria (Steinman et al., 2006). It is agreed that the adverse events and consequent emergency department visits due to inappropriate prescribing are the most potentially avoidable/preventable events (M. Chan et al., 2001; Nickel et al., 2013; Opondo et al., 2012). The reason is that they are due to drugs already considered to be inappropriate for elderly or due to recognised drug-drug interactions and hence the risk of prescribing those drugs is already known (Juurlink et al., 2003). Due to higher incidence of hospitalisations and higher use of unnecessary medications, PIP is associated with greater health care utilization rates and costs (Akazawa et al., 2010).

Table 2.6: Summary of Studies on the Association between Polypharmacy and Falls among the Older Population.

Reference	Study Design	Participants (n)	Polypharmacy definition	Falls risk*
⩾ 4 drugs/day				
Tromp et al;2001(Tromp et al., 2001)	Prospective	n=1285; ≥65 yrs Community dwelling	≥4 drugs/day	Falls [OR=1.3; CI (1.0-1.7); p<0.05] Recurrent falls [OR=1.5; CI (1.0-2.3); p<0.05]
Ziere et al; 2006(Ziere et al., 2006)	Cross-sectional	n=6928 Median age 70.6 yrs Community dwelling	≥4 drugs/day	3 drugs/day [OR=1.4; CI (1.1-2)] 4 drugs/day + 1 falls risk[OR=1.6; CI (1.1-2.1)]
Buatois et al; 2010(Buatois et al., 2010)	Prospective	n=1618; ≥ 65 yrs Community dwelling	≥4drugs/day	OR=1.66; CI (1.06–2.60); p=0.025
Freeland et al;2012(Freeland et al., 2012)	Longitudinal	n=118; ≥65yrs Community Dwelling	≥4 drugs/day	OR=1.14; CI (1.02-1.27); p=0.02 each additional medication= 14% ↑ fall risk
Mizukami et al;2013(Mizukami et al., 2013)	Cross-sectional	n=602; ≥ 65 yrs Community Dwelling	≥4prescription drugs/day	OR=2.6; CI (1.1-6.6); p < 0.05
Wu et al; 2013(Wu, Chie, Yang, Liu, et al., 2013)	Cross-sectional	n=671; ≥65yrs Community hospital	≥4 drugs	OR=2.08; CI (1.17-3.70); p<0.05
⩾5 drugs/day				
Nishtala et al;2014(Nishtala, Narayan, et al., 2014)	Cross-sectional	n=537387; ≥ 65 yrs Community Dwelling	≥5 drugs/day	RR=1.792 ; CI (1.659–1.936); p<0.05
Kojima et al;2012(T. Kojima et al., 2012)	Longitudinal	n=17276; ≥65yrs Community Dwelling	≥5 drugs/day	No. of drugs [OR=1.30; CI (1.08-1.57); p <0.05] ≥5/day[OR=4.5; CI (1.7-12.2); p<0.0005]
Gnjidic et al;2012(Gnjidic et al., 2012)	Longitudinal	n=1705; >70yrs Community dwelling	≥5 drugs/day	OR=1.7; CI (1.03-1.12); p=0.002
Number of Medications				
Formiga et al;2008(Formiga et al., 2008)	Cross-sectional	n=1225; ≥65yrs Hospital based	No. of prescription drugs	OR=1.123; CI (1.069-1.181); p=0.0001
Corsinovi et al;2009(Corsinovi et al., 2009)	Longitudinal	n=62; ≥65 yrs Geriatric hospital	No. of medications	RR=1.226; β=0.204; CI (1.22-1.340); p<0.001

OR=Odds ratio; RR= Relative Risk; CI= 95% Confidence Interval
† OR & RR are reported for risk of falls occurrence unless otherwise specified

Prevalence studies in older people in Ireland have shown rates of prescription of one or more PIP as 22% in the primary care setting, 35% in acute hospital care and 60% in nursing home care using the STOPP criteria (O'Mahony et al., 2010). A Serbian study involving older primary care patients with one or more prescribed medications,

found the prevalence of PIP as 27.3% while patients with more than four prescriptions had a higher risk for PIP (Vezmar Kovacevic et al., 2014). The prevalence of PIP in hospitalized Taiwanese elderly was 63.8% while in the community health centre was 27.5% according to Beers criteria (H.-Y. Lai et al., 2009; Lin et al., 2011). A retrospective community Japanese study involving 6628 adults aged ≥65 years, reported that 43.6% were prescribed at least one PIP according to Beers criteria (Akazawa et al., 2010).

So far, the most convincing evidence for PIP exists for psychotropic medications which are commonly inappropriately prescribed to the elderly over past 50 years (Dell'osso et al., 2013). An analysis of 2.5 million Medicare beneficiaries living in nursing homes showed that 27.6% of residents were receiving at least one psychotropic drug with only 41% compliance to the available prescribing guidelines while the remaining 60% were being prescribed these medications without proper indications, as duplicative drugs with different trade names or in inappropriate doses (Briesacher et al., 2005). Long-acting benzodiazepines are the most common PIP among the psychotropics, other classes of PIP identified according to studies are, antihistamines, muscle relaxants/ antispasmodics and anticholinergics (Akazawa et al., 2010; H.-Y. Lai et al., 2009; Lin et al., 2011; Vezmar Kovacevic et al., 2014).

A Malaysian study identified 23.7% of PIP among their participants according to STOPP criteria while 32.7% according to Beers criteria. The common PIP identified were nifedipine, chlorpheniramine and diphenhydramine, antihistamines, duplication of drug classes, glibenclamide and anticholinergic agents. Higher number of medications and longer stay at nursing home were identified as predictors of PIP for both Beers and STOPP criteria (Chen et al., 2012). None of the study on the prevalence of PIP has been performed among older community residents or hospitalised elderly.

While Beers' criteria has been widely used in the international literature, various other tools have also been developed to assess the inappropriateness of prescribing amongst older adults e.g. IPET (Improving Prescribing in the Elderly Tool), MAI (medication appropriateness index) and STOPP/START, the prevalence of PIP varies according to the applied criterion. Caution should be exercised in applying these criteria developed in other regions where medication availability in the local market may be limited. Therefore, the criteria with more categories and a higher percentage of local market drug availability tend to detect more PIP (C. B. Chang et al., 2011).

Recent literature has shown STOPP to be superior to Beers' criteria in detecting PIP among older adults in all health care settings, although there were some differences across settings (Conejos Miquel et al., 2010). Prospective data showed that STOPP criteria detected adverse drug effects that were causal or contributory to acute hospitalisation in older people 2.8 times more frequently than Beers' criteria (O'Mahony et al., 2010). A systematic review of 19 studies involving older adults having at least one inappropriate medication found that 78.9% of studies were conducted in the USA, 73.7% of those used Beers criteria while the rest used Zhan, which is derived from on Beers criteria (Guaraldo et al., 2011). However Beers' criteria has limited application outside the US settings, a systematic review found that the STOPP criteria is not only more sensitive but it has also been used to review the medication profiles in Europe, Asia and North America amongst community dwelling, acute care and long-term care older patients (Hill-Taylor et al., 2013). One prospective hospital study on 744 adults aged >65 years and regular intake of drugs found that STOPP identified almost twice the number of hospital admissions (11.5%) as compared to Beers' criteria (6%) (Gallagher et al., 2008).

2.5.1. Potentially Inappropriate Prescriptions and Falls

Studies involving older adults using one or more medications at baseline have identified that elderly with PIP have a significantly increased risk of falls, however, none of the studies have assessed the association between PIP and recurrent falls. While PIP is significantly associated with adverse drugs events among older adults, table 2.7 shows the list of those studies which found that some classes of FRID are the commonest PIP among older adults.

2.6. Role of Comorbidities in fallers with Chronic and Multiple medications

Medications are prescribed in response to a disease, the prevalence of diseases among the older population is higher with around 92% of all older adults having at least one chronic disease (Sibley et al., 2014), 60% of hospital patients have at least one comorbidity and 37% have two or more. Multimorbidity, the coexistence of two or more chronic conditions also becomes prevalent with increasing age with 84% of adults aged over 65 years having two or more chronic conditions as compared to 35% of those aged 45 to 65 years (Page et al., 2010). A population-based study identified that 67% of the older adults had multimorbidity, which increased with age, from 50% for persons under age 65 years to 62% for those aged 65–74 years and 81.5% for those aged ≥85 years (Salive, 2013). Multimorbidity is strongly associated with the risk of adverse drug events among older people (Evans et al., 2005; Salive, 2013), the existence of three or more comorbidities increases the risk for having a severe adverse drug event by 2.9–12.6-fold (Page et al., 2010). Moreover, multimorbidity is associated with elevated risk of death, disability, poor functional status, poor quality of life (Salive, 2013).

Table 2.7: Studies showing PIP and drugs associated with falls among older adults.

Reference	Study Design	Participants (n)	PIP Criteria	Association with Falls
Eager et al(Egger et al., 2006)	retrospective cross-sectional study	800 patients aged > or =65 years Hospital patients	Beers criteria	This was largely because of a higher prescription rate of platelet aggregation inhibitors in combination with low-molecular-weight heparins and benzodiazepines in patients with a history of falls and syncope.
Berdot et al(Berdot et al., 2009)	Prospective, Multicentre	n=6343; ≥ 65 yrs Non-institutionalized elderly selected by electoral roles	Beer's criteria	PIP users had an increased risk of falling which was due to long-acting benzodiazepines (OR=1.4; 95%CI, 1.1–1.0), other psychotropics (OR, 1.7; 95%CI 1.7–2.7) medication with anticholinergic properties (OR = 1.6; 95%CI, 1.2–2.1).
Fiss et al (Fiss et al., 2011)	Prospective	n=744; ≥65 yrs, Community dwelling, regular intake of drugs.	Beer's criteria	The intake of PIP was associated with falls (φ: 0.1074; P= 0.0244).
Dalleur et al (Dalleur et al., 2012)	cross-sectional study	hospital302 frail older persons	STOPP	PIMs (prevalence 48%) mainly involved benzodiazepines, aspirin and opiates. PIP related admissions were associated with falls.
Liu et al (Liu et al., 2012)		65 years and520 records of elderly medical ward inpatients	STOPP and START	36.2% of the population had at least one PIP. Benzodiazepines, neuroleptics and first generation antihistamines were commonest PIP associated with falls.
Wahab et al(Wahab et al., 2012)	Prospective	n=100; Mean age=65 yrs; Hospital patients	STOPP criteria	PIP were associated with falls, the most frequently encountered PIM was opiates prescribed in patients with recurrent falls (12.3 %), followed by benzodiazepines in fallers (10.1 %).
Borensetein et al (Borenstein et al., 2013)	Cross-sectional	n=214; Mean age=75 yrs; Hospital patients	Beer's criteria	PIP were associated with falls (OR = 3.05; 95% CI = 1.19, 7.83)
Frankenthel et al(Frankenthal et al., 2013)	Prospective	n=382; ≥ 65 yrs; taking atleast one medication; Geriatric Hospital	STOPP/START	The increased PIP was significantly associated with falls (OR: 1.16, 95 % CI 1.021–1.32)
Ailabuni et al (Ailabouni et al., 2015)	Cross-sectional	N=102 , ≥65 years; residential care homes	STOPP criteria	Antipsychotics, opiates and benzodiazepines accounted for approximately 50% of the PIP exposures and were associated with a medium/high falls risk.
Manias et al (Manias et al., 2015)	Cross-sectional study	65 years and over hospital100	STOPP criteria	92 PIP were detected in 54 patients. The commonest PIP medications that adversely affected individuals who were prone to falls.
San-Jose et al (San-Jose et al., 2015)	prospective multicentre study	hospitals aged 85 years and over 336patients	Beers and STOPP criteria	47.2% of had at least one Beers-listed PIM, 63.3% at least one STOPP-listed PIM. Use of benzodiazepines in patients who are prone to falls (18.3%)

Increase in multimorbidity is significantly related with falls, the risk of falls increases linearly with the increasing number of comorbidities from low to moderate and high (Calderón-Larrañaga et al., 2012). The data from the Canadian community health survey involving 16,357 adults aged ≥65 years reported that both the number and pattern of chronic conditions were related to falls. The fall risk was significantly greater

in individuals with one, two, four, five and six or more chronic conditions as compared to those with none disease (Sibley et al., 2014). Studies have identified that cerebrovascular, chronic obstructive airways and renal disease, osteoporosis, diabetes, hypertension, Parkinson's disease and stroke dementia, depression, and malignancy are significantly related with falls (Johal et al., 2009; Jorgensen et al., 2014; Lee et al., 2006; Sibley et al., 2014; Tilling et al., 2006). The presence of these falls related comorbidities also increase the incidence of hip and humeral fractures after the fall (Jorgensen et al., 2014)

The possible mechanism for the association between comorbidities and falls is the age related decline of functional performance due to the increase in number of diseases (Guo et al., 2003). Another reason behind this association is that the increased consumption of treatment drugs which follows these illnesses. However, this association is complex as it is difficult to determine whether falls could be attributed to physical illness or polypharmacy, in fact, the multifactorial nature of falls dictates that it to be a combination of both as well as additional factors (Coimbra et al., 2010). It is only possible to attribute falls to a medicine alone should that particular drug be inappropriately prescribed or when falls occur within few days after starting or changing a medicine and subsequent discontinuation of the culprit drug then results in resolution of falls symptoms (Sorock et al., 2009). However, even in these cases, other established risk factors may be existing, and the introduction of the culprit drug may simply tip the balance. In a cross-sectional study among hospitalized elderly patients where mean number of diseases was 7.7, the existence of multimorbidities actually led to polypharmacy (Mizokami et al., 2012).

There have been few studies on the association of falls with simultaneous existence of polypharmacy and polymorbidity. In a cross-sectional survey of 4050

women aged 65-79 years, Lawlor et al argued that as multiple pathologies and multiple medications co-exist, it's the number of chronic diseases rather than the number of medications that is associated with increased risk of falls (Lawlor et al., 2003). A cross-sectional study, including community-dwelling older adults reported that medical morbidity contributed significantly to falls instead of the number of medications (M. A. Han et al., 2013). The longitudinal study by Kojima et al, however, found polypharmacy to be an independent risk factor for falls and not polymorbidity (T. Kojima et al., 2012). A Spanish study involving 733 residents aged ≥65years suggested that the risk of falls increases when polypharmacy it coexists with multimorbidity of a minimum three diseases (Damian et al., 2013). The study by Lee et al involving community-dwelling men and women aged ≥65 years reported that although medications are associated with falls and recurrent falls this association is mediated through the underlying medical diagnoses and neuromuscular impairment (Lee et al., 2006).

2.7. Impact of Medication Withdrawal Interventions on falls

A study from Netherlands analysing pharmacotherapy of 102 home-dwelling older patients (≥75 years, using ≥4 medicines continually) reported that 98% of their prescriptions could be modified with the use of regular medication reviews (Denneboom et al., 2006). From the above review it can be deducted that instead of number of medications, the type of medications i.e. FRID or anticholinergics and inappropriate medications play a significant role in falls. The reason behind the association of polypharmacy and falls is the increased prevalence of all three medication related falls risk factors i.e. FRID, anticholinergics and PIP along with polypharmacy. Reducing unnecessary prescriptions improves drug compliance and patients' quality of life, reduces medication errors as well as adverse drug events which

translates into cost-savings through the reduction of medication and hospitalisations costs (Frankenthal et al., 2014). The American Geriatrics Society/British Geriatric Society Joint Falls Prevention Guidelines 2010, now advocate careful medication reviews for all older fallers (AGS/BGSguidelines, 2011). However, few trials including high risk fallers at baseline have positively demonstrated a reduction in the risk of falls with the withdrawal of culprit medications or reduction of dose burden (van der Cammen et al., 2014).

One systematic review concluded that polypharmacy withdrawal was shown to improve cognitive function but it had no significant effect on falls prevention (van der Cammen et al., 2014). The medication withdrawal trials on PIP have also shown positive results for deprescribing. A study reviewed the drugs of 10,364 adults aged ≥65 years and successfully reduced inappropriate medications from 66.7%. to 31.3% during the 6-month follow-up, the highest rate of discontinuation was observed for anticholinergics (Starner et al., 2009). One systematic review including 31 trials concluded that while some medications can be safely withdrawn, withdrawal of diuretics was unsuccessful primarily when heart failure was present medications (Iyer et al., 2008).

The evidence for longer term benefit of medication withdrawal is only demonstrated by a few studies evaluating the withdrawal of psychotropic medications (Iyer et al., 2008). However contrarily, one systematic review including 22 quantitative studies on PIP reduction concluded that interventions to reduce inappropriate prescribing of antipsychotic medications might be effective but for the shorter term (Thompson Coon et al., 2014). Among other drug trials, the available evidence shows the benefits of psychotropic withdrawal as an effective intervention on falls reduction, as adverse drug events due to these medications are more common and easily

preventable than non-psychotropic medicines (Rothschild et al., 2007).

Table 2.8: Effect of Medication Withdrawal Interventions on Falls among older adults.

Reference	Study Design	Participants (n)	Intervention	Association with Falls
Campbell et al (Campbell et al., 1999)	RCT	n=93; ≥ 65 yrs; Community participants, taking psychotropics	Gradually withdrew psychotropics	Psychotropic withdrawal led to a 66% reduction in falls rate during 44 weeks of follow up. But it was difficult to achieve permanent withdrawal as 47% of the participants from the medication withdrawal group in a study started taking their withdrawn medications again only after one month of completion of trial
Velde et al(van der Velde, Stricker, et al., 2007)	Prospective	n=139; ≥65 yr; Geriatric Outpatients; ≥1 fall in past year	FRID i.e. psychotropics, cardiovascular drugs, analgesics, antidiabetics & anticholinergics	The risk of fall for overall drug withdrawal was reduced (HR, 0.48; 95% CI; 0.23, 0.99), however cardiovascular drugs showed highest fall risk reduction during three months of follow up.
Iyer et al (Iyer et al., 2008)	Systematic review	n=8972; ; ≥65 yrs; Hospital patients	Psychotropic drug Withdrawal	Withdrawal of psychotropic medications was associated with a reduction in falls.
Salonja et al (Salonoja et al., 2012)	Prospective	n=528 ; ≥65 yrs, Community dwelling, at least one fall	Withdrew psychotropics	Withdrawal of psychotropics, especially benzodiazepines played an important role by lowering the risk of falls during the year.
Van der Cammen (van der Cammen et al., 2014)	Review	n=382; ≥ 65 yrs; atleast one medication; Geriatric Hospital	Psychotropic drug Withdrawal	Withdrawal of psychotropics reduced fall rate
Frankenthel at al (Frankenthal et al., 2014)	RCT	n=359; ≥65 yrs Chronic care geriatric facility.	Withdrew drugs according to STOPP/START criteria	The average number of falls in the intervention group dropped significantly (P = .006).

Based on currently available literature on the adverse effects of polypharmacy, FRID and PIP, we can deduce that regular review of medications is advisable among older patients who are receiving multiple regularly prescribed medications. The medication review among fallers should consider the risk factors of falls as well as presence of comorbidities first followed by assessment of inappropriate drugs.

Unnecessary or duplicative medicines should be withdrawn and medications necessary for disease management should be replaced with safer alternatives or dose titrated. The withdrawal of inappropriate drugs and anticholinergics could achieve the dual benefits of both decreasing the number of drugs and hence the risk from culprit medicines. Table 2.8 shows the available studies for the effect of medication withdrawal on falls among older adults. However, in all those studies the long-term effects of withdrawal on end organ damage, quality of life and survival rates have not been evaluated, in spite of their beneficial effects on falls reduction.

2.8. Summary

The elderly have the highest prevalence of falls and multiple comorbidities; they are the highest users of medications and respond differently to drugs than do younger people. With the literature review concluded, we can identify some clear problems for the elderly fallers. While plenty of studies have listed the positive association between medications and falls, there are certain methodological problems in determining the exact contribution of drugs to falls and more importantly the contribution of untreated diseases on falls if those drugs are deprescribed. Attributing the cause of an older person falling to polypharmacy or a single medication or inappropriate prescribing alone is difficult because of various confounding variables, some of which are listed above. Because of the difficulty in measuring the effects of the drugs themselves, many studies used a simple count of drugs for polypharmacy and FRID; polypharmacy and FRID co-exist and overlap and the comparison between polypharmacy and FRID count associated with falls is also non-existent, which would be helpful in focussed medication reviews for older fallers. The review also identified that in spite of certain drugs being widely accepted as culprits for falls, none of the studies have involved their

mechanisms or mediators to get a clearer picture of this triad of medications, comorbidities and falls. A research on this would also help in retaining the drug necessary for disease management while improving the mediator in reducing falls. The prescription of drugs among elderly fallers is a challenging situation because of the fine line between the benefit of drug for the disease it is prescribed and it's higher dose or number resulting in serious recurrent falls. However, interestingly, the existence of PIP although widely mentioned in the literature to be responsible for serious and preventable adverse drug events has never been evaluated among the sample of recurrent fallers. The evaluation of PIP with a criteria may provide firm basis for the deprescribing of certain drugs which may reduce the risk of future falls. The studies on medication withdrawal also have limitations of being feasible for frail older adults with history of falls and multiple serious comorbidities and whether they are applicable and beneficial for longer term. In spite of the higher risk of falls among Malaysian elderly, no study exists on the association between medications and falls in this region. There is a need for additional research and documentation about the association of medication and their correlation to falls among the urban community dwellers in Malaysia.

CHAPTER 3: METHODOLOGY

3.1. Study design and setting

This study has two arms: Cross sectional arm involving case control comparisons between faller and nonfaller groups and longitudinal arm where fallers were randomised to interventions or non-interventions and then followed prospectively for a period of 12 months to record falls. The sample of fallers was included from a single centred randomized-controlled trial of individually-tailored multifactorial intervention for older Malaysian fallers residing in the community, known as "Malaysian Falls Assessment and Intervention Trial (MyFAIT)". It was based in a large teaching hospital in Kuala Lumpur, the detailed protocol for MyFAIT protocol is published elsewhere (P. J. Tan et al., 2014). The study was approved by University of Malaya Medical Centre Ethics Committee (925.4). Written and Informed consent was then obtained from all study participants.

3.2. Sample:

3.2.1. Inclusion and Exclusion Criteria of participants

The inclusion criteria for fallers recruited into MyFAIT was age ≥65 years, with two or more falls or one injurious fall (Injuries classified according to ICD-10 definition) in the previous year because these factors are shown to be strongly associated with the amplified risk of future falls high risk of future falls (AGS/BGSguidelines, 2011; Ambrose et al., 2013; Wu, Chie, Yang, Kuo, et al., 2013). The participants aged 65 years and older with no history of falls over the past year were recruited as "control subjects" for case control comparisons.

Exclusion criteria (for both cases and controls) were a clinical diagnosis of dementia (ICD-10 definition), severe physical disabilities (unable to stand) and major

psychiatric illness or psychosis. The participants with dementia were excluded because the previous falls studies including dementia patients have yielded inconclusive results, suggesting that separate interventions should be conducted for individuals with dementia.

3.2.2. Sample Size

The sample size of 352 participants (cases and controls) was calculated for an unmatched case-control study with 95% confidence interval and 80% power ($\alpha = 0.05$) to detect an effect size of 0.30 which is small to medium effect size (G*Power 3.1.9.2.).

For the prospective intervention study, the sample size of 208 participants was calculated, 104 in each arm, which will provide 80% power to detect a 40% reduction in the number of individuals who experience falls to 30% in the intervention group assuming that without intervention, 50% of individuals will experience a subsequent fall (Close et al., 1999)

3.2.3. Mechanism of recruitment

Fallers were the participants who were discharged from the primary care clinics, geriatric medicine clinics and the emergency department of the hospital due to falls. Non-fallers were the volunteer participants recruited through media and word-of-mouth advertising from the hospital catchment area.

The reporting of case control study follows the STROBE Statement along with references to STROBE and the broader EQUATOR guidelines (Simera et al., 2010) while the CONSORT statement is used as a guideline to design the flow of participants' progress through the prospective study arm.

3.3. Data Collection

Both the fallers (cases) and nonfallers (controls) were invited to attend the "falls clinic" for the baseline assessment and evaluation which lasted approximately 2 hours per participant. The assessment was performed for all the participants by a team comprising of geriatricians, psychiatrist, ophthalmologist, physiotherapist and researchers who have received training in administration of all assessment items. The non-fallers (controls) only received baseline assessment necessary for case control analysis, while the fallers were subjected to randomisation into intervention and control groups afterwards by a computer-generated random number sequence. The intervention group were subjected to individualized treatment programs by the geriatrician while the non-intervention group continued to receive conventional care by their respective medical practitioners. The prescribed treatment in MyFAIT was targeted at six specific treatment modalities: medication review intervention, falls education, exercise intervention, home hazards intervention, cardiovascular intervention and visual intervention.

Falls diaries with daily entries were used to record falls occurrences, and were returned monthly for one year from randomization. These diaries were written in the three main languages of Malaysia; Malay, English and Mandarin, due to varying cultural and educational backgrounds. Prompts were provided in the falls diaries, which include how and when a fall occurred, or if there were injuries sustained after their fall. Participants were contacted every 2 months by telephone calls to encourage complete diary returns.

3.3.1. Basic Demographics

A structured history was obtained from all participants which included enquiry regarding (i) basic sociodemographics (ii) detailed falls history i.e. occurrence, time and mechanism, related symptoms and the complications of falls.

3.3.2. Comorbidity Assessment

The participants were interviewed by a geriatrician for comorbidity assessment which included self-reported medical history. This was recorded into standardised form under categories which included diabetes, hypertension, any respiratory disorder, arthritis, osteoporosis, hearing disorders, depression, thyroid diseases, eye diseases (cataract, glaucoma) and vascular diseases (diagnosis of myocardial infarction, angina, stroke, transient ischemic attack or peripheral vascular disease).

3.3.3. Medication assessment

Patients were asked to bring in their written prescriptions and actual medications to their appointments in order to collect a comprehensive list of prescribed and over the counter medicines. A careful list of medicines, as well as their doses and duration of use was obtained via face-to-face interviews using a standardised case record form. Medications were grouped according to the British National Formulary, 67th Edition (BNF, 2014). Topical and herbal medications were not considered in the analysis.

3.3.4. Assessments during the visit

1. Height and weight were recorded.
2. Blood pressure readings were obtained in the supine position followed by three minutes of standing using an oscillometric blood pressure device (Omron HEM-7200) (the details are described in chapter 5).
3. Physical strength and balance performance scores were assessed using TUG, FR and GS according to standard procedures (the details are described in chapter 6) (P. J. Tan et al., 2014).
4. Other assessments performed were: visual assessment by visual acuity, contrast sensitivity, and binocular vision; 12-lead electrocardiogram (ECG);

psychological and quality-of-life assessments using psychometric questionnaires. Complete cardiovascular and neurological assessments were also performed by the geriatricians according to the disease history and symptomatology of participants.

3.3.5. Data Processing and Statistical Analysis

The Statistical Package for Social Science (SPSS) software version 21.0 (Chicago, IL,USA) was used for statistical analysis. The data was collated into the database at the time of assessment, and entered in SPSS after cleaning and organisation.

a. **Univariate Analysis:** The frequencies were expressed as mean (± standard deviation) or median (interquartile range) for continuous data and evaluated for normal distributions. The comparisons were then made between fallers and non-fallers using the independent t-test for parametric and Mann-Whitney U test for non-parametric variables. Categorical data were expressed as frequencies with percentages in parentheses with differences between groups expressed as odds ratios with 95% confidence intervals; statistical significance was tested with the Chi-squared test.

b. **Multivariate Analysis:** Because our goals was to examine the effect of controlling for multiple chronic conditions on the association between falls and specific class of medications, the method for multivariate analysis for specific variables is described in the respective chapters.

CHAPTER 4: THE CONSUMPTION OF TWO OR MORE FALL RISK INCREASING DRUGS RATHER THAN POLYPHARMACY IS ASSOCIATED WITH FALLS

4.1. Introduction:

Polypharmacy as well as FRID are regarded as well documented factors for falls (Gnjidic et al., 2012; Kojima et al., 2011; Milos et al., 2014; van der Velde, Stricker, et al., 2007). The commonly adopted practice of merely counting drugs as polypharmacy is arguably no longer relevant to evidence-based prescribing, as polypharmacy in individuals with multiple chronic conditions is often inevitable. Moreover, while polypharmacy includes the total medication count of a patient, some older adults may be using less risk drugs than others making counting of total medication impossible to calculate falls risk. The presence of polypharmacy therefore may not necessary imply increased falls risk if medications associated with higher risk of falls are avoided. Polypharmacy increases the risk of FRID use which is responsible for previously established association between polypharmacy and falls, while polypharmacy without the presence of FRID may not be associated with falls, hence the term "polypharmacy" may not be valid for fallers. But none of the studies have demonstrated that it might be the FRID count and not the total medication count/ polypharmacy which are associated with falls. We hypothesized that the established association between polypharmacy and falls among older people is attributable to the use of multiple FRID.

4.2. Objective

We conducted a case-control study comparing individuals at high risk of falls with non-fallers to determine the relationship between polypharmacy and FRID with the risk of recurrent and injurious falls among community dwelling older adults.

4.3. Methodology

The setting, participants, baseline demographics, medication collection assessment as described in chapter 3.

Statistical Analysis: After the univariate analysis as described in chapter 3, potential confounders were identified from comparison of basic characteristics between fallers and non-fallers and were adjusted for in subsequent models using multivariate logistic regression methods and the differences between groups were expressed as odds ratios with 95% confidence intervals. A p-value of <0.05 was considered statistically significant.

4.4. Results

4.4.1. Recruitment and baseline demographics

A total of 442 participants who attended the "falls clinic" were assessed initially. Eighty four participants were excluded based on whether they did not meet the inclusion criteria or fulfilled exclusion criteria or had missing data. Data on 358 participants, 202 fallers and 156 non-fallers was analysed; the baseline demographics are summarized in Table 4.1. Fallers were significantly older than non-fallers and were significantly more likely to have diabetes, vascular disorders and eye diseases. Fallers had significantly lower SBP but were not significantly more likely to have OH as compared to non-fallers. The scores of physical performance i.e. TUG, FR and GS were significantly poorer among fallers.

Table 4.1: Baseline characteristics of fallers and non-fallers.

Basic characteristics (N=358)	Fallers† n=(202)	Non-Fallers‡ (n=156)	p-value
Age (years), mean ± SD	75.2(±7.1)	72.2(±5.5)	<0.001***
Male Gender, n(%)	65(32.2)	51(32.7)	0.923
Body Mass Index (kg/m^2), mean ± SD	24.2(±3.7)	24.5(±4)	0.481
Smoker, n(%)	7(3.5)	7(4.5)	0.612
Alcohol, n(%)	15(7.4)	15(9.6)	0 .452
Medical History, n(%)			
Diabetes	69(34.2)	30(19.2)	0.002**
Hypertension	115(56.9)	77(49.4)	0.173
Respiratory disorders	9(4.5)	6(3.8)	0.791
Arthritis	44(21.8)	40(25.6)	0.378
Osteoporosis	19(9.4)	15(9.6)	0.936
Hearing disorders	14(6.9)	7(4.5)	0.332
Depression	6(3.0)	2(1.3)	0.231
Thyroid diseases	13(6.4)	16(10.3)	0.192
Eye diseases	95(47)	52(33.3)	0.009**
Vascular diseases	41(20.8)	18(11.5)	0.032*
Blood Pressure			
Supine SBP, mean ± SD	130(24.8)	135.6(20.3)	0.04*
Supine DBP, mean ± SD	66.2(15)	66.6(15.0)	0.78
OH, n(%)	52(15.7)	28(17.9)	0.09
Physical Performance, n(%)			
TUG ≥ 13.5s	101(50)	31(21.8)	<0.001
FR ≤ 18cm	59(29.2)	13(8.3)	<0.001
Reduced RGS	149(73.8)	85(54.5)	<0.001
Reduced LGS	157(77.7)	96(61.5)	0.001

SD=standard deviation, Data presented are mean (SD) for continuous and number (%) for categorical data. Vascular disease=diagnosis of myocardial infarction, angina, stroke, transient ischemic attack or peripheral artery disease. Grip strength reduced; <20kg women, <30kg men

***p≤.001, **p≤.01, *p≤.05

†Recurrent or injurious falls in the past 12-months

‡No falls in the past 12 months

4.4.2. Medications among participants

Medication intake was significantly greater among fallers, with 85.7% of fallers and 64.7% of non-fallers using at least one drug (OR=3.0; 95%CI, 1.8-4.9; p≤0.001). Use of biguanides, sulfonylureas, α-blockers, A2RA, anti-anginals, PPI, NSAID and dyslipidemics were found to be significantly associated with falls following univariate analysis. Non-steroidal anti-inflammatory drugs were the only class of medications which remained associated with falls after adjustment for age, gender and comorbidities (Table 4.2).

Table 4.2: Medications among Fallers and Non-fallers

Drug use (N=358)	Fallers (n=202)	Non-Fallers (n= 156)	OR (95%CI)	OR† (95%CI)	OR‡ (95%CI)
Fall Risk Increasing Drugs					
Cardiovascular drugs, n(%)					
α-blockers	20(9.9)	6(3.8)	2.8(1.1-7.1)*	0.1(0.8-5.5)	2.7(0.9-7.7)
β-blockers	39(19.3)	24(15.4)	1.3(0.8-2.3)	1.1(0.7-2.1)	1.2(0.7-2.3)
ACE-inhibitors	33(16.3)	23(14.7)	1.1(0.6-2.1)	1.0(0.6-1.8)	0.9(0.5-1.7)
A2RAs	37(18.3)	15(9.6)	2.1(1.1-4.0)*	1.7 (0.9-3.4)	1.6(0.8-3.2)
Calcium channel blockers	64(31.7)	40(25.6)	1.4(0.8-2.1)	1.1(0.7-1.7)	1.3(0.6-1.7)
Diuretics	27(13.4)	14(9.0)	1.6(0.8-3.07)	1.6(0.8-3.2)	1.6(0.8-3.4)
Nitrates	8(4.0)	4(2.6)	1.5(0.5-5.3)	1.0(0.3-3.5)	0.9(0.2-3.4)
Anti-anginal agents	14(6.9)	3(1.9)	3.8(1.1-13.5)*	2.7(0.8-10.0)	2.2(0.6-8.8)
Analgesics n(%)					
NSAID	71(10.4)	3(1.9)	5.9(1.7-20.2)**	6.2(1.8-21.5)**	6.2(1.7-22.1)**
CNS Medicines					
Benzodiazepines	10(5)	4(2.6)	1.9(0.6-1.4)	1.3(0.3-4.5)	1.3(0.3-4.8)
Antidepressants	7(3.5)	3(1.9)	1.8(0.4-7.1)	1.6(0.3-6.5)	1.6(0.3-6.8)
Antiparkinsonians	9(4.5)	5(3.2)	1.4(0.4-4.2)	1.4(0.4-4.2)	1.2(0.3-2.9)
Endocrine Medicines					
Thyroid medications	9(4.5)	8(5.1)	0.7(0.3-2.2)	0.73(0.3-2.0)	0.82(0.3-2.6)
Anti- diabetic drugs, n(%)					
Insulin	8(4.0)	4(2.6)	1.5(0.5-5.3)	1.9(0.6-6.6)	1.1(0.3-4.0)
Biguanides	41(20.3)	14(9.0)	2.5(1.4-4.9)*	2.5(1.3-4.8)**	1.7(0.7-4.1)
Sulfonylureas	35(17.3)	9(5.8)	3.4(1.6-7.3)**	3.1(1.4-6.7)**	2.2(0.9-5.6)
DPP4I	13(6.4)	6(3.8)	1.7(0.6-4.6)	1.5(0.57-4.3)	1.0(0.3-2.8)
Other antidiabetics	2(1.0)	0(0.0)	n/a	n/a	n/a
Drugs Other than Fall Risk Increasing Drugs, n(%)					
H2RA	4(2)	3(1.9)	1.0(0.2-4.6)	2.5(0.9-7.7)	0.66(0.1-3.4)
PPI	16(7.9)	4(2.6)	3.2(1.1-9.9)*	2.4(0.8-7.7)	2.9(0.9-9.4)
Dyslipidaemic agents	103(51.0)	63(40.4)	1.5(1.0-2.3)*	0.91(0.2-4.1)	1.3(0.9-2.1)
Steroids	6(3.0)	3(1.9)	1.3(0.3-5.5)	1.4(0.8-2.6)	0.63(0.1-2.9)

**p≤0.01, *p≤0.05; OR= Odds Ratio; CI= Confidence Interval, DPP4I=Dipeptidyl Peptidase 4 Inhibitors, PPI=Proton pump Inhibitors, H_2RA=Hydrogen$_2$ receptor antagonists, NSAIDs Non-steroidal anti-inflammatory drugs, CNS= Central Nervous system, FRID=fall-risk increasing drugs

†adjusted for age alone, ‡ Each model is adjusted for age, gender, BMI, Comorbidities (Diabetes, Hypertension, Depression, Thyroid diseases, Eye diseases, vascular disease)

4.4.3. Polypharmacy versus FRID

Table 4.3 displays the results of univariate analyses exploring the relationship between polypharmacy and FRID with falls. There was a significant correlation between increased number of prescribed drugs with the increased FRID count (r=0.84, p≤0.001). The use of ≥2FRID was significantly associated with polypharmacy (OR, 27.2, 95%CI, 13.4-55.1; p≤0.001). Both polypharmacy as well as FRID count were significantly associated with falls (Table 4.3).

Table 4.3: Medication count and FRID count among fallers and nonfallers.

Drug use (N=358)	Fallers (n= 202)	Non-Fallers (n= 156)	OR(95%CI)	P value
Medication Count				
No. of prescribed drugs, median(IQR)	4(4)	2(4)	-	<0.001***
Polypharmacy, n(%)	81(40.1)	36(23.1)	2.23(1.4-3.6)	0.001**
FRID Count				
No, of FRID, median(IQR)	2(3)	1(2)	-	<0.001***
1 FRID, n(%)	35(17.3)	37(23.7)	0.7(0.4-1.1)	0.132
≥2 FRID, n(%)	122(60.4)	53(34.0)	2.9(1.9-4.5)	<0.001***

***p≤0.001, **p≤0.01, *p≤0.05; OR= Odds Ratio; CI= Confidence Interval, FRIDS= fall-risk increasing drugs, Polypharmacy=5 or more prescription drugs, ǂ ≥2 FRID excluded (n=183), ‡Polypharmacy excluded (n=240)

The use of one FRID only was not associated with falls but ≥2FRID were significantly associated with falls (OR, 2.9; 95%CI,1.9-4.5.; p≤0.001). After adjusting for age and comorbidities, the significant association between polypharmacy and falls was attenuated (OR, 1.6; 95%CI, 0.9-2.8; p=0.07) while the use of ≥2FRID remained significantly associated with falls (OR, 2.9; 95%CI, 1.6-5.1; p ≤0.001) (Table 4.4, Model 1). After additional adjustment for physical performance scores (TUG, FR and GS) and blood pressure, ≥2FRID instead of polypharmacy remained an independent predictor for falls (Table 4.4, Model 2). Furthermore when individuals with ≥2FRID were excluded, the presence of polypharmacy was also not associated with falls among the remaining participants (Table 4.4, Model 3). Conversely, when participants with polypharmacy were excluded, the use of ≥2 FRID remained significantly associated with falls (OR, 3.1; 95%CI,1.4-6.8; p=0.003) (Table 4.4, Model 4).

Table 4.4: Logistic Regression Models for Falls against polypharmacy and ≥2 FRID.

	Polypharmacy		≥2 FRID	
	Adjusted OR (95%CI)	p-value	Adjusted OR (95%CI)	p-value
Model 1[‡]				
All Participants (n=358)	1.6(0.9-2.8)	0.073	2.9(1.6-5.1)	≤0.001***
Model 2[◊]				
All Participants (n=358)	1.6(0.9-2.9)	0.102	2.8(1.4-5.3)	0.001**
Model 3				
≥2 FRID excluded (n=183)	1.1(0.3-4.2)	0.841	-	-
Model 4				
Polypharmacy excluded (n=240)	-	-	3.1(1.4-6.8)	0.003**

***p≤0.001, **p≤0.01, *p≤0.05; OR= Odds Ratio; CI= Confidence Interval, FRIDS= fall-risk increasing drugs, [‡] Each model is adjusted for age, gender, BMI, Comorbidities (Diabetes, Hypertension , Depression, Thyroid diseases, Eye diseases Vascular diseases; [◊] Each model is adjusted for age, gender, BMI, Comorbidities (Diabetes, Hypertension , Depression, Thyroid diseases, Eye diseases ,Circulatory diseases), Supine blood pressure, Timed up and go, Functional reach and Grip strength.

4.5 Discussion

The association of polypharmacy with falls was attenuated while ≥2FRID remained an independent factor for falls in the final adjusted models. The individual FRID classes of antihypertensives, antidiabetics or central nervous system drugs which have previously been considered to be strongly associated with falls (A. Huang et al., 2012) were not associated with falls. Non-steroidal anti-inflammatory drugs were significantly associated with falls after multivariate adjustment for age, gender and comorbidities. The use of ≥2FRID remained a significant predictor for falls even when individuals with polypharmacy were excluded, while polypharmacy was not associated with falls when individuals with ≥2FRID were excluded. Our findings therefore suggest that the previous assumptions that polypharmacy is associated with falls can be explained by increased risk of multiple FRID which correlated strongly with polypharmacy.

Traditional assumptions exist about the association between different drug classes with the increased risk of falls, however, it is confounded by the association between inevitable medication use with increasing age and comorbidities. Therefore, as the prevalence of multiple chronic conditions increases with age,(Salive, 2013) the use of medications also increases with one in every fourth older adult taking five or more prescription medicines (Linjakumpu et al., 2002). Our results demonstrating that polypharmacy is not associated with falls after adjustments for comorbidities are consistent with Lawler et al's findings suggesting that amongst multiple chronic conditions and polypharmacy, multiple comorbidities were independent predictors of falls (Lawlor et al., 2003).

The presence of polypharmacy, however, increases the likelihood of multiple FRID use. Our study therefore suggests that the increase in risk of falls linked to multiple drug use in previous studies is attributable to the use of multiple FRID. Our findings are similar to that found in a study conducted in a hospital setting by Bennett et al who reported that the number of FRID on the patients' prescriptions on discharge was associated with a greater risk of recurrent falls (Bennett et al., 2014). Similarly another study by Milos et al (Milos et al., 2014) suggested that fallers in their study were on significantly more FRID than non-fallers.

Ziere et al (Ziere et al., 2006) and Richardson et al (Richardson et al., 2015) evaluated falls risk associated with polypharmacy along with FRID and reported that the inclusion of at least one FRID with polypharmacy predisposes an older adult to falls. However as both the above mentioned studies included middle aged and elderly cohorts, the findings among older adults were compared to those of middle aged individuals. As the use of CNS medications increases with age and is an established factor for falls, the main FRID in both studies were CNS drugs. In our study, involving

community dwelling adults, although CNS drugs or other individual drug class was not significantly associated with falls, the combined use of ≥2FRID increased the falls risk, regardless of the presence of polypharmacy.

Velde et al (van der Velde, Stricker, et al., 2007) demonstrated that the withdrawal of FRID reduced the risk of falls over a short follow-up period of two months in an intervention study involving 139 patients attending the geriatrics outpatient department. The main FRID withdrawn in this study were sedatives, antihypertensives and analgesics. However, it cannot be determined whether it was possible to sustain FRID withdrawal for a longer duration of time among the older adults with multiple chronic conditions. According to a systematic review, only the withdrawal of psychotropic medications amongst all other drugs has been effective in reducing falls (van der Cammen et al., 2014) but Campbell et al claimed that medication withdrawal among geriatric patients, though achievable, may not be sustainable for the longer term (Campbell et al., 1999). While cautious medication review is now considered an integral part of multifaceted falls interventions (AGS/BGSguidelines, 2011), our study provides the evidence to support current opinions that the traditional approach of merely reducing the total number of medications consumed may no longer be applicable. In the management of chronic diseases, the use of multiple medications may no longer be avoidable in order to effectively reduce the risk of future occurrence of adverse outcomes which may outweigh the risk of falls (Gage et al., 2005). Future studies should now evaluate whether the approach of reducing FRID alone without taking into account polypharmacy may be sustainable for longer durations as well as effective in reducing falls risk without increasing the risk of other adverse health outcomes.

The significant association between multiple FRID and not individual FRID with falls suggests that the increased risk of falls may be due to either the cumulative burden of FRID or drug-drug interactions between individual FRID. The study by Wilson et al reported a cumulative increased load of two FRID classes; sedatives and anticholinergics, calculated by using a drug burden index, to be significantly associated with an increased risk of falls (Wilson et al., 2011). Similarly, a population based longitudinal study by Callisaya et al reported that an increased daily dose of antihypertensives, which is considered a FRID drug class, increases the risk of falls among older adults (Callisaya et al., 2014). While our study is in agreement with these findings and suggests that the use of multiple FRID is associated with recurrent or injurious falls in older adults, it remains to be established, whether the risk of falls can be reduced by avoiding multiple FRID taking into account the loss of benefit of secondary prevention of other chronic conditions.

To our knowledge this was the first study to suggest the use of FRID with a cut off of ≥2FRID predicts increased risk of recurrent or injurious falls rather than polypharmacy in isolation, while the presence of polypharmacy in the absence of multiple FRID use is not associated with recurrent or injurious falls. Our collection of medication data by face-to-face interviews and cross-checking of patients' prescriptions as well as medication packages minimized the risk of missing or erroneous medication data. Our cross-sectional design, however, is a limitation with regards to the ability to assign causation between FRID and falls, and our reliance on retrospective falls recall may be subjected to recall bias. This study, however, firmly paves the ground for the direction of future studies on effective medication management for the secondary prevention of falls. The ability to identify an alternative approach rather than relying on avoidance of polypharmacy entirely among fallers with a narrow band of five or more

medications is vitally important, as polypharmacy is now considered inevitable with evidence-based management of chronic diseases.

4.6 Conclusion

Our study has found that the use of ≥2FRID is associated with increased risk of recurrent and injurious falls, while the use of individual FRID in isolation or the presence of polypharmacy itself unlike previous studies was not significantly associated with recurrent or injurious falls. Our findings have important implications for effective risk reduction in the management of chronic diseases where the avoidance of polypharmacy may then deprive the patient of effective prophylactic treatment. Future studies should seek to confirm whether avoidance or withdrawal of multiple FRID among high risk fallers reduces further falls risk with consideration for other adverse outcomes if secondary prophylaxis is withheld in the interest of fall prevention.

CHAPTER 5: THE ASSOCIATION OF ANTIHYPERTENSIVES WITH POSTURAL BLOOD PRESSURE AND FALLS AMONG SENIORS RESIDING IN THE COMMUNITY: A CASE CONTROL STUDY

5.1 Introduction

Among FRID, after the CNS drugs, antihypertensives are the most commonly reported ones to be independently associated with falls among older adults (Gribbin et al., 2010; Leipzig et al., 1999b) in a dose dependent manner (Callisaya et al., 2014; Tinetti et al., 2014). However, there are studies reporting no association or negative association of antihypertensives with falls, making it compulsory to explore the possible mechanism through which antihypertensives could lead to falls.

Orthostatic hypotension is considered a commonly documented adverse effect of antihypertensive treatment (Heitterachi et al., 2002) with studies demonstrating α-blockers, β-blockers and diuretics to be frequently associated with OH (Gribbin et al., 2010; Romero-Ortuno et al., 2013). It is therefore assumed that antihypertensive therapy results in falls through the side-effects of OH or hypotensive episodes (Craig, 1994; Rubenstein et al., 1990). However, these studies have evaluated fallers unilaterally without the inclusion of a control population.

Available large studies (Callisaya et al., 2014; Tinetti et al., 2014) on the association between antihypertensives with falls have employed medication databases or cohort study information which did not include postural blood pressure measurements. Furthermore, previous studies had not considered evaluating the triangular relationship between antihypertensive use, postural blood pressure changes and the risk of falls. We hypothesized that postural blood pressure drop is a mediating factor for falls associated with antihypertensive use. Therefore, the objectives of this

study were to examine the associations of antihypertensives with postural blood pressure drop among older individuals with and without a history of falls, and subsequently employing statistical modelling to evaluate the role of postural blood pressure changes in falls associated with antihypertensive use.

5.2 Methodology

The setting, participants, baseline demographics, medication collection assessment as described in chapter 3.

5.2.1. Blood pressure lowering drugs were divided into the following main classes: ACE-I, A2RA, β-blockers, CCB, thiazide diuretics and α-blockers. Combination drugs were separated into their respective discrete classes (e.g. Diovan HCT which contained Valsartan and Hydrochlorothiazide was classified into both A2RA and thiazide diuretic groups and counted as 2 antihypertensive medications).

5.2.2. Baseline Measurements

Participants were interviewed by a geriatrician and an established diagnosis of hypertension was recorded if the participant reported physician diagnosed hypertension and/or was on existing blood pressure lowering therapy, regardless of the recorded blood pressure at the time of assessment.

5.2.3. Blood Pressure Measurements

Blood pressure was measured at the falls clinic between the hours of 1.00 pm to 4.00pm and participants were advised to take their regular prescribed medications on the day of assessment. One recumbent reading was obtained after 10 minutes of supine rest. Three standing readings were obtained at 1 minute, 2 minutes and 3 minutes after assuming the erect posture. All blood pressure measurements were obtained with an automated blood pressure machine (Omron HEM-7200). Orthostatic hypotension was

diagnosed if a systolic blood pressure drop of 20mmHg or greater or diastolic blood pressure drop of 10 mmHg or greater was observed within three minutes of standing according to the consensus definition (Freeman et al., 2011). Minimal standing SBP was the lowest recorded SBP measurement amongst the three BP recordings obtained at 1, 2 and 3 minutes after assuming the erect posture.

5.2.4. Statistical Analysis

For categorical outcomes of OH and falls, multivariate logistic regression methods were used to control for potential confounders. As minimal SBP was a continuous variable, independent t test was applied to test statistical significance and mean differences in minimal SBP were adjusted for confounders using linear regression methods. A p-value of <0.05 was considered statistically significant. Statistical modelling using binary logistic regression analysis method was employed to determine the mediation effects of postural blood pressure changes on falls associated with antihypertensive use. This was determined by examining the associations by step-wise adjustment of potential confounders. If the independent variable (antihypertensive use) was no longer statistically significant after the addition of a new variable (OH or minimal standing SBP) within the model, then the new variation was considered a potential mediator for the relationship between the independent variable and dependent variable.

5.3. Results

5.3.1. Recruitment and baseline demographics

A total of 442 participants were assessed initially. Eighty participants were excluded as they either did not meet the inclusion criteria or fulfilled exclusion criteria. Blood pressure data was incomplete for four individuals, who were then excluded from the analyses. Data on medication and blood pressure measurements from a total of 358

participants which included 202 fallers and 156 non-fallers were subsequently analyzed. Fallers were significantly older than non-fallers and they had significantly more comorbidities, with diabetes, eye diseases and circulatory diseases being significant among fallers. There was no significant difference between fallers and non-fallers with regards to gender, body mass index, hypertension, osteoporosis, depression, thyroid diseases and other chronic conditions (Table 5.1).

Table 5.1: Comparison of Baseline Characteristics of Fallers and Non-fallers .

Characteristics	**Fallers[†] (n=202)**	**Non-Fallers[‡] (n=156)**	**p-value**
Age (Years), mean ± SD	75.2 ±7.1	72.2(±5.5)	<0.001***
Male Gender, n(%)	65(32.2)	51(32.7)	0.92
Body Mass Index (kg/m2), mean ± SD	24.2 ±3.7	24.5(±4.0)	0.48
Smoker, n(%)	7(3.5)	7(4.5)	0.61
Alcohol, n(%)	15(7.4)	15(9.6)	0.45
Medical History, n(%)			
Diabetes	69(34.2)	30(19.2)	0.002**
Hypertension	115(56.9)	77(49.4)	0.17
Respiratory disorders	9(4.5)	6(3.8)	0.78
Arthritis	44(21.8)	40(25.6)	0.37
Osteoporosis	19(9.4)	15(9.6)	0.93
Hearing disorders	14(6.9)	7(4.5)	0.33
Depression	6(3)	2(1.3)	0.47
Thyroid diseases	13(6.4)	16(10.3)	0.18
Eye diseases	95(47)	52(33.3)	0.009**
Circulatory diseases	41(20.8)	18(11.5)	0.03*
Neoplasm	4(2)	9(5.8)	0.05*
No. of co-morbidities, mean ± SD	2.3(±1.6)	1.8 (±1.5)	0.01**
Min SBP[a] (mmHg). mean ± SD	128(±27.3)	135.7(±24.7)	0.01**
Min DBP[b] (mmHg), mean ± SD	67(±16.7)	69.8(±17.3)	0.13

SD=standard deviation
***p≤.001, **p≤.01, *p≤.05
[†]Recurrent or injurious falls in the past 12-months
[‡]No falls in the past 12 months
[a]Minimal standing SBP was the lowest recorded reading of SBP amongst the three standing
[b]Minimal standing DBP was the lowest recorded reading of DBP amongst the three standing measurements

5.3.2. Blood Pressure Measurements

Table 5.2 summarises the supine and erect blood pressure measurements of the participants. In the supine position, the systolic blood pressure (SBP) of fallers was

significantly lower than non-fallers, which was no longer significant following adjustment for age and comorbidities. After assuming the upright posture, there was no significant difference in standing SBP measurement at 1 min, but SBP at 2 and 3 minutes were significantly lower among fallers than non-fallers. These remained significant after adjustment of age and number of comorbidities. There was no significant difference in supine and standing diastolic blood pressure (DBP) at any time point between fallers and non-fallers. There was no significant difference in the prevalence of OH [fallers, 52(25.7) vs. nonfallers, 28(17.9); p=0.08] between the two groups using the pre-defined criteria; however mean minimal SBP during standing was significantly lower in fallers (Table 5.1).

Table 5.2: Postural Blood Pressure Measurements Among Fallers and Non-Fallers.

Blood Pressure	Fallers† (n=202)	Non-Fallers‡ (n=156)	Mean Difference (95%CI)	Unadjusted p-value	Adjusted Mean Difference§ (95%CI)	Adjusted p-value§
Supine (mmHg), mean (±SD)						
Baseline SBP	130(24.8)	135.6(20.3)	4.6(0.05-9.2)	0.04*	4.5(0.23 to 9.2)	0.06
Baseline DBP	66.2(15)	66.6(15.0)	0.4(-2.6 to 3.5)	0.78	0.73(-2.4-3.9)	0.65
Standing (mmHg), mean (±SD)						
SBP at 1 min	134.2(27.9)	139.6(26.5)	5.3(-0.33 to 11.1)	0.06	5.3(-0.56 to 11.2)	0.07
SBP at 2 min	139.1(26)	146.2(24.0)	7.1(1.7-12.3)	0.009**	7.7(2.3-13.2)	0.006**
SBP at 3 min	139.1(27)	146.5(24.2)	7.3(1.9-12.8)	0.008**	7.6(2.1-13.3)	0.007**
DBP at 1 min	71.1(17)	72.2(18.2)	1.6(-2.0 to 5.3)	0.37	0.32(-3.3 to 4.1)	0.86
DBP at 2 min	72.8(17)	75.2(16.2)	2.4(-1.1 to 5.9)	0.17	1.1(-2.4 to 4.6)	0.54
DBP at 3 min	72.8(16.2)	75.7(15.3)	2.8(-0.47 to 6.1)	0.09	1.3(-1.9 to 4.6)	0.43

SBP=systolic blood pressure, DBP=diastolic blood pressure; OH= orthostatic hypotension; CI= Confidence Interval
***p≤0.001, **p≤0.01, *p≤0.05
†Recurrent or injurious falls in the past 12-months
‡No falls in the past 12 months
§adjusted for age and number of comorbidities using linear regression

5.3.3. Antihypertensive Medications and Falls

Among the total sample, 126 fallers and 77 non-fallers were taking at least one antihypertensive drug (OR=1.7; 95%CI, 1.1-2.5; p=0.01). With univariate analyses of individual classes of antihypertensives, α-blockers and A2RA were associated with falls. However, this finding was no longer significant following adjustment for age difference alone (Table 5.3). Fallers were significantly more likely to be on two or more antihypertensives following univariate analysis (OR=1.97; 95%CI, 1.2-3.1; p=0.005), but this was not statistically significant after adjustment for age and number of co-morbidities (OR=1.6; 95% CI, 0.95-2.6; p=0.07) (Table 5.3).

Table 5.3: The Association between Antihypertensive Classes and Falls, Orthostatic Hypotension and Min SBP.

	Falls		**Orthostatic Hypotension**		**Minimal SBP**	
Antihypertensives	**Unadjusted OR(95%CI)**	**Adjusted OR[§] (95%CI)**	**Unadjusted OR(95%CI)**	**Adjusted OR[§] (95%CI)**	**Mean difference[c] (95%CI)**	**Adjusted mean difference[ŧ] (95%CI)**
α-blockers	2.7(1.1-7.0)***	2.2(0.82-5.81)	1.9(0.83-4.5)	1.83(0.75-4.4)	13.5(3.6 to 23.4)***	14.1(3.3 to 24.8)***
β-blockers	1.3(0.75-2.3)	0.98(0.54-1.8)	1.5(0.81-2.7)	1.28(0.67-2.5)	3.7(-3.5 to11.0)	3.7(-3.3 to 11.4)
ACE-I	1.1(0.63-2.0)	1.1(0.61-2.1)	1.3(0.69-2.5)	1.29(0.65-2.6)	0.05(-8.2 to 8.3)	0.59 (-8.3 to 7.2)
A2RA	2.1(1.1-4.0)***	1.7(0.9-3.5)	1.2(0.6-2.3)	1.09(0.53-2.2)	3.1(-4.3 to10.5)	3.7(-4.3 to 11.7)
CCB	1.3(0.84-2.1)	1.0(0.63-1.73)	0.98(0.56-1.7)	0.86(0.48-1.5)	-0.77(-6.7 to 5.2)	-0.53(-6.9 to 5.8)
Diuretics	1.5(0.78-3.1)	1.5(0.78-3.2)	2.2(1.1-4.4)*	2.2(1.1-4.4)***	-1.3(-10.7 to 8.1)	-1.1(-9.9 to 7.7)
Nitrates	1.6(0.46-5.3)	0.89(0.24-3.2)	1.7(0.52-6.1)	1.6(0.45-5.8)	-6.0(-21.3 to 9.2)	-5.8 (-21.5 to 9.9)
Any antihypertensive	1.7(1.1-2.5)	1.4(0.94-2.3)	1.5(0.93-2.6)	1.6(0.8-3.3)	4.4 (-1.1 to 9.9)	4.4(-1.2 to 10.2)
≥2 antihypertensives	1.97(1.2-3.1)**	1.6(0.95-2.6)	1.5(0.85-2.5)	1.37(0.79-2.3)	2.8(-3.1 to 8.8)	3.4(-3.0 to 9.9)

ACE-I, Angiotensin converting enzyme inhibitors; A2RA, angiotensin II receptor antagonists; CCB, calcium channel blockers;
*** p≤0.001, ** p≤0.01, * p≤0.05; OR= Odds Ratio; CI= Confidence Interval
[§] adjusted for age and number of comorbidities using binary logistic regression.
[ŧ] adjusted for age and number of comorbidities using linear regression

5.3.4. Antihypertensives versus Orthostatic Hypotension and Minimal standing SBP

Regardless of the history of falls, individuals with OH were significantly more likely to be on diuretics even after adjustment for age (p=0.02), but no significant decrease in minimal SBP was observed with diuretic use. While the use of α-blockers is associated with significantly lower minimal standing SBP (p=0.01), OH was not associated with α- blocker use. The antihypertensive classes of β-blockers, CCB, ACE-I and A2RA were not associated with OH or decreased minimal standing SBP. There was no significant difference in the number of anti-hypertensives used between individuals with and without OH. Similarly the minimal standing SBP did not differ with number of antihypertensives (Table 5.3).

5.3.5. Multivariate Analyses

Multivariate analysis was employed to determine the influence of OH and minimal standing SBP on the relationship between the antihypertensive use and falls (Table 5.4). Model 1 confirms that the relationship between the use of any antihypertensive drug and falls was unattenuated by the presence of OH, while Model 2 confirms that the presence of OH did not alter the significant association between the use of 2 or more antihypertensives and falls. Model 3 denotes that both the use of any antihypertensive and minimal standing SBP were independently associated with falls and Model 4, similarly indicated that the use of two or more antihypertensives and minimal standing SBP were also independently associated with falls. Model 5 indicates that minimal standing SBP remained an independent predictor for falls despite the inclusion of age or comorbidities in the model.

Table 5.4. Logistic Regression Models to Determine the Influence of Postural Blood Pressure Changes on the Relationship between Antihypertensives and Falls.

OR=odds ratio, CI=confidence interval, Min SBP=Minimal systolic blood pressure

Models	Adjusted OR (95%CI)	p-value	R^2
Orthostatic Hypotension and Antihypertensive Use			
Model 1			0.03
Any hypertensive	1.6(1.1-2.5)	0.02*	
Orthostatic hypotension	1.5(0.89-2.5)	0.12	
Model 2			0.04
≥2 antihypertensives	1.9(1.2-3.1)	0.008**	
Orthostatic hypotension	1.5(0.9-2.6)	0.12	
Minimal SBP and Antihypertensive Use			
Model 3			0.04
Any hypertensive	1.6(1.1-2.5)	0.02*	
Min SBP (per mmHg)	0.99(0.98-0.99)	0.02*	
Model 4			0.05
≥2 antihypertensives	1.9(1.2-3.2)	0.007**	
Min SBP (per mmHg)	0.99(0.08-0.99)	0.02*	
Model 5			0.102
Age (per year's increase)	1.1(1.0-1.1)	0.001***	
No. of comorbidities	1.0(0.91-1.2)	0.45	
≥2 antihypertensives	1.5(0.91-2.6)	0.10	
Min SBP (per mmHg increase)	0.99(0.98-0.99)	0.01**	

***p≤0.001, **p≤0.01, *p≤0.05

5.4. Discussion

Our case-control study uniquely examined the relationships between BP lowering therapy with recurrent or injurious falls and postural blood pressure variations. Treatment with medications from any antihypertensive drug class was not associated with falls; instead use of multiple antihypertensives exhibited significant association with falls, which was only attenuated by the age and number of comorbidities. Orthostatic hypotension, according to the existing consensus definition, was not associated with the risk of recurrent or injurious falls. Minimal standing SBP, however, was significantly lower among fallers as compared to controls. The increased risk of falls observed with antihypertensive use was not mediated by OH or minimal standing

SBP, but was influenced by the inevitable age differences between our fallers and non-faller controls.

By opting to select cases from individuals with recurrent or injurious falls and controls from those with no history of falls in the previous year, we excluded those with a history of only one non-injurious fall in the previous year. As the risk factors for one time fallers and recurrent fallers (two or more) differ, it is the recurrent faller who would benefit to the greatest extent from fall prevention efforts and from the negative outcomes associated with multiple falls (AGS/BGSguidelines, 2011; Ambrose et al., 2013; Fletcher et al., 2002), therefore this study only focused on the latter group of older adults.

Although orthostatic hypotension has formerly been reported as a risk factor of falls (Craig, 1994; Ooi et al., 2000; Rubenstein et al., 1990), this study suggests that it is the presence of a lower SBP while standing rather than the presence of OH alone that determines the risk of recurrent or injurious falls. A recent meta-analysis demonstrated that in spite of lower cardiovascular morbidity and mortality among older hypertensive adults on antihypertensive therapy than those without treatment, mild treatment was effective for all ages over 65years and strict SBP control presented no added advantage (Goeres et al., 2014). Our study superimposes this report by suggesting that use of antihypertensives is only beneficial with mild consumption whereas a strict SBP control, may present higher risk for falls. While the prevalence of hypertension increases markedly with age (van Rossum et al., 2000), age-related decline in blood pressure is also prominent in older adults, which is the marker of poor or deteriorating health (Hakala et al., 1998) and may be associated with syncope (Yiu et al., 2006) and recurrent falls (Heitterachi et al., 2002). One longitudinal study found that among older adults, the changes in blood pressure are related to health, with a rise of 1.5mmHg per

year among healthy elderly while a drop among the older adults with multiple co-morbidities and this co-morbidity related drop was more prominent with SBP than DBP (Starr et al., 1998). The prevalence of lower SBP while standing among our fallers might then be explained by the significant number of comorbidities. Furthermore, the report by Odden et al suggested that frail older adults might benefit from slightly higher blood pressure, to overcome age-related loss of vascular elasticity and sustain perfusion of vital organs (Odden et al., 2012). Of note, the difference in standing SBP among our fallers was only observed if standing SBP was measured at 2minutes and beyond. Our findings support that of Kario et al who reported that individuals with a history of falls and a standing SBP below 140 mmHg had an increased risk of falling(Kario et al., 2001). Before further conclusions can be drawn, prospective evaluation of the relationship between minimal standing SBP at 2 or 3minutes and falls occurrence is warranted, in order to develop a clear cut-off for minimal standing SBP or an accurate predictive score while taking into account minimal standing SBP, age, history of recurrent and injurious falls alongside other potential predictors for falls.

Our study has provided a deeper insight into the link between postural blood pressure and antihypertensives among older fallers. The measurement of standing SBP may represent a useful parameter in determining how aggressively SBP should be treated among geriatric population, with increasing age and history of falls currently being the only available decision aid(James et al., 2014). Our findings contradict those of a previous study that various classes of antihypertensives are associated with falls (Wong et al., 2013) and choosing one class over the other may reduce the risk of falls. On the contrary, our results indicate that the use of two of more antihypertensives regardless of class of medication might be associated with high risk of falls.

Callisaya et al (Callisaya et al., 2014) stated that increased antihypertensive burden, calculated by the ingested dose of each antihypertensive divided by the recommended maximal daily dose, increases the risk of falls, independent of drug classes. While our study supports this finding, it suggests that the simple method of counting number of antihypertensives may also be effective in predicting falls risk. The association of multiple antihypertensives with falls was attenuated with age adjustment, as reported by Gu and colleagues (Gu et al., 2006) that the use of multiple antihypertensives increases with increasing age. A multicentre longitudinal study found that lower SBP along with use of two or more antihypertensives significantly contributed to mortality among their institutionalized octogenarians (Benetos et al., 2015). Although we did not find the association of use of two or more antihypertensives with SBP but as the authors suggested that the safety of using multiple antihypertensives in elderly patients with lower SBP "raises a cautionary note", our findings do suggest that 2 or more antihypertensives and lower standing SBP are independently linked with falls and if they co-exist they may amplify falls risk.

While orthostatic hypotension was related with uncontrolled blood pressure as suggested by the findings of the British Women Heart and Health study (BWHHS), the number of antihypertensives and use of β-blockers were not associated with OH in our study. Instead, diuretic use was linked with OH, unlike that reported by the BWHHS(Kamaruzzaman et al., 2010). In addition, using currently agreed definitions for OH, there was no significant relationship between OH and falls. While this suggests that the use of multiple blood pressure lowering agents may be associated with higher-risk of future falls through currently unexplained mechanisms, it also suggests that the diagnostic criteria for OH may require revision(Frith et al., 2014).

To our knowledge, our study was the first to include the evaluation of postural blood pressure measurements, antihypertensive use and falls in the same participants. The limitations of the study are as follows. As a case-control study, it was unable to determine any causal relationship between antihypertensive therapy and falls, which will be a subject of a future prospective study which, however, requires larger sample sizes for adequate statistical power. Falls in our study were identified through retrospective recall, the prospective study will therefore need to consider the use of fall diaries to minimize recall bias(Ganz et al., 2005).

5.5. Conclusion

Individuals with a history of at least two falls or one injurious fall, had significantly lower standing SBP obtained 2-3 minutes after assuming the upright posture rather than immediately. Orthostatic hypotension was not associated with recurrent or injurious falls. While falls were also associated with the regular use of two or more antihypertensive drugs as compared to non-faller controls, this was not mediated by minimal standing SBP, challenging previous assumptions that antihypertensive are linked to falls through their blood pressure lowering effects. A prospective study evaluating actual falls outcome with regards to blood pressure changes among older individuals prescribed antihypertensive therapy is now warranted to accurately identify factors associated with increased risk of falls, which will be invaluable for effective blood pressure lowering among the older population.

CHAPTER 6. ANTICHOLINERGIC BURDEN IS ASSOCIATED WITH RECURRENT AND INJURIOUS FALLS IN OLDER INDIVIDUALS

6.1. Introduction:

The drugs with anticholinergic activity are the most widely prescribed FRID among older adults (Carriere et al., 2009; Fox et al., 2011). In addition, recent studies have reported the anticholinergic cognitive burden (ACB) of drugs to be associated with poor mobility, functional decline, psychomotor slowing (Cao et al., 2008; Fox et al., 2014; Landi et al., 2014; Nebes et al., 2007) as well as falls among older adults (Aizenberg et al., 2002; Dauphinot et al., 2014; Wilson et al., 2011). However, studies have not evaluated the anticholinergic effects of drugs among community-dwelling older people at particularly high risk of recurrent falls. Furthermore, previous studies had not, evaluated mobility and balance performance in relation to the use of anticholinergic drugs in a single study. We hypothesized that the use of drugs with ACB leads to falls through their effects on mobility and balance. Therefore, the objective of this study was to examine the association between ACB of drugs with falls and subsequently employing statistical modelling to evaluate the mediating effects of mobility and balance on anticholinergic associated falls among community dwelling older adults.

6.2. Methodology

The methodology of study population and recording of basic characteristics, medication recording (chapter 3) and blood pressure have been explained earlier (chapter 4).

6.2.1. Physical function

The Timed-Up and Go (TUG) and Functional Reach (FR) tests were conducted to provide indicators of gait speed and balance respectively. The TUG test is considered as an appropriate clinical tool to measure functional mobility among older adults (Herman et al., 2011). For TUG, the participants were instructed to walk a distance of 3-metres at their normal pace, from and back to a seated start position, on a 46cm high arm-chair. Functional reach was defined as the distance between arm's length and maximal forward reach achieved using a fixed base of support (Duncan et al., 1990). The participants were instructed to stand with their feet shoulder width apart next, and to raise their arm at 90°, parallel to the wall. A one-metre ruler was placed at shoulder (acromion) height, parallel to the participant's arm and the distances were recorded at the location of the 3rd metacarpal. After noting down the initial reach, the final distance was recorded (in centimetres) as the participants leaned forward without stepping or losing the balance. The difference between the two measurements was recorded as the FR of the participant.

Participants were instructed to grip the Jamar dynamometer with maximal strength with their dominant hand, followed by their non-dominant hand while seated and elbows bent at 90°. Three readings for each hand were obtained, the average of which was considered as the final grip strength. All the above tests were demonstrated with one trial run. Shoes were kept on for these tests and walking aids were allowed for TUG if required.

6.2.2. Anticholinergic Burden

The total anticholinergic burden for each participant was calculated using the validated Anticholinergic Cognitive Burden(ACB) Scale (Fox et al., 2011).The drugs were classified as having absent, possible or definite anticholinergic properties . The

total ACB was then calculated using the formula; Total ACB =[number of score1 anticholinergic drugs]+[number of score2 anticholinergic drugs*2]+[number of score 3 anticholinergic drugs*3]. We categorized patients' ACB status into 2categories (no ACB=total score 0; positive ACB= total score≥1) for comparison of characteristics between the no ACB and positive ACB fallers and non-fallers.

6.2.3. Statistical Analysis

The continuous data of TUG, FR and GS were dichotomized to form binomial variables (poorer TUG ≥13.5sec and poorer FR ≤18cm, reduced GS≤ 20kg for women, ≤30kg for men). A p-value of <0.05 was considered statistically significant. Statistical modelling using logistic regression methods was employed to determine the mediation effects of TUG and FR on falls associated with ACB. This was determined by examining the associations by step-wise adjustment for potential confounders. If the independent variable (ACB score) was no longer statistically significant after the addition of a new variable (TUG or FR) in the model with falls as the dependent variable, then the new variable was considered a potential mediator for the relationship between the independent variable and dependent variable (falls). Potential confounders were identified from comparison of basic characteristics between fallers and non-fallers and were adjusted for in subsequent models. However, as numerous medical conditions with potential collinearity were significantly different between groups, we adopted the approach of adjusting for the number of comorbidities, instead of individual comorbidities, to address multicollinearity.

6.3. Results

6.3.1. Recruitment and baseline demographics

Four hundred and twenty eight participants, 263 fallers and 165 non-fallers were recruited into the study. Fallers were significantly older with significantly more

comorbidities and more medications. Diabetes, visual problems, hypertension, hearing disorders and circulatory diseases were significantly increased among fallers. The measures of gait and balance i.e. TUG and FR were significant for falls but not upper limb strength i.e. GS (Table 6.1).

Table 6.1: Characteristics and Anticholinergic Cognitive Burden Among Fallers and Non-fallers.

Characteristics	**Fallers[a] (n=263)**	**Nonfallers[b] (n=165)**	**Mean difference/OR (95% CI)**	**P value[c]**
Age, mean(±SD)	75.3(7.3)	72.13(5.5)	3.1(1.8-4.4)	<0.001
BMI, mean(±SD)	23.75(4.1)	24.13(4.0)	0.4(0.3-1.2)	0.33
Characteristics	**Fallers[a] (n=263)**	**Nonfallers[b] (n=165)**	**OR(95% CI)**	**P value[d]**
Male, n(%)	84(31.9)	55(33.3)	1.0(0.7-1.6)	0.76
Smoking, n(%)	15(5.7)	7(4.2)	1.3(0.5-3.4)	0.50
Alcohol, n(%)	23(8.7)	17(10.3)	0.8(0.4-1.6)	0.59
Medical History				
Diabetes, n(%)	95(36.1)	29(17.6)	2.6(1.6-4.2)	<0.001
Visual problems, n(%)	132(50.2)	51(30.9)	2.2(1.5-3.3)	<0.001
Hypertension, n(%)	155(58.9)	74(44.8)	1.7(12-2.6)	0.004
Circulatory diseases, n(%)	45(17.1)	14(8.1)	2.2(1.2-4.2)	0.01
Hearing disorders, n(%)	28(10.6)	7(4.2)	2.6(1.1-6.3)	0.01
Neoplasm, n(%)	6(2.3)	10(6.1)	0.36(0l.1-1.1)	0.04
Arthritis, n(%)	68(25.9)	38(23.0)	1.1(0.74-1.8)	0.51
Osteoporosis, n(%)	25(9.5)	16(9.7)	0.97(0.5-1.8)	0.94
Asthma, n(%)	18(6.8)	9(5.5)	1.2(0.5-2.9)	0.56
Thyroid disorders, n(%)	17(6.5)	15(9.1)	0.69(0.3-1.4)	0.31
Orthostatic Hypotension, n(%)	62(23.6)	29(17.6)	1.4(0.88-2.3)	0.14
Physical Performance Scores, n(%)				
TUG ≥ 13.5s	134(51)	34(20.6)	3.9(2.5-6.2)	<0.001
FR ≤ 18cm	78(29.7)	13(7.9)	4.8(2.6-9.1)	<0.001
Reduced RGS	201(76.4)	89(53.9)	2.7(1.7-4.2)	<0.001
Reduced LGS	212(80.6)	101(61.2)	2.9(1.8-4.6)	<0.001
Total ACB Score, n(%)				
ACB≥1	75(28.5)	29(17.6)	1.8(1.1-3.0)	0.01

SD=standard deviation; OR= Odds ratio; CI Confidence Interval
ACB= Anticholinergic cognitive Burden; TUG= timed up and go, FR=functional reach
LGS= grip strength in left hand; RGS=grip strength in right hand; Reduced Grip strength ≤20kg women, ≤30kg men
[a]Recurrent or injurious falls in the past 12-months, [b]No falls in the past 12 months, [c]Student's t-test, [d]Chi-squared test;

6.3.2. Anticholinergic Burden Score and Falls

Seventy five (28.5%) fallers and 29(17.6%) non-fallers had an ACB score of ≥1, which was significant for falls (OR, 1.8; 95%CI; 1.1, 3.0; p=0.01) (Table 1). When

the characteristics of participants with an ACB score ≥ 1 and those with ACB score of 0 were compared, age, gender, number of co-morbidities and use of medicines, poorer TUG and poorer FR were statistically significant for ACB score ≥ 1 while grip strength, baseline blood pressure or prevalence of orthostatic hypotension did not show any association (Table 6.2).

Table 6.2: Characteristics of sample population according to the anticholinergic cognitive burden score.

Total participants N=458	**ACB=0 n=324**	**ACB≥1 n=71**	**Mean Difference /OR(95%CI)**	**p-value[a]**
Age mean(SD)	73.3(6.6)	76.5(7)	3.2(1.6-4.6)	0.0001
Systolic blood pressure, mean(SD)	130(22)	132(22)	1.8(-3.1 to 6.7)	0.45
Diastolic blood pressure, mean(SD)	67(15)	67(14)	0.14(-3.1 to 3.3)	0.93
Total participants N=458	**ACB=0 n=324**	**ACB≥1 n=71**	**OR (95%CI)**	**p-value[b]**
Falls (yes) n(%)	188(58)	75(72.1)	1.8(1.1-3.0)	0.01
Gender (Male)	95(29.3)	44(42.3)	0.56(0.35-0.89)	0.01
Smoking n(%)	15(4.6)	7(6.7)	1.4(0.58-3.7)	0.39
Alcohol n(%)	26(8)	14(13.5)	1.7(0.89-3.5)	0.09
Orthostatic Hypotension n(%)	68(21)	23(22.1)	1.1(0.62-1.8)	0.80
TUG ≥ 13.5s, n(%)	110(34)	58(55.8)	2.4(1.5-3.7)	0.0001
FR ≤ 18cm, n(%)	53)16.4)	38(36.5)	2.8(1.7-4.7)	0.0001
Reduced Rt GS, n (%)	210(64.8)	80(76.9)	1.6(0.95-2.7)	0.07
Reduced Lt GS, n(%)	231(71.3)	82(78.8)	1.3(0.78-2.4)	0.25
No of comorbidities Median(IQR)	2(2)	2(2)	n/a	0.0001[c]
No of medications[◊] Median(IQR)	2(4)	5(4)	n/a	0.0001[c]

TUG= timed up and go, FR=functional reach, GS=grip strength, Grip strength reduced <20kg women, <30kg men
[◊]Calculated after excluding the drugs in ACB scale, [a]Student's t-test, [b]Chi-squared test [c]Mann Whitney U test.

Subgroup analysis was performed by investigating the ACB score separately according to the faller and non-faller groups. Age and number of co-morbidities were significantly associated with a positive ACB score in both groups. Timed up and go performance was significantly poorer among ACB positive subgroups in both fallers and nonfallers while FR performance was only poorer among the fall participants with

positive ACB score. Grip Strength was not statistically significant between those with or without positive ACB score (Table 6.3).

Table 6.3: Subgroup analysis of participants as fallers and nonfallers according to the ACB score.

Characteristics	**Fallers† (n=263)**			**Nonfallers‡ (n=165)**		
	ACB=0 n=188	ACB≥1 n=75	P value	ACB=0 n=136	ACB≥1 n=29	P value
Age, mean(±SD)	74.7)7.2)	76.8(7.5)	0.03[a]	71.4(5.2)	75.6(5.8)	<0.001[a]
Number of comorbidities, median (IQR)	2(3)	3(2)	0.004[b]	1(2)	2(3)	0.01[b]
Measures of upper limb and lower limb strength, n(%)						
TUG ≥ 13.5s	86(45.7)	48(64)	0.009[c]	24(17.6)	10(34.5)	0.04[c]
FR ≤ 18cm	43(22.9)	35(46.7)	0.0001[c]	10(7.4)	3(10.3)	0.61[c]
Reduced RGS	138(73.4)	63(84)	0.19[c]	72(52.9)	17(58.6)	0.69[c]
Reduced LGS	147(78.2)	65(86.7)	0.20	84(61.8)	17(58.6)	0.58[c]
Type of Falls n(%)						
Indoor	109(58.3)	45(59.2)	0.89[c]	-	-	-
Outdoor	107(57.2)	43(56.6)	0.92[c]	-	-	-
Injuries	87(46.5)	43(56.6)	0.13[c]	-	-	-
Medication use[◊]						
Number of drugs[◊] Median(IQR)	3(4)	5(5)	0.0001[b]	1(3)	4(3)	0.0001[b]
Antihypertensives *n(%)*	93(49.5)	62(82.1)	0.0001[c]	46(35.1)	22(83.2)	0.0001[c]
Analgesics *n(%)*	50(26.7)	40(52.6)	0.0001[c]	17(12.6)	9(30)	0.02[c]
Psychotropics *n(%)*	10(5.3)	18(23.7)	0.0001[c]	4(3)	4(13.3)	0.01[c]
Antidiabetic drugs *n(%)*	53(28.3)	26(34.2)	0.34[c]	13(9.6)	8(26.7)	0.01[c]
Antiparkinsonians *n(%)*	2(1.1)	5(6.6)	0.01*[c]	1(0.7)	1(3.3)	0.24[c]
Blood pressure (BP) mean(±SD)						
Systolic BP mean(±SD)	125.6(21.6)	132.3(24.7)	0.03[a]	135.2(20.1)	133.4(19.2)	0.66[a]
Diastolic BP mean(±SD)	66.4(14.1)	67.8(13.7)	0.45[a]	67.4(15.1)	64.3(13.1)	0.31[a]
OH *n(%)*	44(23.4)	18(24)	0.92[c]	24(17.6)	5 (17.2)	0.95[c]

[◊]Calculated after excluding the drugs with ACA; [a]student's t test, [b]Mann Whitney U test, [c]Chi squared test

6.3.3. Multivariate Analyses

The unadjusted models show that both an ACB score of 1 or greater and GS are independent predictors of falls (models 1 and 2) but the association between ACB ≥1 and falls was attenuated and became non-significant with the insertion of TUG and FR into the models (models 3 and 4). After adjusting for age and gender, ACB ≥1 was no

longer significant with GS (models 5&6) and remained non-significant by the presence of TUG and FR (models 7&8).The similar results were observed after adjusting of age, gender and number of co-morbidities (models 9, 10,11,12). The association between TUG, FR, GS and falls remained significant after adjusting for age, gender and number of comorbidities (Table 6.4).

Table 6.4: Logistic Regression Models to Determine the Influence of Timed up and Go and Functional Reach on ACB associated Falls.

	Unadjusted models	**Adjusted for age and gender**	**Adjusted for age, gender and number of comorbidities**
	Model 1	Model 5	Model 9
Reduced RGS	2.6(1.7-4.1)***	2.1(1.3-3.4)**	1.9(1.2-3.1)**
ACB >=1	1.7(1.1-2.9)*	1.5(0.9-2.6)	1.4(0.8-2.4)
	Model 2	Model 6	Model 10
Reduced LGS	2.8(1.7-4.6)***	2.3(1.4-3.8)**	2.1(1.3-3.5)**
ACB >=1	1.8(1.1-2.9)*	1.5(0.9-2.6)	1.4(0.85-2.4)
	Model 3	Model 7	Model 11
TUG ≥13.5s	3.7(2.4-5.9)***	3.1(1.9-5.0)***	2.8(1.7-4.6)***
ACB >=1	1.4(0.88-2.4)	1.3(0.81-2.2)	1.3(0.76-2.1)
	Model 4	Model 8	Model 12
FR≤18cm	4.5(2.4-8.5)***	3.7(1.9-7.1)***	3.4(1.8-6.6)***
ACB >=1	1.4(0.89-2.4)	1.3(0.8-2.2)	1.2(0.7-2.1)

***p≤0.001, **p≤0.01, *p≤0.05
ACB=anticholinergic cognitive burden; TUG=timed up and go; FR=Functional Reach; RGS=right grip strength; LGS=left grip strength
Model 1,2,3,4 adjusted separately for TUG or FR or RGS or LGS;
Model 5,6,7,8 adjusted age and gender and (TUG or FR or RGS or LGS)
Model 9,10,11,12 adjusted for age, gender, number of comorbidities and (TUG or FR or RGS or LGS)

6.4. Discussion

In this study, we found that the use of any ACB drug was significantly associated with falls and increased age along with poorer dynamic balance and gait speed. Grip strength was significantly associated with falls but not with a positive ACB score. The significant association between a positive ACB score and falls was attenuated when controlled for TUG and FR but not by GS, thus suggesting that TUG

and FR are the potential mediating factors through which anticholinergic medications may precipitate falls.

Nearly half of our participants (46.1%) were on at least one medication with anticholinergic activity, which is similar to that reported by other studies (Carriere et al., 2009; Fox et al., 2011; Landi et al., 2014). Using the Anticholinergic Burden Scale, Aizenberg and colleagues were the first to report that higher anticholinergic activity was significantly associated with increased rate of falls(Aizenberg et al., 2002). Two studies have used the Drug Burden Index (DBI), to assess the association of falls with the cumulative load of sedatives and anticholinergic drugs in different settings (Dauphinot et al., 2014; Wilson et al., 2011). Wilson et al found increased DBI to be independently associated with falls prospectively among institutionalized older people (Wilson et al., 2011). Dauphinot et al demonstrated a significant increase in the risk of falls among older adults with increased DBI during their hospital stay (Dauphinot et al., 2014). However, sedatives alone are considered as independent predictors of falls among older adults (Woolcott et al., 2009) and drugs with anticholinergic activity include beta-blockers, colchicine, ranitidine and other commonly prescribed drugs to older adults, and not merely psychotropics. A recent meta-analysis of eighteen studies involving different ACB scales, found ACB to be associated with falls along with cognitive impairment and all-cause mortality (Ruxton et al., 2015).

Our results suggest that falls associated with ACB medications are potentially mediated by the deterioration in lower limb function measured with TUG and FR. The TUG test is a composite measure of response time, limb girdle strength, gait initiation, gait speed and dynamic balance, widely used as a screening test for gait and balance disorders in research and clinical practice (AGS/BGSguidelines, 2011). Functional reach is a convenient measure of dynamic balance. Landi et al analysed a population of

1490 nursing home residents and reported that a higher score in the anticholinergic risk scale was associated with a greater likelihood of functional decline, poor physical performance and a higher rate of falls (Landi et al., 2014). Our findings are further supported from the study by Nebes et al, who examined the cumulative anticholinergic load of older community residents by testing their serum anticholinergic activity (Nebes et al., 2007). Although they excluded the participants with impaired cognition and psychiatric illnesses or taking any psychotropic medications at baseline, they found that elevated serum anticholinergic activity was significantly associated with the slow gait speed and response time. Furthermore, a recent metaanalysis reported that five of their eight included studies reported a decline in physical function among users of anticholinergics (Fox et al., 2014).

Anticholinergics are well known for their cognitive effects in older adults (Cao et al., 2008; Carriere et al., 2009; Fox et al., 2011; Fox et al., 2014; Landi et al., 2014; Salahudeen et al., 2014) and cognitive impairment itself is an independent risk factor for falls (Harlein et al., 2011). The study by Herman et al added a new dimension to the existing knowledge about cognition and TUG by stating that the transferring and turning component of TUG might be utilizing intact cognitive resources (Herman et al., 2011).The mediating effects of TUG in our population can be explained by TUG being affected by the cognitive effects of anticholinergic activity thus leading to falls. An interesting study by Cao et al reported that anticholinergic drug burden was independently associated with cognitive impairment and deterioration of all four domains of physical function leading to balance difficulty, mobility difficulty, slow gait, difficulty with chair stands, weak grip strength and upper extremity limitations (Cao et al., 2008). Our study has also found ACB associated functional decline to be a mediator for falls by evaluating gait speed and limb girdle strength using TUG test and

balance limitations using FR test. There is insufficient evidence in the literature to explain the mechanisms behind the particular role of FR and ACB associated falls.

Grip strength, which is a widely known marker of general frailty and sarcopenia, although related to falls, was not associated with ACB. The lack of association between ACB and GS supports our early hypothesis that anticholinergics adversely affect physical function not by reducing overall strength, but through its central effects which dictates reaction time, speed and functional balance. The antimuscarinic activity of anticholinergic drugs inhibits receptors in the forebrain, particularly in the basal ganglia, groups of nerve cells responsible for the coordination of movement. This cholinergic blockade in the brain is responsible for decline in motor and executive function (Nebes et al., 2007). Furthermore, normal ageing is accompanied by an increased sensitivity to the blockade of the muscarinic receptors and increased permeability of blood brain barrier (Kersten et al., 2014) thus enhancing the anticholinergic effects of medications, leading to significant deterioration in physical function and consequently leading to falls.

Our selected participants were at high risk of future falls with their history of injurious or recurrent falls (AGS/BGSguidelines, 2011). The ACB score although lower was still statistically significant, suggesting that medications with mild anticholinergic properties, among high risk fallers exacerbate their risk of falls. Similarly the impact of age and comorbidities on ACB score and falls is also comparable to previous studies (Carriere et al., 2009; Feinberg, 1993), because the number of comorbidities tends to increase with age along with the medications prescribed for the treatment of diseases. Different methods have been used by researchers to assess the anticholinergic activity of prescribed medications including: the anticholinergic risk scale, anticholinergic burden scale, drug burden index and

measuring serum anticholinergic activity. The measure of serum anticholinergic activity is the gold standard to measure the ACB burden of drugs and ACB scale is based on the affinity of drugs for muscarinic receptors of drugs and scored according to their clinical relevance (Ruxton et al., 2015). The study by Pont et al found that the ACB scale is the most reliable and clinically relevant among other available scales (Pont et al., 2015). A study conducted using nine anticholinergic scales found that the ACB scale identified not only the highest exposure to anticholinergic medications in the population but was also most likely to predict adverse outcomes of clinical interest(Salahudeen et al., 2014). The ACB scale is more sensitive than other available scales in detecting adverse outcomes, according to the meta-analysis by Ruston et al, with per unit increase in the ACB scale doubling the odds of all-cause mortality, which was not the case with any other scales (Ruxton et al., 2015).

Our study was the first to explore the association of drugs with anticholinergic properties and falls using the ACB scale in the community setting and was also the first to relate measures of mobility with ACB associated falls. However, as it was a cross sectional study, causal relationships could not be established. Hence a future adequately powered prospective study is warranted to consolidate this association. Falls were recorded retrospectively and therefore may be subject to recall bias. In additional, future studies should also include adequately sensitive assessments of higher mental function as well as lower limb function.

6.5. Conclusion

Our study suggests that ACB is associated with reduced lower limb function leading to falls among older adults. The TUG and FR are therefore potentially useful tools to assess the adverse anticholinergic activity of medications on older individuals, and may be useful risk indicators prior to the prescription of medications with

anticholinergic activity. In addition to medication review and withdrawal interventions, it would be interesting to explore whether concomitant physiotherapy which improves TUG and FR may reduce ACB induced falls risk. Consolidated evidence from the prospective and intervention studies is now required to further explore this association.

CHAPTER 7: ASSOCIATION OF INAPPROPRIATE PRESCRIPTIONS WITH FALLS AMONG COMMUNITY DWELLING OLDER ADULTS

7.1. Introduction

The increase in total number of medications/polypharmacy and FRID among older individuals is linked to the increased risk of potentially inappropriate prescriptions (PIP)(Weng et al., 2013). While, numerous studies have described the association between polypharmacy and falls, few studies have studied the relationship between PIP and falls, particularly in the context of secondary prevention among older individuals at high risk of falls(A. Zia et al., 2015b). Potentially inappropriate prescriptions are drug prescriptions in which potential harm from established relative contra-indications, interactions and side-effects outweigh the expected benefit of the prescribed drug, particularly where safer alternatives are available(Frankenthal et al., 2013). Several criteria have been developed to detect PIP among older adults. These include the Beer's criteria, medication appropriateness index (MAI), inappropriate prescribing in elderly tool (IPET) and the Screening Tool for Older Person's Prescriptions (STOPP) criteria. The MAI detects the overall prescribing quality in ten different domains e.g. indication, effectiveness, cost; but does not provide guidance on the appropriateness of specific medications(Hanlon et al., 1992).The Canadian tool IPET, consisting of a list of 14 most prevalent prescriptions, has only been used in Canada and in a solitary Irish study outside Canada(Page et al., 2010). The Beer's criteria, a list of 30 drugs to be avoided in the elderly regardless of the diagnosis, has dominated the international literature. However, the Beer's criteria is limited by lack of sensitivity, missing drug-drug interactions and duplicate drug classes. Furthermore, there is no evidence for subsequent reduction of adverse drug events following adjustment of inappropriate prescriptions detected by the Beer's criteria. Its

applicability outside the United States is also questionable due to the non-availability of certain drugs in other countries named in the Beer's criteria (Wahab et al., 2012).

The newer STOPP criteria has evidence of good inter-rater reliability, inclusion of both American and European medications(Page et al., 2010) and is documented to detect almost 2.8 times more adverse drug events than Beer's criteria(O'Mahony et al., 2010). It has been recently been upgraded to STOPP2 (O'Mahony et al., 2015). However, STOPP or STOPP2 have never been employed in the detection PIP among a community-dwelling sample of older fallers. This study, therefore, aimed to determine the association between PIP identified by STOPP2 and falls in community dwelling older adults and to identify factors associated with PIP among older individuals with recurrent and injurious falls.

7.2. Methods

The methodology for setting, participants and collection of baseline demographics, medication assessment, blood pressure readings, orthostatic hypotension, gait and balance (TUG, FR and GS) have been explained earlier.

7.2.1. Criteria for Potentially Inappropriate Prescriptions

The STOPP (screening tool of older person's potentially inappropriate prescriptions) criteria was formulated and validated by a panel of 18 experts in geriatric pharmacotherapy in 2006(Gallagher et al., 2008). It consisted of 65 criteria arranged according to physiological systems and medical diagnosis i.e. cardiovascular system, central nervous system, musculoskeletal system, urogenital system, endocrine system, duplicate drugs, falls risk increasing drugs and analgesics. Based on expanding evidence based therapeutics, STOPP was upgraded by a 19 member expert panel to 80 criteria, known as STOPP2 (O'Mahony et al., 2015). The new STOPP categories

created were antiplatelet/anticoagulant drugs, renal function drugs and drugs that increase anticholinergic burden. We used version 2 of the STOPP to detect inappropriateness of prescribing based on the medical history and medication use of fallers and non-fallers.

7.2.2. Statistical Analysis:

After the univariate analysis, multiple group comparisons were performed using logistic regression with dummy variables. The total prescriptions issued to participants were assessed and analysed according to faller and non-faller groups. For further analysis, participants were grouped into PIP=0 versus PIP≥1. Potential confounders for the risk of falls according to significant differences in basic characteristics i.e. age, gender, blood pressure, polypharmacy and comorbidities were adjusted for using multivariate logistic regression and the differences between groups were expressed as odds ratios (OR) with 95% confidence intervals(CI). A p-value of <0.05 was considered statistically significant. The best predictor model for increased risk of falls using PIP as an independent variable was also obtained. A further exploratory multivariate analysis was performed after the exclusion of non-fallers, to determine the predictors of PIP among fallers.

7.3. Results:

7.3.1. Recruitment and Baseline Demographics

We recruited 428 participants, 263 fallers and 165 non-fallers into the study. Fallers were significantly older, and had significantly more comorbidities than non-fallers. Diabetes, visual problems, hypertension, hearing disorders and circulatory diseases were significantly increased among fallers. Fallers and non-fallers were on a median (interquartile range) of 4(4) and 2(3) drugs respectively (p≤0.001). The

measures of gait and balance i.e. TUG, FR and grip strength were also as significantly poorer among fallers (Table 7.1).

Table 7.1: Basic Characteristics of the whole population.

Characteristics	Fallers[a] (n=263)	Nonfallers[b] (n=165)	OR(95% CI) or mean difference (95%CI)	P value[c]
Age, mean(±SD)	75.3(7.3)	72.13(5.5)	-	<0.001[d]
Male, n(%)	84(31.9)	55(33.3)	1.0(0.7-1.6)	0.76
Smoking, n(%)	15(5.7)	7(4.2)	1.3(0.5-3.4)	0.50
Alcohol, n(%)	23(8.7)	17(10.3)	0.8(0.4-1.6)	0.59
BMI, mean(±SD)	23.75(4.1)	24.13(4.0)	-	0.33[d]
Marital Status, n(%)				0.16
Single	14(8.1)	19(7.2)		
Married	124(75.2)	186(70.7)		
Widowed	27(16.4)	58(22.1)		
Living Alone, n(%)	12(7.3)	21(8)	1.1(0.52-2.3)	0.78
Living with Spouse, n(%)	92(55.8)	138(52.5)	0.87(0.59-1.2)	0.51
Living with Children, n(%)	80(48.5)	133(50.6)	1.1(0.73-1.6)	0.67
Medical History				
No of comorbidities Median(IQR)	2(2)	2(2)	n/a	<0.001***
Diabetes, n(%)	95(36.1)	29(17.6)	2.6(1.6-4.2)	<0.001**
Visual problems, n(%)	132(50.2)	51(30.9)	2.2(1.5-3.3)	<0.001**
Hypertension, n(%)	155(58.9)	74(44.8)	1.7(12-2.6)	0.004**
Circulatory diseases, n(%)	45(17.1)	14(8.1)	2.2(1.2-4.2)	0.01
Hearing disorders, n(%)	28(10.6)	7(4.2)	2.6(1.1-6.3)	0.01*
Neoplasm, n(%)	6(2.3)	10(6.1)	0.36(0.1-1.1)	0.04*
Arthritis, n(%)	68(25.9)	38(23.0)	1.1(0.74-1.8)	0.51
Osteoporosis, n(%)	25(9.5)	16(9.7)	0.97(0.5-1.8)	0.94
Asthma, n(%)	18(6.8)	9(5.5)	1.2(0.5-2.9)	0.56
Thyroid disorders, n(%)	17(6.5)	15(9.1)	0.69(0.3-1.4)	0.31
Medication History				
No of medications[◊] Median(IQR)	4(4)	2(3)	n/a	<0.001***
Polypharmacy, n(%)	36(21.8)	111(42.2)	2.6(1.7-4.1)	0.001
Blood Pressure				
Systolic blood pressure, mean(SD)	134.8(20.3)	127.5(22.7)	n/a	0.001**
Diastolic blood pressure, mean(SD)	66.8(14.8)	66.8(13.9)	n/a	0.98
Orthostatic Hypotension, n(%)	62(23.6)	29(17.6)	1.4(0.88-2.3)	0.14
Physical Performance Scores, n(%)				
TUG ≥ 13.5s	134(51)	34(20.6)	3.9(2.5-6.2)	<0.001***
FR ≤ 18cm	78(29.7)	13(7.9)	4.8(2.6-9.1)	<0.001***
Reduced grip strength	215(81.7)	101(61.2)	2.9(1.8-4.6)	<0.001***
Potentially Inappropriate Prescriptions				
PIP=1	59(22.4)	38(23)	1.5(0.9-2.4)	0.09
PIP= 2	47(17.9)	14(8.5)	3.2(1.6-6.2)	<0. 001***
PIP≥ 3	50(19.0)	9(5.5)	5.4(2.5-11.5)	<0. 001***
PIP≥1	156(59.3)	61(37)	2.5(1.6-3.7)	<0. 001***

***p≤0.001, **p≤0.01, *p≤0.05

SD=standard deviation; OR= Odds ratio; CI Confidence Interval

TUG= timed up and go, FR=functional reach, Reduced Grip strength ≤20kg women, ≤30kg men

[a]Recurrent or injurious falls in the past 12-months; [b]No falls in the past 12 months

[c]Chi-squared test unless otherwise indicated; [d]Student's t-test

OH= Orthostatic Hypotension, SBP=systolic blood pressure, DBP=diastolic blood pressure, TUG=timed up and go, FR=functional reach, circulatory diseases= as any history of myocardial infarction, angina, stroke, TIA, or peripheral artery disease.
PIP=potentially inappropriate prescriptions

7.3.2. Potentially Inappropriate Prescriptions among Participants

We detected a total of 223 PIPs among our population according to STOPP2. The presence of PIP were significantly associated with falls (OR,1.8; 95%CI, 1.4-2.2; p<0.001). When we dichotomised PIP into no PIP and PIP≥1, 156(59.3%) of fallers and 61(37%) of non-fallers had at least one PIP (OR= 2.5; 95%CI; 1.6-3.7; p≤0.001) (Table 7.1).

The most common PIP among our sample were drugs for the endocrine system: sulphonylureas with a long duration of action (57 prescriptions). This was followed by the use of beta-adrenergic receptor blockers among diabetics with hypoglycemic episodes (30 prescriptions). The use of two or more drugs with anticholinergic properties (23 prescriptions) was also higher (see appendix 7.A for complete list).

7.3.3. Univariate Analysis for Factors Associated with Potentially Inappropriate Prescribing

The subanalysis for comparison of characteristics among fallers and nonfallers with no PIP and PIP≥1 showed that both groups with PIP≥1 were significantly more likely to be older, and had more comorbidities and medications. They were also significantly more likely to be diabetic and hypertensive, and were more likely to have OH and poorer TUG score among both fallers and non-fallers. Fallers with PIP≥1, in addition were more likely to be female, as well as have a preponderance of eye and circulatory diseases, and poorer FR score (Table 7.2).

Table 7.2: Characteristics of sample population according to PIP score.

	Fallers (n=263)				Non-Fallers (n=165)			
	No PIP (n=107)	**≥1 PIP (n=156)**	**OR(95%CI)**	**p-value**	**No PIP (n=104)**	**≥1 PIP (n=51)**	**OR(95%CI)**	**p-value**
Falls n(%)								
Indoor Falls	60(56.1)	94(60.3)	1.1(0.72-1.9)	0.49	-	-	-	-
Outdoor Falls	59(55.1)	91(58.3)	1.1(0.69-1.8)	0.60	-	-	-	-
Injurious Falls	49(45.8)	81(51.9)	1.2(0.78-2.1)	0.32	-	-	-	-
Basic Demographics								
Age, mean(SD)	73.8(7.2)	76.3(7.2)	1.0(1.0-1.1)[§]	0.004**	71.4(4.8)	73.2(6.3)	1.0(1-1.1)	0.05*
Gender (Male), n(%)	26(24.3)	58(37.2)	0.5(0.3-0.9)	0.02*	33(31.7)	22(36.1)	0.82(0.42-1.6)	0.56
Smoker, n(%)	7(6.5)	8(5.1)	0.7(0.27-2.1)	0.62	2(1.9)	5(8.2)	4.5(1-24.2)	0.05*
Alcohol, n(%)	10(9.3)	13(8.3)	0.8(0.4-2.1)	0.77	9(8.7)	8(13.1)	1.5(0.58-4.3)	0.36
BMI, mean(SD)	23.2(4.2)	24.1(3.9)	1.0(0.99-1.1)[§]	0.06	23.8(4.3)	24.5(3.5)	1.0(0.96-1.1)	0.32
Comorbidities, median(IQR)	2(3)	3(3)	-	<0.001***	1(3)	2(1)	-	<0.001***
Diabetes, n(%)	0(0)	95(60.9)	0.4(0.5-0.4)	<0.001***	0(0)	29(47.5)	0.2(0.1-0.3)	<0.001***
Hypertension, n(%)	47(43.9)	108(69.2)	2.8(1.7-4.7)	<0.001***	32(30.8)	42(68.9)	4.9(2.5-9.8)	<0.001***
Thyroid disease, n(%)	8(7.5)	9(5.8)	0.7(0.3-2.0)	0.58	7(6.7)	8(13.1)	2.1(0.71-6.1)	0.16
Eye disease, n(%)	42(39.3)	90(57.7)	2.1(1.2-3.4)	0.003**	29(27.9)	22(36.1)	1.4(0.74-2.8)	0.27
Circulatory disease, n(%)	10(9.3)	35(22.4)	2.8(1.3-5.9)	0.006**	7(6.7)	7(11.5)	1.7(0.59-5.4)	0.29
Arthritis, n(%)	25(23.4)	43(27.6)	1.2(0.71-2.2)	0.44	22(21.2)	16(26.2)	1.3(0.63-2.7)	0.45
Neoplasm, n(%)	2(1.9)	4(2.6)	1.3(0.24-7.6)	0.71	7(6.7)	3(4.9)	0.7(0.17-2.8)	0.63
Asthma, n(%)	7(6.5)	11(7.1)	1.1(0.40-2.8)	0.87	4(3.8)	5(8.2)	2.2(0.578-8.6)	0.23

Table 7.2 continued

Medication count, median(IQR)	2(4)	5(4)	-	<0.001$^{\Delta}$***	0(2)	4(4)	-	<0.001$^{\Delta}$***
Polypharmacy n(%)	16(15)	95(60.9)	8.8(4.7-16.4)	<0.001***	9(8.7)	27(44.3)	8.3(3.-19.6)	<0.001***
Blood Pressure								
SBP, mean(SD)	124.3(19.7)	129.8(24.4)	1.0(0.99-1.0)	0.26	135.1(18.5)	134.4(18.4)	1.0(0.08-1.0)	0.65
DBP, mean(SD)	65.5(13.7)	67.7(14.1)	1.0(0.98-1.0)	0.49	67.8(14.1)	65(15.8)	0.98(0.96-1.0)	0.20
OH n(%)	18(16.8)	44(28.2)	1.9(1.05-3.5)	0.03*	13(12.5)	16(26.2)	2.4(1.1-5.6)	0.02*
Physical Performance Scores								
TUG≥13.5s, , n(%)	38(35.5)	96(61.5)	2.8(1.6-4.7)	<0.001***	14(13.5)	20(32.8)	3.0(1.4-6.5)	0.004**
FR≤ 18cm, , n(%)	21(19.6)	57(36.5)	2.3(1.3-4.1)	0.004**	5(4.8)	8(13.1)	2.9(0.9-9.3)	0.06
Reduced grip strength, , n(%)	84(78.5)	131(84)	1.4(0.7-2.9)	0.26	58(55.5)	43(70.5)	1.6(0.8-3.2)	0.17

[§] mean difference with 95% confidence interval.

[Δ]p value calculated by using Mann Whitney U test; ***p≤0.001, **p≤0.01, *p≤0.05

OH= Orthostatic Hypotension, SBP=systolic blood pressure, DBP=diastolic blood pressure, TUG=timed up and go, FR=functional reach, circulatory diseases= as any history of myocardial infarction, angina, stroke, TIA, or peripheral artery disease.

7.3.4. Multivariate Analysis (Table 7.3)

Multivariate logistic regression was first used to adjust for potential confounders; PIP remained an independent predictor of recurrent and injurious falls (Model 1). Moreover, PIP, age, blood pressure, and poorer TUG and FR formed the best predictor model for recurrent and injurious falls (R^2= 0.276) (Model 2). Subsequently, when control participants were excluded; polypharmacy, TUG and OH were independent predictors of PIP among fallers (R^2=0.329) (Model 4).

Table 7.3: Multivariate Analysis to Determine Association of PIP with Falls and Factors Associated with Potentially Inappropriate Prescribing Among Fallers.

Falls (N= 428, fallers=263, nonfallers=165)				**PIP (fallers, n=263)**			
Characteristics	**OR(95%CI) ŧ**	**P value**	**R^2**	**Characteristics**	**OR(95%CI) ŧ**	**P value**	**R2**
Model 1			*0.315*	*Model 3*			*0.699*
Age	1.0(0.9-1.1)	0.17		Age	1.0(0.9-1.1)	0.79	
Gender	1.4(0.8-2.4)	0.17		Gender	0.7(0.3-1.7)	0.54	
Diabetes	1.2(0.6-2.5)	0.59		Diabetes	0.9(0.4-2.7)	0.99	
Hypertension	0.8(0.5-1.4)	0.55		Hypertension	1.1(0.5-2.6)	0.71	
Eye diseases	1.8(1.1-3.0)	0.02*		Eye diseases	1.2(0.5-2.8)	0.53	
Hearing disorders	0.9(0.3-2.6)	0.91		Circulatory diseases	0.6(0.2-1.7)	0.82	
Circulatory diseases	1.2(0.5-2.6)	0.59		Polypharmacy	4.7(1.8-11.7)	0.001**	
SBP at rest	0.9(0.8-0.9)	<0.001***		TUG≥ 13.5s	1.4(0.6-3.3)	0.39	
DBP at rest	1.0(1.0-1.1)	0.01*		FR≤ 18cm	1.5(0.6-3.7)	0.35	
TUG≥ 13.5s	2.0(1.1-3.5)	0.01*		Orthostatic hypotension	9.9(4.1-23.5)	<0.001***	
FR≤ 18cm	3.5(1.6-7.5)	0.001**					
Reduced grip strength	1.6(0.9-2.9)	0.09					
PIP	*1.4(1.0-1.8)*	*0.03**					
Model 2			*0.276*	*Model 4*			*0.329*
Age	1.0(1.0-1.1)	0.03*		Polypharmacy	8.4(4.4-16.1)	<0.001***	
SBP at rest	0.9(0.8-0.9)	<0.001***		TUG≥ 13.5s	2.3(1.2-4.1)	0.003**	
DBP at rest	1.0(1.0-1.1)	0.02*		Orthostatic hypotension	8.4(4.4-16.1)	0.001**	
TUG≥ 13.5s	2.1(1.2-3.6)	0.004**					
FR≤ 18cm	3.5(1.6-7.2)	0.001**					
PIP	1.5(1.1-1.9)	<0.001***					

***p≤0.001, **p≤0.01, *p≤0.05, ŧ analysed using binary logistic regression. TUG=timed up and go, FR=functional reach

7.4. Discussion

The presence of at least one PIP identified with STOPP2 was independently associated with falls in our cross-sectional study. Both fallers and non-fallers with PIP were older with more comorbidities, more medications and poorer gait and balance than those with no PIP. Older age, low blood pressure, deterioration in TUG and FR as well as PIP remained independent predictors for falls in the final model. Moreover, instead of age and gender, the presence of polypharmacy, OH and impaired TUG were independently associated with PIP among fallers.

The commonest PIP identified were linked to diabetes treatment, as our population had a higher proportion of individuals with diabetes which is explained by the high prevalence of diabetes among the South Asian population(Gujral et al., 2013). The preponderance of long acting sulfonylureas detected in our study is comparable to that reported by two previous Malaysian studies conducted in nursing homes, using the STOPP criteria(Al Aqqad et al., 2014; Chen et al., 2012). Hypoglycaemia due to hypoglycemics is a significant risk factor for falls in the older population (Berlie et al., 2010) which could worsen with long acting hypoglycemics. However, the inappropriate prescription of oral hypoglycemics is considered to be one of the most preventable adverse drugs events (Pretorius et al., 2013). The use of β-blockers among diabetics with frequent hypoglycaemia is considered inappropriate, as it could lead to masking of hypoglycemic symptoms by diminishing the adrenergic counter action of low blood glucose levels e.g. diminished occurrence of tremor and heart pounding(Sawicki et al., 2001). However, the frequent use of inappropriate medications for diabetes management among our sample may also be influenced by the limited availability of drugs in both government and private clinics (Hussain, 2008). Community based clinics currently dispense their own medications, with the issues of pharmacy dispensing currently being hotly debated.

The association between anticholinergic medications and falls has been reported in several studies previously (Berdot et al., 2009; Landi et al., 2014; A. Zia et al., 2016). Ageing is accompanied by increased sensitivity to the blockade of muscarinic receptors and increased permeability of the blood brain barrier, thereby enhancing the central nervous system effects of anticholinergic drugs. This cholinergic blockade in the brain is associated with reduced executive and motor functions and poorer gait and balance thus leading to an increased risk of falls (A. Zia et al., 2016). The complete avoidance of anticholinergic medications, however, is not always possible as many prescription and over-the-counter medications contain anticholinergic properties (Landi et al., 2014).

Older individuals with a history of recurrent and injurious falls were more likely to have at least one PIP compared to individuals without falls, this finding is consistent with that reported by several other studies (Berdot et al., 2009; Borenstein et al., 2013; Frankenthal et al., 2013, 2014; McMahon et al., 2014). These studies were mainly cross-sectional and were conducted in hospitals or institutions. An Irish study reported the prevalence of PIP among older fallers presenting to the emergency department to be 53% according to STOPP(McMahon et al., 2014). Two prospective cohort studies performed among hospitalised older adults showed a significant association of PIP with falls using the Beer's criteria (Borenstein et al., 2013) and STOPP criteria(Frankenthal et al., 2013). In addition, one randomised controlled trial in a long-term geriatric care facility revealed a significant reduction in falls following medication review intervention using the STOPP criteria (Frankenthal et al., 2014). However, we were only able to locate one study performed in a community sample. This French longitudinal study observed that users of PIP had a significantly increased risk of falling with a 32% prevalence of PIP among their cohort at baseline according to STOPP criteria (Berdot et al., 2009). Our proportion of individuals on PIP was comparable to the Irish study but higher than the French study, as we recruited high risk older adults

with recurrent or injurious falls at baseline. Our study was therefore the first to evaluate the use of the STOPP2 criteria in a community-dwelling population, and has potentially important implications in the direction of future intervention studies evaluating objective methods of conducting medication reviews for the secondary prevention of falls.

The predictors of PIP were poorer TUG, OH and polypharmacy. A poorer TUG score among fallers with PIP could be explained by the higher anticholinergic burden as the commonest PIP, since higher anticholinergic burden is associated with functional decline and poorer scores of TUG as a result (Landi et al., 2014; A. Zia et al., 2016). The association of OH with PIP could be explained by the higher proportion of fallers with diabetes mellitus, as OH is frequent among diabetics due to the complication of cardiovascular autonomic neuropathy (Gaspar et al., 2016).The occurrence of polypharmacy and hence PIP among fallers was high which is comparable studies linking PIP with polypharmacy(McMahon et al., 2014; Weng et al., 2013). While falling should trigger a medication review as a part of comprehensive assessment, the avoidance of polypharmacy entirely is not possible due to evidence based disease management (Pretorius et al., 2013).Therefore, avoidance of inappropriate polypharmacy during medication reviews according to some defined criteria could be helpful in falls risk reduction(A. Zia et al., 2015b). Hamilton et al also concluded in their prospective study that PIP according to the STOPP criteria are the significantly avoidable serious adverse drug events (Hamilton et al., 2011) which may also prove beneficial for high risk older fallers.

As our study was conducted in the unique setting of community-dwellers in a middle-income developing country of South-East Asia, the generalizability in the global context may be limited. As alluded to earlier, the availability of medications in

healthcare facilities in our setting is limited, for instance, unlike in previous studies, benzodiazepines which have always been considered to be strongly associated with falls (Berdot et al., 2009; McMahon et al., 2014), were less commonly prescribed in our study. The use of narcotic analgesics and tranquilizers in our setting is highly regulated in response to the high prevalence of recreational drug use in this region. However, as few studies on PIP have been conducted in South-East Asia and other developing countries, and none among the fallers, our study has conversely added important insights into PIP in alternative settings.

Our study has useful clinical and research implications for medication review among fallers. The inclusion of PIP rather than just withdrawal of drugs labelled as "falls-risk increasing drugs" during medication reviews may be a more advisable strategy since many are appropriately prescribed for secondary prophylaxis of chronic diseases and their withdrawal could lead to unacceptable increases in risks of adverse outcomes(A. Zia et al., 2015b). Our study therefore paves the ground for future prospective intervention studies to assess the effectiveness of STOPP2 as a tool in the prevention of recurrent or severe falls.

7.5. Conclusion

PIP is significantly associated with falls according to STOPP2. The use of STOPP2 as an objective tool during medication reviews may be beneficial in the assessment and prevention of falls among older adults. Future intervention studies are now required to evaluate the role of STOPP2 in the prevention of falls among older adults.

CHAPTER 8: EFFECT OF MEDICATION REVIEW INTERVENTION AMONG OLDER COMMUNITY DWELLING FALLERS IN MALAYSIA

8.1. Introduction

Previous studies have suggested that polypharmacy is an independent variable for falls in older people, while newer studies showed that in an older person receiving multiple medications, polypharmacy itself or polypharmacy with at least one other FRID may be a strong predictor for falls (Richardson et al., 2015; Ziere et al., 2006). The latest studies however suggest that a stronger link exists between falls and the type as well as number of FRID taken rather than polypharmacy on its own (Hammond et al., 2013). The studies by Milos et al and Bennet el at showed that severe falls and fall injuries were associated with FRID use among the older adults in a dose response fashion (Bennett et al., 2014; Laflamme et al., 2015; Milos et al., 2014).

Among older community dwellers, the FRID related to CNS effects are more likely to increase falls risk (French et al., 2006) followed by cardiovascular drugs (Milos et al., 2014; Poon et al., 2005), antidiabetics (Berlie et al., 2010) and the drugs with anticholinergic activity (Kersten et al., 2014). The systematic review by Hartikainen et al including 29 studies stated that the main group of drugs associated with an increased risk of falling was psychotropics: benzodiazepines, antidepressants, and antipsychotics while antiepileptics and blood pressure lowering drugs were weakly associated with falls (Hartikainen et al., 2007). Therefore, these FRID should ideally be avoided in all older fallers.

The Falls Prevention Guidelines now advocate careful medication reviews for polypharmacy reduction and FRID withdrawal among older adults presenting with falls (AGS/BGSguidelines, 2011). Studies have shown that the single intervention of

medication review and withdrawal for FRID could prove beneficial for falls reduction among older fallers [3,4]. Among older adults with polypharmacy and risk drugs, medication withdrawal not only reduces falls but may also improve drug compliance and patients' quality of life as well as reduce medication errors (Frankenthal et al., 2014). However, while medication review has been advocated in the management of falls by international guidelines, very few trials including fallers at baseline have positively demonstrated a reduction in the risk of falls with the withdrawal of culprit medications or reduction of dose burden (van der Cammen et al., 2014).

8.2. Objective

The objective of this study was to prospectively assess whether it is feasible and effective to perform fall prevention medication reviews and a subsequent FRID withdrawal, swapping with safer alternatives or dose reduction among community dwelling older fallers living in a middle income country.

8.3. Methodology

The setting, participants and baseline demographics methodology has been described in chapter 3. This study was aimed to be a pilot study for a future larger randomised controlled trial to determine the feasibility and effectiveness of medication review intervention among fallers.

8.3.1. Medication Assessment and Review

After obtaining medication data according to procedure mentioned in chapter 3 and recording it according to British National Formulary, 67th Edition (BNF, 2014), FRID were identified according to the metaanalysis by Bloch et al and Woollcott at al (Bloch et al., 2013; Woolcott et al., 2009).

All the participants in the intervention arm and receiving ≥1FRID received careful medication review by the geriatrician. The prescription and dosage of medication was compared against their medical conditions, other risk factors of falls as well as existence of low blood pressure at the time of the blood pressure testing. The medication review consisted of deprescribing of unnecessary or duplicative medications or dose reduction or swapping with safer alternatives of those medications which could not be completely omitted.

8.3.2. Statistical Analysis

Continuous data were evaluated for normal distributions and comparisons were made using the independent t-test or Mann-Whitney U where appropriate. Categorical data were expressed as frequencies and the statistical significance was determined with the Chi-squared test. To determine the effectiveness of the intervention, we conducted a survival analysis using time to first fall as a dependent variable, for which the Kaplan-Meier method was used. To determine the relationship between the intervention time to first fall and time to second fall, a Cox regression analysis was conducted. A p-value of <0.05 was considered statistically significant. Sample size calculations for this study had been described in a previous section (Section 3.2.2)

8.4. Results

8.4.1. Participants and Baseline Demographics

Two hundred and four fallers matched our inclusion criteria; 106(52.2%) fallers were randomised to the non-intervention arm and 98(47.8%) in the intervention arm. The diaries return rate in non-intervention arm was 71(66.4%) while intervention arm was 66(66.3%). The participants who were lost to follow up were excluded from the final analysis i.e. n=35 from the non-intervention group and n=32 from the intervention

group. The analysis was performed for the remaining 66 participants in the intervention group and 71 participants in the non-intervention group (Flow chart 8.1).

Due to randomisation, no differences in the age, gender, BMI, number of comorbidities or any medical condition was observed between the intervention and the non-intervention groups (Table 8.1). There were no significant differences in individual FRID use at baseline between the intervention and non-intervention groups (Table 8.2).

8.4.2. Medication Review Assessment

Medication review was given to the entire intervention group (n=66), it was possible to withdraw, swap or reduce dosage in 21(31.8%) of the 66 fallers in the intervention group; 13 antihypertensives were stopped, 2 were swapped with safer alternatives (alfuzocin was swapped with tamsulosin and nifedipine was switched with amlodipine) while 6 antihypertensives were reduced in dosage due to the lower blood pressure. Figure 2 shows the survival curve, no statistically significant differences were found (log rank test = 1.94; p=0.16). Fig 3 shows the statistical curve for intervention and time to second fall, no significance was observed. Table 8.3 provides the results of the Cox proportional hazard model; there was no difference in the time to first fall (Hazard ratio for time to first fall= 0.90; 95%CI, 0.51-1.50; p=0.71), and time to second fall (Hazard ratio for time to first fall= 0.90; 95%CI, 0.51-1.50; p=0.71) between the intervention and non-intervention groups.

8.5. Discussion

This substudy of a randomised controlled trial demonstrated that although a significant number of fallers were on falls risk drugs; they were provided careful reviews of all their regular medications in the effort to reduce consumption of FRID, it was possible to withdraw, reduce dosage or swap drugs in a very small proportion of

intervention group. No difference was observed in the time to first fall between the intervention and the non-intervention groups after one year of follow up.

Our results are in consistency with other studies which reported that either FRID cannot be reduced or it did not show a significant reduction in falls (Casteel et al., 2011; Sjoberg et al., 2013; Weber et al., 2008) but are opposed to other studies with beneficial effect on falls reduction (Campbell et al., 1999; Frankenthal et al., 2014; Salonoja et al., 2012; van der Velde, Stricker, et al., 2007). There are few possible reasons for the small number of withdrawals than expected, as well as non-effective medication withdrawal intervention. The use of psychotropics among our sample was very small due to their government controlled availability in this region and the relatively low acceptance of psychiatric treatment (Hussain, 2008). The medication withdrawal trials, in general, have shown psychotropic withdrawal to be an effective intervention for falls reduction (Rothschild et al., 2007). Out of four studies (two prospective and two RCT) demonstrating the effect of medication withdrawal on falls reduction; three have shown that the withdrawal of psychotropics led to a significant reduction in falls (Campbell et al., 1999; Frankenthal et al., 2014; Salonoja et al., 2012). However, although the RCT by Campbell et al showed that withdrawal of psychotropics led to a 66% reduction in falls rate during their 44 weeks of follow up, it was difficult to achieve permanent withdrawal as 47% of the participants from the withdrawal group started taking medications only after one month of completion of trial (Campbell et al., 1999). The prospective study by Velde et al was the only one to report benefits of cardiovascular drug withdrawal among other FRID on falls reduction during the three months follow up period (van der Velde, Stricker, et al., 2007). The authors included high risk fallers (≥1 fall in the past year) but intervention was performed amongst those participants with higher number of comorbidities and hence a higher FRID use at baseline. We, on the contrary, tested the potential effectiveness of careful medication review through a

randomized-controlled design with the intention of eliminating potential bias. Many previous studies did not always randomize or were uncontrolled, and hence were inherently biased. Despite this, international guidelines have been drawn from the poor quality evidence available previously.

Another reason for non-feasibility of medication modification after review may be that the high risk fallers have higher number of comorbidities at baseline and FRID include treatment for serious diagnoses (cardiovascular drugs) or symptom management. Among these older adults, their attending physicians may already have considered and tried different drug treatment strategies and hence the geriatrician may be less inclined to change drugs taken for these purposes. Moreover, it should be noted that the follow up periods for the above mentioned studies with successful medication intervention is short and longer term effects of withdrawal on end organ damage, quality of life and survival rates have not been evaluated. This suggests that the shorter term fall reduction benefit of medication withdrawal might pose a bigger harm to the overall health and quality of life of an older adult. Because of this caution of longer term threat, our geriatrician was able to withdraw only a few medications among patients with lower blood pressure or postural drop in blood pressure only and not the ones necessary for the effective management of hypertension, stroke, diabetes or other noncommunicable diseases.

Another reason for negative outcomes may be that we did not use any criteria for inappropriate medication withdrawal or anticholinergic medication withdrawal. We did not choose this approach because none of the previous falls studies on medication withdrawal have used any criteria. The medication withdrawal trials according to inappropriate medication usage have also shown positive results with the highest withdrawal rate seen with anticholinergics (Starner et al., 2009; Thompson Coon et al.,

2014), but they have never been used among a sample of older adults with falls. The RCT by Frankenthal et al included adults aged 65 and older on at least one medication who were then randomized to receive usual pharmaceutical care or undergo medication intervention according to STOPP/START criteria. They found that the intervention group had reduced number of medications, lesser falls and decreased cost due to medications and falls (Frankenthal et al., 2014). Therefore, future studies should consider focussing on inappropriately prescribed drugs among older adults with history of falls and by reducing anticholinergic burden rather than focussing on FRID consisting of inevitable medications for disease management.

While, this study comprised a pre-planned subgroup analysis of a larger randomized-controlled study rather than a study with the designated primary purposes of assessing the effects of medication review among older individuals with recurrent or injurious falls. Nevertheless, to our knowledge, this study represents the only Malaysian study thus far to evaluate medication management using actual falls recurrence as the primary outcome. The prospective design and randomly assigned intervention and non-intervention groups are the strengths of the study. However, as it was a substudy of a multifactorial intervention RCT, our participants in the intervention arm would have also received individually tailored multifactorial interventions including physiotherapy, home safety assessment, visual interventions, cardiovascular assessments and falls education. Moreover, the if the follow up were reduced to three months, we might have gotten a clearer picture of the effect of drug intervention on falls as compared to one year long follow ups where the patients might be put on some new drugs or some drugs might be omitted from their regimens by their physicians as the participants may get older, frailer and develop new pathologies. Moreover, another reason for nonsignificant effect of intervention may also be because the change in the number of FRID was

smaller and the defaulter rate was higher thus this study did not have the power to detect differences.

The results of this subanalysis of a larger randomized controlled study therefore challenge the recommendations of existing guidelines on medication review (AGS/BGSguidelines, 2011). It further supports the results of two previous meta-analyses suggesting the limited evidence on the benefits of cardiovascular medication review on falls outcomes (Cumming, 1998; Leipzig et al., 1999b). As few of our participants were on antipsychotic and other centrally acting drugs, this will explain the discrepancies between our findings and that of previously published studies advocating medication review among older fallers. The findings of our study will now inform the power calculations and study design of a larger, possibly multicentre, randomized controlled study evaluating the potential benefits of details medication review, using the tools evaluated earlier in this thesis, of medication management among older individuals with a history of falls. Outcome measures should include other disease outcomes aside from falls recurrence, and follow-up duration should extend beyond the one year commonly used in falls intervention studies.

8.6. Conclusion

We can conclude that although regular review of medications is advisable among older patients receiving multiple medications but the focus of the medication could not be FRID reduction or withdrawal as it may not be feasible while taking patient's comorbidities and other health factors into account. Therefore, it is emphasized that withdrawal of medications must be individually tailored depending upon patients' cumulative risk factors for the risk of falls, longer term effect of medication withdrawal on comorbidities and after weighing the benefit versus risk ratio.

Table 8.1: Baseline characteristics of the intervention and non-intervention group.

Characteristics	Intervention (n=66)	Non-intervention (n=71)	P value
Age, mean(SD)	75.6(6.7)	77.0(6.8)	0.23
Gender (Male) , n(%)	19(28.8)	28(39.4)	0.19
Smoker, n(%)	1(1.5)	5(7)	0.11
Alcohol, n(%)	2(3)	5(7)	0.28
Body Mass Index, mean(SD)	24.1(3.7)	22.4(3.6)	0.06
Medical History, n(%)			
No. of comorbidities	3(2)	3(2)	0.74
Diabetes	25(37.9)	32(45.1)	0.39
Hypertension	45(68.2)	56(78.9)	0.15
Arthritis	19(28.8)	17(23.9)	0.52
Neoplasm	1(1.5)	2(2.8)	0.60
Thyroid diseases	4(6.1)	4(5.6)	0.93
Circulatory diseases	12(18.2)	15(21.1)	0.63
Cataract	30(45.5)	33(46.5)	0.90
Blood Pressure			
Systolic blood pressure, mean(SD)	131.9(20.4)	125.1(28.1)	0.11
Diastolic blood pressure, mean(SD)	64.2(13.6)	66.4(12.9)	0.35
Orthostatic Hypotension, n(%)	18(25.4)	17(24.8)	0.99

Table 8.2: FRID usage at baseline in the intervention and non-intervention group.

FRID, n(%)	Intervention (n=66)	Non-intervention (n=71)	P value
Antihistamines	7(10.6)	4(5.6)	0.38
Thyroid meds	5(7.6)	3(4.2)	0.40
Alpha-blockers	12(18.2)	7(9.9)	0.15
beta-blockers	20(30.3)	18(25.4)	0.51
ACE_Inhibitors	11(16.7)	14(19.7)	0.64
Angiotensin receptor antagonists	17(25.8)	23(32.4)	0.39
Calcium Channel Blockers	25(37.9)	31(43.7)	0.49
Nitrates	2(3)	3(4.2)	0.22
Proton Pump Inhibitors	5(7.6)	8(11.3)	0.86
NSAIDS	8(12.1)	3(4.2)	0.08
Aspirin	18(27.3)	21(29.6)	0.76
Biguanides	18(27.3)	21(29.6)	0.76
Sulfonylureas	16(24.2)	12(16.9)	0.28
DPP4I	4(6.1)	3(4.2)	0.39
Insulin	4(6.1)	8(11.3)	0.28

Table 8.3: Hazard Ratio for Falls using Cox Regression.

Medical Review	B	Wald Test	P-value	HR(95%CI)
Time to first fall	0.104	0.134	0.715	0.90(0.51-1.5)
Time to second fall	0.146	0.137	0.711	0.86(0.40-1.8)

HR= hazard ratio, CI= confidence Interval, Dependent variable= time until first fall, Independent variable= Intervention versus non-intervention group.

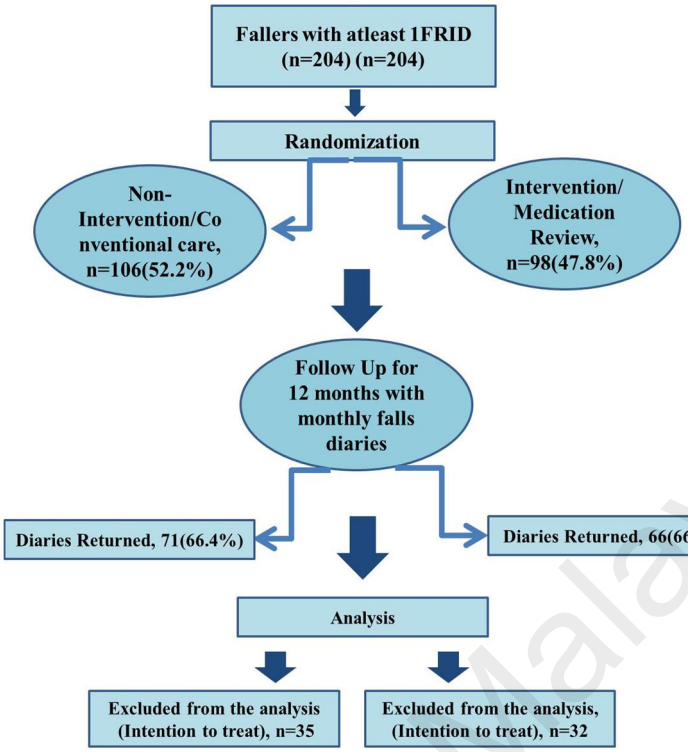


Figure 8.1: Flowchart for Medication Intervention in MyFAIT study.

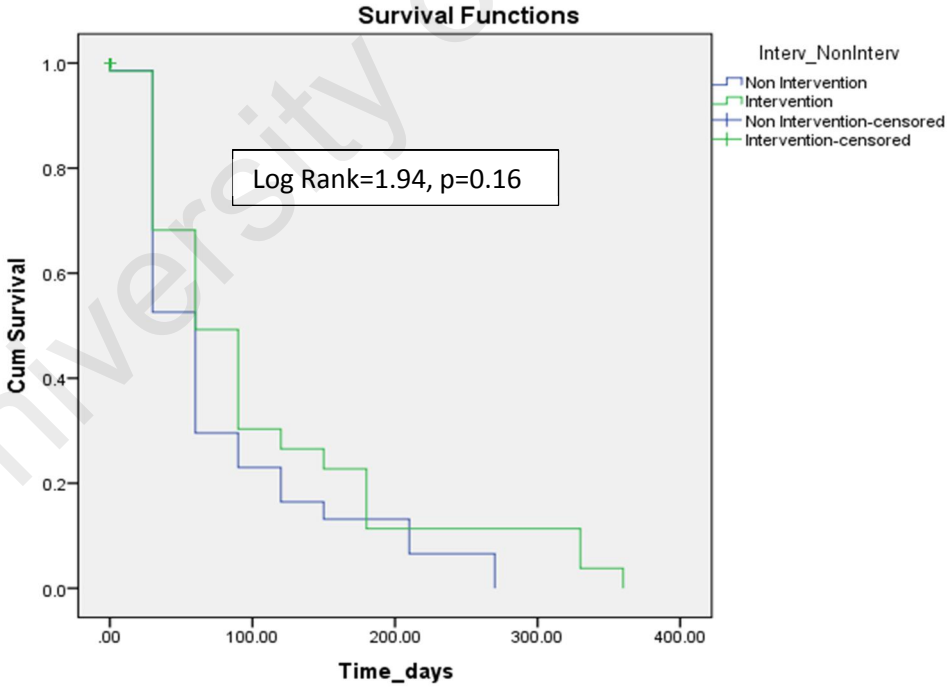


Figure 8.2: Survival Analysis; Comparison between two groups in the incidence of falls that occurred after 12 months of follow up

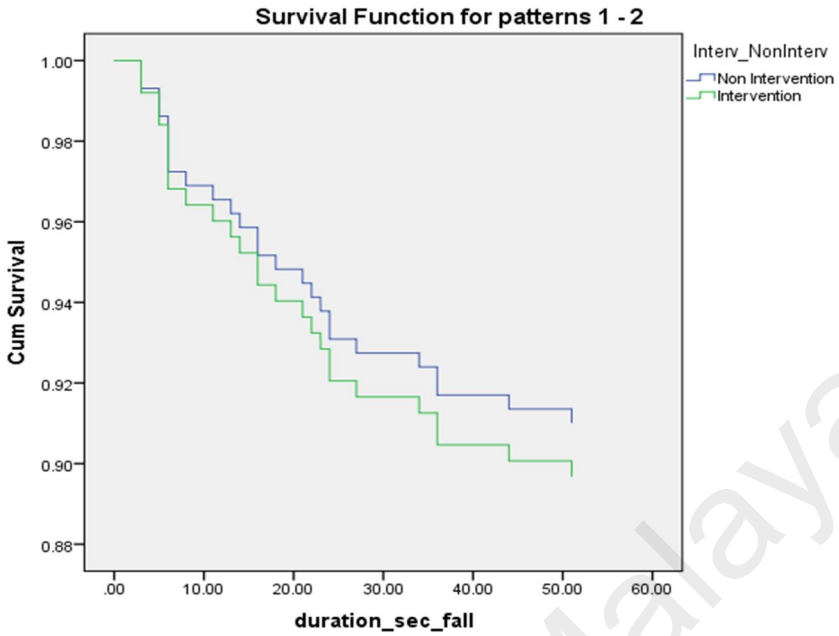


Fig 8.3: survival analysis for time to second fall

CHAPTER 9: CONCLUSION

9.1. Discussion

This study sought to investigate the culprit medications and their mechanisms associated with falls and demonstrated that the use of single FRID is safer and fails to show any association with falls even among our high risk fallers sample. The presence of PIP, multiple FRID and ACB even with the lowest score; instead of polypharmacy is associated with falls among older adults. The prescription of antihypertensive is safer among older adults with history of serious and injurious falls contrary to previous preconceptions. However, lower SBP while standing is significantly associated with falls. The anticholinergic burden is seen to mediate through poor functional performance scores i.e. TUG and FR. An attempt to reduce FRID burden via careful medication review remains, however unsuccessful and it is not feasible to withdraw antihypertensives or antidiabetics etc. without potentially adversely affecting patient's disease management.

The most significant finding of this study is that the individual FRID especially antihypertensives are safer for use among older adults with a history of recurrent or injurious falls. Therefore the medication reviews for older fallers should specifically focus on the multiple FRID, anticholinergic activity of drugs as well as the inappropriateness of drugs instead of counting the total number for prescribed drugs or withdrawing the FRID necessary for optimal disease management. Our study is in line with the recent studies which have now beginning to highlight this issue that the type of medication is more important than the number (Bennett et al., 2014; Milos et al., 2014) . Our study was the first to state that the increased number of high risk medication may be the reason for previously established association between the total number of drugs

and falls. The presence of polypharmacy, therefore, should alarm the physician for the careful review of medication but should not be a criterion for medication withdrawal among older fallers. As, the association of postural blood pressure drop (widely considered as a side effect of antihypertensives), with falls and antihypertensives has never been evaluated in a single study, our study suggests that the presence of lower SBP while standing instead of OH must be evaluated in older fallers irrespective of the use of antihypertensives.

The present study was also the first to suggest that in an older faller with a poor TUG and FR score, anticholinergic burden, even at low doses needs to be evaluated and withdrawal of these drugs should be considered. In addition, the association of PIP with falls using STOPP2 identifies the risk drugs in a systematic way which may therefore make it easier to swap them with safer alternatives without affecting the quality of disease management. The deprescribing of medication based on simple review of the FRID was unfeasible and unsuccessful in the reduction of falls like most studies involving non-psychotropics withdrawals (Casteel et al., 2011; Sjoberg et al., 2013; Weber et al., 2008) because of the obvious greater risk of exposing an older adult to end organ damage and mortality.

While this was the first study to examine the association between medications and falls among older adults in the Malaysia, our study has limitations. First, generalization is an issue because we involved the community dwellers in the urban setting, the use of FRID, over the counter anticholinergics or PIP may be higher in rural areas. Our case control analysis has the limitation that falls were recorded retrospectively and therefore may be subject to recall bias. Moreover, causal relationships could not be established because of its cross sectional design. The prospective study is limited because the adults were followed up for falls only and not

for other comorbidities, compliance and quality of life or adverse drug events because of limited time and resources.

9.2. Future Recommendations

The current study highlights the new dimensions as well as highlights the problem areas in the previously established association between FRID and falls. While it is suggested by our study that the polypharmacy and FRID can no longer be considered as a single entity while assessing the risk of falls for an older adult, there are a few things that should have been done differently. The comprehensive association between postural blood pressure changes, antihypertensives and falls requires prospective intervention studies to determine the blood pressure treatment targets with the justifiable use of antihypertensives for a high risk group of older fallers without increasing the risk of future falls. Moreover, the prospective intervention studies on medication reviews to reduce inappropriate prescribing and anticholinergic load while simultaneously including the patient compliance and effect of those reviews not only on falls but also on pathologies for the longer term may provide useful answers as well as more applicability in terms of clinical outcomes among high risk fallers. The following flow chart (Fig. 9.1) shows a recommendation for future improvement according to the findings of this study.

9.3. Conclusion

The presence of multiple FRID, cumulative anticholinergic burden and PIP is more likely to be associated with falls than mere polypharmacy. While the medication reviews based on polypharmacy and FRID withdrawal have only been successful for psychotropics, the deprescribing of anticholinergics and other inappropriate drugs should be considered for falls prevention among older adults. The presence of low SBP

while standing instead of OH, needs to be evaluated among high risk fallers on antihypertensives. Prescriptions for older patients should be individualized and subject to frequent periodical reviews while consistently striving to minimize inappropriate prescribing. Large, adequately powered , randomized-controlled studies, evaluating the benefits of medicines management informed by anticholinergic burden scores and appropriate prescribing tools and based on recent published knowledge on medications and falls, are now urgently required.

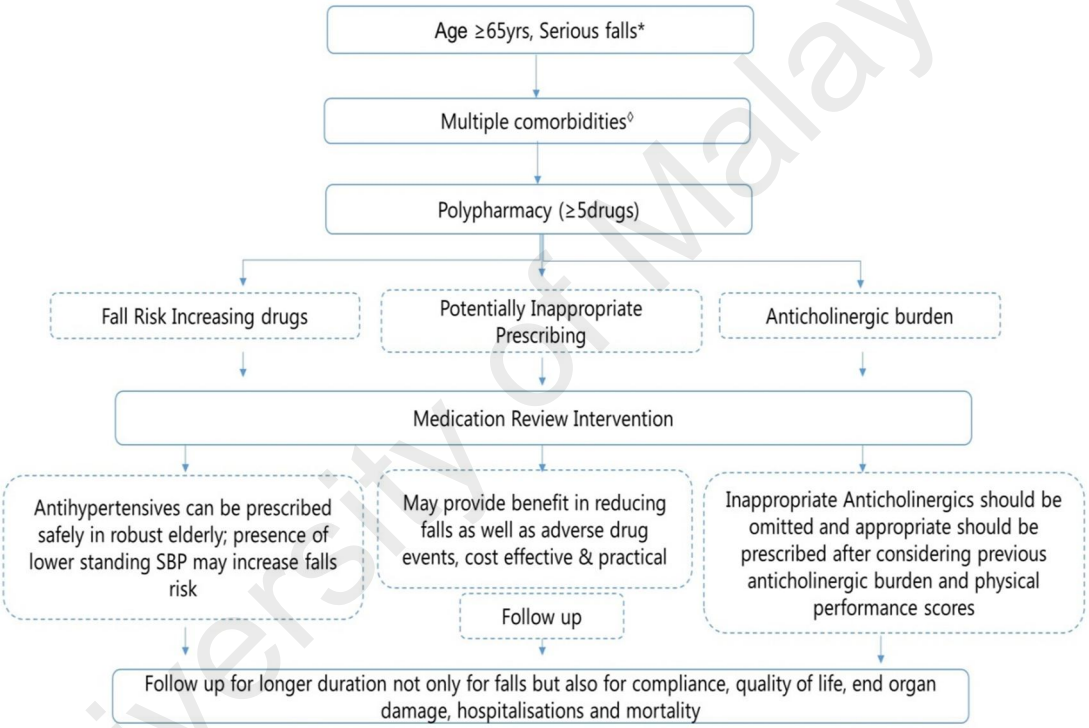


Figure 9.1: Flow chart for evaluation and review of medication among older fallers based on literature review (*, ≥2 falls or 1 fall with injury; ◊, ≥2 comorbidities).

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LIST OF PUBLICATIONS AND PRESENTATIONS

Published

1. Anam Zia, Shahrul B. Kamaruzzaman, Maw Pin Tan, "Blood pressure lowering therapy in older people: does it really cause postural hypotension or falls?" (Review Paper) Published in "Postgraduate Medicine" (ISI-listed, Q2).
2. Anam Zia, Shahrul B. Kamaruzzaman, Maw Pin Tan, "Polypharmacy and Falls in Older People: Balancing Evidence-based Medicine against Falls Risk" (Review Paper) Published in "Postgraduate Medicine" (ISI-listed, Q2).
3. Anam Zia, Shahrul B. Kamaruzzaman, Phyo Kyaw Myint, Maw Pin Tan, "The association of antihypertensives with postural blood pressure and falls among seniors residing in community: a case control study" (Research Paper) accepted by European Journal of Clinical Investigations (ISI-listed Q1).
4. Anam Zia, Shahrul B. Kamaruzzaman, Phyo Kyaw Myint, Maw Pin Tan, "Anticholinergic Burden is Associated with Recurrent and Injurious Falls in Older Individuals" (Research Paper) accepted by Maturitas (ISI-listed, Q2).
5. Anam Zia, Shahrul B. Kamaruzzaman, Maw Pin Tan, "Fall-risk-increasing-drugs account for Polypharmacy associated Falls: a case-control study" (Research paper) submitted to geriatrics and gerontology international (ISI-listed, Q3).

Submitted

6. Anam Zia, Shahrul B. Kamaruzzaman, Maw Pin Tan, "Association of inappropriate prescriptions with Falls among Community Dwelling Older Adults" (Research paper), submitted to Age and Aging.
7. Anam Zia, Shahrul B. Kamaruzzaman, Maw Pin Tan, "Prospective evaluation of the association between medications and recurrent and injurious falls in the

community dwelling older Malaysians" (Research paper), submitted to geriatrics and gerontology international.

ORAL/POSTER PRESENTATIONS

1. Oral Presentation, "Minimal standing blood pressure instead of orthostatic hypotension is associated with recurrent and injurious falls". IAGG Congress 2015, Thailand - 19-22 October, 2015
2. Poster Presentation, "The Number of Fall-risk Increasing Drug is a Risk Factor for Falls in Community Dwelling Older Adults" IAGG Congress 2015, Thailand - 19-22 October, 2015
3. Oral Presentation, "The Relationship between analgesics and Osteoarthritis in Older fallers in a Multi-racial Nation", IAGG Congress 2015, Thailand - 19-22 October, 2015
4. Oral Presentation, "Inappropriate prescribing among community dwelling older fallers". 11th National Geriatric Conference (NGC), August 2015, Kualalumpur.
5. Poster Presentation, "Older Fallers are more likely to Consume Two or More Antihypertensives than Non-fallers" in IAGG, April 2015, Dublin
6. Oral Presentation "Is the number of antihypertensives associated with orthostatic hypotension and falls in the community dwelling elderly?" in Asia Pacific Geriatric Conference, June 2014, Taipei, Taiwan. [Awarded first prize for oral presentation].
7. Oral Presentation "Increased Pulse Pressure and risk of falling in the geriatric population" [oral]. Annual Scientific Meeting 2014, Australia and New Zealand Society of Geriatric Medicine (ANZSGM), May 2014, Melbourne, Australia.

8. Poster Presentation “The Association between Medicines and Falls in the Geriatric Population of Malaysia”. 9th National Geriatrics Conference, September 2013, Kuala Lumpur.
9. Oral Presentation "Medication Associated Falls in Community-dwelling Older Malaysians". 10th National Geriatric Conference (NGC), June 2014, Ipoh. [Awarded prize for best oral presentation].
10. Oral Presentation "Association between Antidiabetic Medications and Falls among Older People ". Malaysian Healthy Ageing Society (MHAS). April 2014, Kuala Lumpur