Sex, Drugs and Dementia

by

Shanna C. Trenaman

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ABSTRACT

Older adults comprise the greatest segment of the population that use medications. Aging, sex and genetic considerations alter medication metabolism which modifies drug exposure, effect and risk of toxicity. Anticholinergic medications are potentially inappropriate for older adults with dementia. This dissertation investigates the issues relating to anticholinergic medications from an interdisciplinary approach: 1) it reviews the pharmacology of anticholinergic drugs including the role of age, sex and genetics in drug pharmacokinetics, 2) uses scoping review methodology to explore sex-differences in drug use by older adults with dementia, 3) describes development of a novel cellular reporter assay to measure and identify anticholinergic medications, 4) completes a drug-use evaluation and sex-based analysis of medication use by older adults with dementia in the province of Nova Scotia including four prescribing cascades and other prescribing indicators, and 5) details patient and stakeholder engagement to develop an intervention to support pharmacist-led deprescribing in primary care.

Older age, female sex and polymorphism of CYP2D6 to a poor metabolizer variant increases drug exposure and risk of adverse drug events related to anticholinergic medication. Prescribing indicators in older adults with dementia in Nova Scotia show concerning trends, including use of anticholinergic medications by 64.1% of Nova Scotia Seniors' Pharmacare Beneficiaries with dementia (NSSPBD). Prescribing cascades occur with 0.2% of NSSPBD receiving a bladder anticholinergic to treat cholinesterase inhibitor induced urinary incontinence and 2.6% using proton pump inhibitors in response to adverse drug reactions caused by high anticholinergic burden. Women have increased exposure to psychoactive medications, but this varies by home setting with men receiving more antipsychotics when they reside in a care home or hospital. Men receive more cholinesterase inhibitors than women. To better identify anticholinergic medications a cell-based assay was explored which shows promise as a viable method to quantify anticholinergic activity of medications. Patients and other stakeholders see benefit in deprescribing and support pharmacist-led deprescribing interventions in primary care which can begin to address the concerning level of anticholinergic medication use in older adults with dementia.

LIST OF ABBREVIATIONS AND SYMBOLS USED

ACB	Anticholinergic Cognitive Burden
AD	Alzheimer's Disease
ADNI	Alzheimer's Disease Neuroimaging Initiative
ADME	Absorption, Distribution, Metabolism, and Excretion
ADS	Anticholinergic Drug Scale
ANOVA	Analysis of Variance
ARS	Anticholinergic Risk Scale
ATC	Anatomical Therapeutic Chemical
AUC	Area Under the Curve
$AUC_{0\text{-}8h}$	Area Under the Curve from time 0 to time 8 hours
$AUC_{0\text{-}t}$	Area Under the Curve from time 0 to time of interest
$AUC_{0\text{-}\infty}$	Area Under the Curve from time 0 to time infinity
AUC_{∞}	Area Under the Curve at time infinity
BPSD	Behavioural and Psychological Symptoms of Dementia
BVRT	Benton Visual Retention Test
°C	Degrees Celsius
CHRM1	Cholinergic Receptor Muscarinic 1 (human)
CI	Confidence Interval
CIHI	Canadian Institute for Health Information
C_{Max}	Maximum Concentration often referring to maximum concentration in serum in pharmacokinetic analysis
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
CYP	Cytochrome P450
D_2	Dopamine 2 Receptors
DAD	Discharge Abstract Database
DBI	Drug Burden Index
DIS	Drug Information System
DMSO	Dimethyl Sulfoxide
EC_{50}	Half Maximal Effective Concentration

EC_{80}	80% of the Maximal Effective Concentration
ECG	Electrocardiogram
EM	Extensive Metabolizer
EPIC	The European Prospective Investigation Into Cancer in Norfolk
F	Oral Bioavailability
g	Gram
GPCR	G-protein Coupled Receptor
h	Hour
H2RA	Histamine-2 Receptor Antagonist
HDNS	Health Data Nova Scotia
5-HMT	5-hydroxymethyl tolterodine
HVLT-R	Hopkins Verbal Learning Test
^{3}H-QNB	Tritiated Quinuclidnyl Benzilate
HR	Hazard Ratio
HT	Plate Reader version
IADL	Instrumental Activities of Daily Living
IC_{50}	Half Maximal Inhibitory Concentration
ICD	International Classification of Diseases Clinical Modification
IM	Intermediate Metabolizer
IST	Information Sampling Task
IR	Immediate Release
IV	Intravenous
kg	Kilogram
L	Liter
M	Molar
m	Meter
M receptor	Muscarinic Receptor
M1 receptor	Muscarinic 1 Receptor
M2 receptor	Muscarinic 2 Receptor
M3 receptor	Muscarinic 3 Receptor
M4 receptor	Muscarinic 4 Receptor

M5 receptor	Muscarinic 5 Receptor
MAI	Medication Appropriateness Index
MED	MSI Physician's Billings
mg	Milligram
min	Minute
mL	Milliliter
MMSE	Mini-Mental State Examination
ms	Millisecond
MSI	Medical Services Insurance
MSSU	Maritime Strategy for Patient Oriented Research Support Unit
NB	New Brunswick
ng	Nanogram
nmol	Nanomol
NSAID	Non-Steroidal Anti-inflammatory Drug
NS	Nova Scotia
NSSP	Nova Scotia Seniors' Pharmacare
NSSPB	Nova Scotia Seniors' Pharmacare Beneficiaries
NSSPBD	Nova Scotia Seniors' Pharmacare Beneficiaries with Dementia
OR	Odds Ratio
PHARM	Nova Scotia Seniors' Pharmacare Database
PIM	Potentially Inappropriate Medication
PPI	Proton Pump Inhibitor
PM	Poor Metabolizer
QRS	In electrocardiography refers to a combination of the Q wave, R wave and S wave, the "QRS complex"
QT	In electrocardiography the time from the start of the Q wave to the end of the T wave
QT_A	In electrocardiography refers to the QT apex, the interval measured from the onset of the QRS complex to the apex of the T wave
QT_c	QT interval corrected for heart rate
RR	Relative Risk

Rx	Prescription
SAA	Serum Anticholinergic Activity
SD	Standard Deviation
SPOR	Strategy for Patient Oriented Research
SSRI	Selective Serotonin Reuptake Inhibitor
t	Time
$t_{1/2}$	Elimination Half-Life
TBC	Total Body Clearance
T-wave	In electrocardiography, the T wave represents the repolarization of the ventricles
T_{End}	End Time of T-wave
T_{Max}	Maximum Time
T_{peak}	Time at the Peak of T-wave
U2OS	Human Bone Osteosarcoma Epithelial Cells
µg	Microgram
UK	United Kingdom
µL	Microliter
µM	Micromolar
UK	United Kingdom
UM	Ultra-Rapid Metabolizer
USA	United States of America
V_d	Volume of Distribution
VITAL	Vital Statistics Database

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CHAPTER 1 INTRODUCTION

Medications play a major positive role in maintaining health and preventing morbidity and mortality (GBD 2017 Causes of Death Collaborators, 2018; Lichtenberg, 2005, 2019a, 2019b). However, not all medication use provides benefit exceeding associated risks. Potentially inappropriate medication (PIM) is a common term that refers to medications used with risks that may exceed benefits (By the 2019 American Geriatrics Society Beers Criteria® Update Expert Panel, 2019; By the American Geriatrics Society 2015 Beers Criteria Update Expert Panel, 2015; Cross et al., 2017; Lund et al., 2010; O'Mahony et al., 2015). PIM use is predictive of adverse drug events. Increasing inappropriateness, as measured by a one-point increase in the Medication Appropriateness Index (MAI) has been associated with a 13% increase in the odds of an adverse drug event (Lund et al., 2010).

The use of multiple medications is known as polypharmacy (Masnoon et al., 2017; Taghy et al., 2020). Polypharmacy is very common. Two out of every three Canadians over the age of 65 take at least five different prescription medications and one out of every four Canadians over the age of 65 take at least ten different medications (Canadian Institute of Health Information, 2016; Rotermann et al., 2014). This high level of medication use increases the likelihood of PIM use, which is an enormous problem for the healthcare system (Fried & Mecca, 2019; Sharp et al., 2019). Observational studies in the USA identify between 21 and 99% of community-dwelling older adults being prescribed a PIM (Lund et al., 2010; Zhan et al., 2001). High medication use, PIM use and age increases risks from medications for older adults. Adults 65 years of age and older are at a two-fold greater risk of drug-related hospitalization due to an adverse drug event (Cresswell et al., 2007; Pirmohamed et al., 2004). Harms of polypharmacy disproportionally effect the greatest users of medications, who are older adults, and these harms are more significant for older adults with dementia as they may experience further impaired cognition (Moga et al., 2017) and increased mortality (Cross et al., 2017).

To help guide clinicians, many respected authorities have developed tools to identify PIM use and assist with improving prescribing. Two commonly used tools in Geriatric

Medicine are the Beers criteria (By the 2019 American Geriatrics Society Beers Criteria® Update Expert Panel, 2019; By the American Geriatrics Society 2015 Beers Criteria Update Expert Panel, 2015) and the STOPP/START criteria (Khodyakov et al., 2017; O'Mahony et al., 2015) both of which offer guidance to clinicians as to which medications increase the risk of adverse outcomes for older adults. These tools compile expert opinion on best practice for prescribing in older adults, however their existence does not guarantee they will be followed.

In addition to older adults with dementia being prescribed and exposed to more medications, there are other considerations that increase the risk of adverse drug events. Advanced age and presence of some medical conditions can precipitate alterations in drug pharmacokinetics, drug pharmacodynamics, and disruptions in the blood brain barrier, all of which alter drug exposure and contribute to the increased risk of adverse drug events (Aichhorn et al., 2005; Marazziti et al., 2013). Sex and genetic differences play a role in drug disposition which influences drug exposure, risk of adverse events and toxicity (Adehin & Bolaji, 2015; Aichhorn et al., 2005; Bebia et al., 2004; Degen & Phillips, 1996; Gorski et al., 1998; Grossman et al., 1963; Krecic-Shepard, Barnas, et al., 2000; Marazziti et al., 2013; McCune et al., 2001; Ou-Yang et al., 2000; Oztekin et al., 2005; Paine et al., 2005; Tamminga & Ossterhuis, 1999). Gender may also play a role in medication use. Societal and cultural pressures and norms lead to gendered prescribing practices which influence medication use (Assari et al., 2019; Schnegg et al., 2019). Gender-based analysis studies show that women experience more adverse drug events than men (Alturki et al., 2020; Rydberg et al., 2018; Sørup et al., 2020; Watson et al., 2019). Increased adverse events in women is likely a multifactorial phenomenon explained by both sex and gender differences (Paula A. Rochon et al., 2018; Salahudeen et al., 2015; Schoot et al., 2019; Waade et al., 2012).

Due to the high rates of chronic medication use in older adults, PIM is of concern in this population. Managing PIM use in older adults with dementia becomes more difficult for clinicians because during their disease progression they lose the ability to adequately describe their own medication needs and must rely on caregivers to advocate and manage

their medication use. Understanding PIM in this context is a complex issue. A complete analysis of PIM use must include all facets of medication use from the properties of the drug itself that may make it PIM (i.e. profile of adverse events, cost, or lack of efficacy), the effect of the body on the drug (pharmacokinetics), the effect of the drug and any metabolites on the body (pharmacodynamics), drug-drug interactions, and patterns of medication use (from the complaints that patients and caregivers seek treatment for to the choices of prescribers, and duration of therapy). Most of these factors are subject to influence due to the sex or gender of the medication user and/or prescriber. In sum, study of PIM must identify problem medications, identify those using the medications and then create interventions palatable to PIM users that can safely lead to PIM discontinuation. This dissertation takes an interdisciplinary approach to the study of medications that are PIM due to their anticholinergic activity in older adults with dementia. The interconnected research projects included first a literature review that examined how age, sex and genetic polymorphisms of CYP enzymes affected anticholinergic drugs, which informed the drugs that needed to be included in the pharmacoepidemiological survey of drug use by older adults with dementia. This was combined with the results of a scoping review that placed the Nova Scotia experience of drugs used by older adults with dementia in the current body of literature.

Knowing which drugs confer the greatest risks to older adults with dementia was part of the objective. But given the serious sequelae from anticholinergic medications and the limitations of the current anticholinergic drug scales, the cell based assay was investigated to hopefully be able to better identify which drugs have anticholinergic activity. With better identification of potentially inappropriate medication, future pharmacoepdemiological surveys of drug use may better gauge medication use at a population level. Investigation of drug use at the population level was either in the context of prescribing cascades or general markers of appropriate drug use to identify targets for intervention that could improve care. Then preliminary work was done to determine how one could engage with patients or stakeholders to design an intervention that would be palatable to people who may benefit from stopping a medication that may carry more risk than benefit with a focus on the drug classes identified as most concerning through the previous 5 projects. All of these projects are united in their theme

of better understanding PIM use in older adults and consideration of the results support the many components of medication rationalization which includes up-titration of evidence based therapies and discontinuation of therapies that are PIM or confer a greater risk than benefit.

CHAPTER 2 SEX, AGE AND GENETIC CONSIDERATIONS IN THE PHARMACOKINETICS OF ANTICHOLINERGIC MEDICATIONS

2.1 Anticholinergic Medication Use in Older Adults

Anticholinergic medications are PIM for older adults. Clinical experience and research demonstrate an increased risk of serious adverse drug events and mortality related to the use of anticholinergic drugs in older adults (table 1). Due to variability in the anticholinergic activity of individual medications, one in isolation may fail to cause any noticeable effect but when combined two, three, or more anticholinergic agents the total anticholinergic burden can result in an adverse event (Ancelin et al., 2006; Fox et al., 2011; Han et al., 2001; S. Hilmer et al., 2009; Kalisch Ellett et al., 2014; Koyama et al., 2014; Lechevallier-Michel et al., 2005; Myint et al., 2015). Anticholinergic medications have the potential to cause mild adverse effects such as; flushing, mydriasis with loss of accommodation, fever, constipation, urinary retention (Ochs et al., 2012), and more serious events such as; increased risk of cardiovascular events (Myint et al., 2015), increased risk of delirium or cognitive impairment (Golinger et al., 1987; Han et al., 2001; Mulsant et al., 2003), increased risk of emergency department visit (S. Trenaman, 2014), increased risk of hospital admission (Kalisch Ellett et al., 2014) and increased all-cause mortality (Myint et al., 2015). With these sequelae from anticholinergic drugs, the pharmacokinetics, pharmacodynamics, expected effect and toxicity are all important to understand in the context of older adults.

Age, sex and genetic polymorphisms of cytochrome P450 (CYP) enzymes affect how anticholinergic medications are metabolized and their resulting effects in older adults. Older adults may be at increased risk of exposure to anticholinergic drugs due to changes in pharmacokinetic processes with age. Sex also may contribute to differences in pharmacokinetic processes. CYP enzymes are subject to genetic variation which can influence clinical effect or toxicity of drugs that are substrates for these enzymes (Cabrera et al., 2009). The following chapter reviews the current knowledge on how age, sex, and genetic polymorphisms of CYP2D6, CYP2C19 and CYP3A4 affect the pharmacokinetics of anticholinergic drugs in order to understand how to best predict and avoid adverse events related to these medications in older adults.

Table 1: Studies that have investigated the risk of serious adverse drug events and mortality related to the use of anticholinergic drugs in older adults

Study Authors/Design	Study Population	Study Objective	Drug Measure	Adverse Event
Myint et al (Myint et al., 2015) Cohort Study	25,639 men and women 40-79 years old from general practice registers in the EPIC-Norfolk cohort, UK followed for >10 years	To examine the relationships between total anticholinergic burden, all-cause mortality, and cardiovascular disease	Total anticholinergic burden score using an anticholinergic burden scale	Higher rates of all-cause mortality and cardiovascular disease in group with higher anticholinergic burden score
Hilmer et al (S. Hilmer et al., 2009) Cohort Study	3,075 community-dwelling Medicare recipients aged 70-79 years, recruited from April 1997 to June 1998 in eastern USA	To determine if total drug burden exposure over 5 years is associated with reduced functional capacity at year 6	Drug Burden Index (DBI) (calculated based on anticholinergic agents and sedative use)	Higher DBI at years 1, 3 and 5 was consistently associated with poorer function at year 6; with a reduction in gait speed and grip strength
Chew et al (M. Chew et al., 2005) Cohort Study	35 inpatients in a geriatric inpatient ward between February 2000 and April 2002 with behavioural and psychological symptoms of dementia (BPSD)	To examine association between serum anticholinergic activity (SAA) and cognitive performance in patients with moderate-to-severe dementia	SAA as measured by a radioreceptor competitive binding assay	Moderate negative correlation between SAA and Mini-Mental State Examination (MMSE) score
Golinger et al (Golinger et al., 1987) Cohort Study	25 patients in the surgical intensive care unit over a 3-month period	To determine presence of delirium and to estimate risk of delirium using SAA	Assay for SAA was performed on each sample by a radioreceptor method	The mean SAA was significantly higher for the delirious (4.67±3.3 ng/mL) versus non-delirious (0.81±1.0 ng/mL) patients

Study Authors/Design	Study Population	Study Objective	Drug Measure	Adverse Event/Outcome
Mulsant et al (Mulsant et al., 2003) Cohort Study	201 randomly selected from a cohort of English-speaking adults ≥65 years who had serum samples collected between March 1995 and September 1997	To examine the relationship between SAA and cognitive performance in a cohort of community dwelling individuals	SAA as measured by a radioreceptor method	SAA was strongly associated with cognitive impairment and those participants with SAA higher than the 90th percentile were 13 times more likely to have an MMSE score below the 10th percentile than participants with an undetectable SAA
Han et al (Han et al., 2001) Cohort Study	Inpatients ≥65 years of age with delirium, admitted to medical or geriatric services	To evaluate the association between use of anticholinergic medications and severity of delirium	Anticholinergic medication use calculated by: 1. Summer's Drug Risk Number 2. Clinician-rated anticholinergic score 3. Number of anticholinergic medications 4. Number of non-anticholinergic medications 5. Total number of medications	Increase in delirium severity was significantly associated with the clinician-rated anticholinergic score and the number of anticholinergic medications for both those with and without baseline dementia

Study Authors/Design	Study Population	Study Objective	Drug Measure	Adverse Event/Outcome
Haab et al (Haab et al., 2006) Noncomparative, open-label study	719 adults (85.1% women), mean age 57.3 years, with 29.9% aged ≥65 years who had completed a feeder darifenacin study	The primary objective was to assess the long-term safety, tolerability and efficacy of darifenacin in patients with overactive bladder	Darifenacin controlled release 7.5 or 15 mg orally once daily	The most commonly reported adverse events were dry mouth (23.3%) and constipation (20.9%) and 0.4% of patients reported hypertonia, somnolence or paresthesia
Ancelin et al (Ancelin et al., 2006) Cohort Study	372 elderly participants without dementia aged >60 years randomly selected from 63 general practitioners in the Montpellier region of southern France	To assess the potential of anticholinergic drugs as a cause of non-degenerative mild cognitive impairment in older adults	From an extensive literature review a table was created associating known anticholinergic drugs with their SAA and participant's records were examined to classify the anticholinergic burden from 0 to 3	Anticholinergic drug users had poorer simple reaction time, attention, immediate and delayed visuospatial memory, narrative recall, verbal fluency, object naming, visuospatial, construction and anticholinergic drug use was a significant predictor of mild cognitive impairment (OR 5.12; 95% CI[1.94 to 13.51])

Study Authors/Design	Study Population	Study Objective	Drug Measure	Adverse Event/Outcome
Lechevallier-Michel et al (Lechevallier-Michel et al., 2005) Cross-sectional Study	3,777 subjects among French elderly ≥65 years, living in the community in two administrative areas in southwestern France	The aim of this study was to assess the association between the use of drugs with anticholinergic properties and cognitive performance among community-dwelling older adults	Anticholinergic drugs from seven therapeutic classes were examined: antihistamines, gastrointestinal and urinary antispasmodics, antiemetics, bronchodilators, antiparkinsonian drugs, antidepressants and antipsychotics	Current use of anticholinergic drugs was significantly associated with low cognitive performance on cognitive tests (MMSE, BVRT, IST) among community-dwelling older adults
Geller et al (Geller et al., 2012) Cohort Study	50 cognitively intact women aged ≥55 years seeking treatment for overactive bladder	To investigate the effect of trospium chloride extended release, on cognitive function in postmenopausal women in a clinic setting	Hopkins Verbal Learning Test (HVLT-R) assessed at day 1, week 1, 4 and 12 of treatment with trospium chloride	At week 1 there was a decline in the HVLT-R learning subscale (p=0.029), at week 4 the HVLT-R Total Recall subscale score improved over baseline (p=0.02)
Hill et al (Hill et al., 2007) Noncomparative, open-label study	716 patients aged ≥65 years with overactive bladder who had first completed 12 weeks of a feeder study	To determine the long-term safety, tolerability and efficacy of darifenacin in patients ≥65 years of age	Darifenacin 7.5 mg once daily for 2 weeks then 15 mg once daily with monitoring of safety, tolerability and efficacy	Dry mouth and constipation led to discontinuation in 2.3 and 4.2% of participants respectively, cardiovascular and peripheral/CNS adverse events were infrequently reported; 1.4% and 3.3% respectively

Study Authors/Design	Study Population	Study Objective	Drug Measure	Adverse Event/Outcome
Armstrong et al (Armstrong et al., 2007) Pooled data from 2 multicenter, randomized, double-blind, parallel group trials	1,168 patients ≥18 years of age with a diagnosis of overactive bladder, as defined by urge urinary incontinence, urgency and frequency	To describe the safety and tolerability of extended-release oxybutynin at 10 mg once daily and to compare the safety profile with that of tolterodine 4 mg once daily	Extended-release oxybutynin 10 mg once daily, immediate-release tolterodine 2 mg twice daily and extended-release tolterodine 4 mg once daily were compared over 12 weeks	Approximately 10% of participants had one or more adverse events associated with the nervous system, with no clinically relevant differences across the three treatment groups (extended-release oxybutynin, 10.2%; extended-release tolterodine, 8.3%; and immediate release tolterodine, 10.9%)
Koyama et al (Koyama et al., 2014) Cohort Study	4,606 women ≥65 years of age recruited in Minneapolis, Minnesota; Portland, Oregon; Baltimore, Maryland; or Monongahela Valley, Pennsylvania between 1986 and 1988	To determine whether anticholinergic load is associated with a higher risk of functional impairment and low cognitive performance	Anticholinergic load measured using the total score on the Anticholinergic Cognitive Burden (ACB) scale	A one-unit increase in ACB score was significantly associated with one or more new Instrumental Activities of Daily Living (IADL) impairments (OR 1.11; 95% CI [1.04 to 1.19]) and with worse cognitive performance

Study Authors/Design	Study Population	Study Objective	Drug Measure	Adverse Event/Outcome
Fox et al (Fox et al., 2011) Longitudinal Study	13,004 participants representative of the population aged ≥65 living at home or in institutions in England and Wales	To identify if the use of medications with possible and definite anticholinergic activity increases the risk of cognitive impairment and death in older people	Each participant's anticholinergic burden was calculated using the ACB	A dose-response relationship was observed between increased total ACB score and MMSE decline, with a score of 4 or more on the ACB associated with a 0.34 (95% CI [0.01 to 0.67]) lower MMSE score than those not taking anticholinergics and for each 1 point increase in ACB, the odds of death increased by 26% (OR 1.26; 95% CI [1.20 to 1.32])
Kalisch Ellett et al (Kalisch Ellett et al., 2014) Cohort Study	36,015 subjects from the Australian veteran community, which includes veterans and war widows and widowers with median age 80	To examine the effect of use of anticholinergic medications on the risk of hospitalization for confusion, dementia, or delirium	The estimated daily number of anticholinergic medications were expressed as no medication or one, two, three or more anticholinergic medications	The risk of hospitalization was greater when using two (RR 2.58; 95% CI [1.91 to 3.48]), or three or more anticholinergic medications (RR 3.87; 95% CI [1.83 to 8.21]) than when participants were not exposed to anticholinergic medications

2.2 Data Sources for Review

To fully investigate how age, sex and genetic polymorphisms of the CYP enzymes can influence the pharmacokinetics of anticholinergic medications the Medline database was searched using all dates available (1950-January 2020). The initial search included the terms age, sex, anticholinergic agent and pharmacokinetics. This preliminary search did not identify many appropriate articles for development of a review. Of note, there was a lack of recent studies carried out on human subjects. A second search was carried out with the limits of human subjects, English language and clinical trials. In this more directed search each topic of sex, age,CYP2C19, CYP2D6, and CYP3A4 was searched in combination with anticholinergic and pharmacokinetics. This second search strategy allowed identification of more specific and more recent studies. This was not meant to be an exhaustive summary of all available literature on the topic but instead a review of the literature to inform clinical decision making about anticholinergic drug use in older adults. In areas where there were insufficient studies identified, further searches were completed using the specific pharmacokinetic parameter of interest (absorption, distribution, metabolism, hepatic metabolism, glucuronidation, intestinal metabolism, elimination) with each of the search terms sex, age and CYP2C19, CYP2D6 and CYP3A4. In addition, the Web of Science database was used to search for any more recent studies that had cited each of the included articles.

2.3 Study Selection and Data Extraction

Selected references were reviewed if they reported on human subjects and were in the English language. Review articles were used to identify original studies of relevance. Studies were examined if they reported on sex, gender, or age-related differences in any aspect of drug pharmacokinetics or metabolism of anticholinergic drugs. Any studies that reported on the genetic polymorphisms of CYP2C19, CYP2D6 or CYP3A4 and the effect on anticholinergic medications were reviewed as these are the most common CYP enzymes involved in the metabolism of anticholinergic drugs.

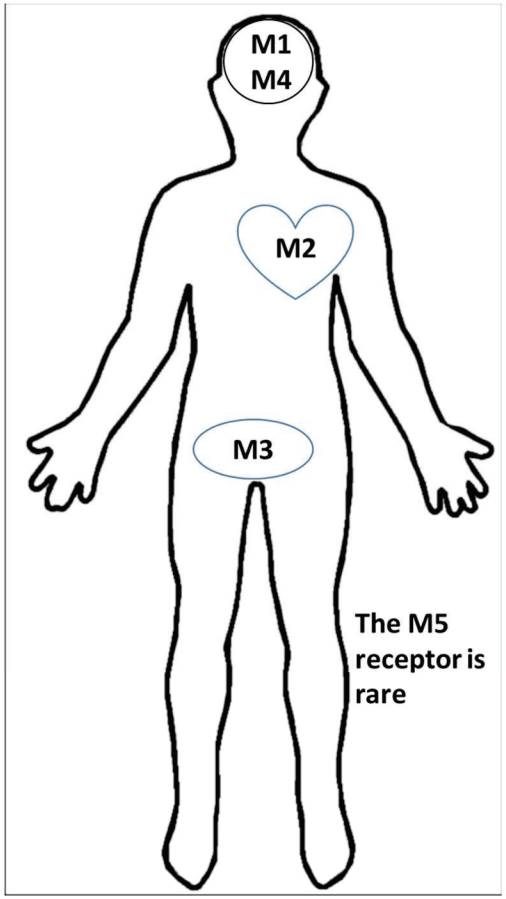
2.4 Data Synthesis

2.4.1 Anticholinergic Receptors and Signaling

The term anticholinergic agent has become synonymous with drugs that antagonize the muscarinic acetylcholine (M) receptor. The M receptor is a G-protein coupled receptor (GPCR) that resides on the cell membrane. It is comprised of seven alpha helices that span the cell membrane and it possesses an extracellular binding domain that when activated causes a conformational change in the receptor that induces dissociation of the trimeric G protein-complex into the free and active Gα and Gβγ subunits. The Gα and Gβγ subunits activate enzyme effectors or ion channels which regulate intracellular concentrations of secondary messengers such as cyclic adenosine monophosphate, cyclic guanosine monophosphate, diacylglycerol, inositol trisphosphate, diacylglycerol, arachidonic acid, sodium, potassium or calcium cations depending on the receptor subtype (Goodman et al., 2006). Gα and Gβγ activity is terminated by activation of an endogenous high-affinity GTPase located in the Gα subunit which hydrolyzes the terminal γ-phosphate of Gα-guanosine triphosphate to Gα-guanosine diphosphate which then binds Gβγ to reform the trimeric G protein-complex (Stryer, 1991; Svoboda et al., 2004). In response to prolonged signaling, receptors can be internalized by separation from the effector and binding to small endosomes. This desensitizes the receptor by reducing the number of receptors on the cell surface. This occurs in response to receptor phosphorylation which is often related to a hormone response (Svoboda et al., 2004; Svoboda & Milligan, 1994). The five M receptor subtypes and their associated functional response to agonism and antagonism are described in figure 1. M1, M3 and M5 receptors all couple with Gq/11 and lead to release of calcium from the sarcoplasmic reticulum. M2 and M4 receptors are coupled to Gi proteins and their activation leads to inhibition of adenylyl cyclase (Khan et al., 2002; Murthy & Makhlouf, 1997).

2.4.2 Serum Anticholinergic Activity and Anticholinergic Burden

M receptor antagonists have limited therapeutic use and are predominantly bladder antispasmodics used to treat urinary incontinence. Many other medications have anticholinergic properties despite the M receptor not being the intended receptor for effect (Rudolph et al., 2008; Tune et al., 1992). Drugs that have the side effect of



Receptor	Most Common Locations	Functional Response (agonism)	Anticholinergic Side Effect (antagonism)
M1	Cerebral cortex, hippocampus and striatum, autonomic ganglia, gastric and salivary glands, enteric nerves	Increase cognitive function – learning and memory Increase seizure activity	Delirium, sedation, confusion
M2	CNS, heart, smooth muscle, autonomic nerve terminals	Heart – SA node: slowed spontaneous depolarization, hyperpolarization, decrease HR AV node: decrease conduction velocity Atrium: decrease refractory period, decrease contraction Ventricle: slight decrease in contraction	Increased heart rate, arrhythmia
M3	CNS, smooth muscle and glands	Increase contraction (predominantly in bladder smooth muscle) Increase secretion (predominant in salivary glands) Increase tremor	Urinary retention, decreased salivation
M4	CNS forebrain	Inhibition of neurotransmitter release	Delirium, sedation, confusion
M5	Rare – CNS and periphery	Facilitates dopamine release Involved with drug seeking behaviour	Reduced drug seeking

Figure 1: Description of the five muscarinic receptor subtypes, their distribution throughout the body, and effect of agonism or antagonism at each muscarinic receptor subtype.

anticholinergic activity tend to have a lower level of anticholinergic activity. However, if multiple drugs with low levels of anticholinergic activity are combined the anticholinergic activity is additive and the total anticholinergic burden is the cumulative anticholinergic activity of the combination of agents (Buostani, 2008; Carnahan et al., 2006; Hilmer et al., 2007; Rudolph et al., 2008).

Measurement and prediction of anticholinergic burden is complex. The original radioreceptor assay designed by Tune and Coyle (Tune & Coyle, 1980) measured anticholinergic activity in a serum sample by measuring the competitive inhibition of a known potent antimuscarinic agent, tritiated quinuclidinyl benzilate (^{3}HQNB), with the anticholinergic agents present in the serum sample. The drug burden index (DBI) (Hilmer et al., 2007), anticholinergic drug scale (ADS) (Carnahan et al., 2006), anticholinergic risk scale (ARS) (Rudolph et al., 2008), and anticholinergic cognitive burden scale (ACB) (Buostani, 2008) and many others (Welsh et al., 2018) have been developed to predict antimuscarinic load without using blood samples. These scales vary quite significantly in their development and their ability to predict clinical outcomes. This is likely because they all rely on some level of judgement instead of purely objective measures. For the purposes of this review the medications on the ACB scale (see appendix 1) (Buostani, 2009) are focused on as those with anticholinergic activity and an ability to antagonize the M receptor.

The anticholinergic activity of a medication is dependent upon many factors, including: the drug's binding to the M receptor, the absorption and distribution to tissues (including the brain), the concentration in circulation, intestinal and hepatic cytochrome P450 (CYP) metabolism and drug transport, the presence of any active metabolites that are produced, the rate of elimination of the parent drug from the body, and the elimination of any active metabolites. Since pharmacokinetics can be affected by *sex, age* and *genetic polymorphisms* (CYP enzymes) these all must be known and considered when determining the anticholinergic activity expected in the medication user and to then rationalize the use of anticholinergic medications in clinical practice.

2.5 Sex

Sex differences in pharmacokinetics is a topic that has been explored with respect to some anticholinergic medications. There is also study of sex-related differences in pharmacokinetics of drugs that are not anticholinergic but which the study findings may be considered and then applied to anticholinergic agents related through structure, metabolic pathway or route of elimination. Results of the search for studies that examined sex differences in anticholinergic drug pharmacokinetics as their primary objective are listed in table 2.

Initially drug *absorption* was studied using radiolabeled cellulose and some, but not all of these studies showed that gastric and colonic emptying was slowed in women (Bennett et al., 2000; Córdova-Fraga et al., 2008; Degen & Phillips, 1996; Madsen, 1992; Madsen & Graff, 2004; Sadik et al., 2003; Stephen et al., 1986). Slower gastric and colonic emptying in women may increase drug oral bioavailability. Stratifying by age showed that the rate of gastric emptying of postmenopausal women and men was similar (Hutson et al., 1989) and both significantly faster than premenopausal (younger) women (Sadik et al., 2003). Gastric pH is higher in females (Grossman et al., 1963) which may increase absorption of basic medications such as tricyclic antidepressants, many of which are quite potently anticholinergic. This difference in gastric pH was quantified by Feldman and Barnett in 1991 as a mean pH of 2.79 for women and 2.16 for men, which was due to reduced acid secretion in women (Feldman & Barnett, 1991). The greater stomach size in men allows for more fluid to be contained therein which can improve both the rate and extent of dissolution of introduced oral dosage forms for men in comparison to women. In contrast, intestinal pH has not been found to differ by sex (Lindahl et al., 1997; Perez de la Cruz Moreno et al., 2006). While CYP enzymes are most prominent in the liver, they also exist in the intestinal enterocytes, where they can contribute to the first pass metabolism of orally administered drugs. Intestinal CYP3A4 metabolism has been shown inconsistently to exhibit sex differences. Early reports suggested CYP3A4 substrates verapamil and midazolam have increased bioavailability in women (Gorski et al., 1998; Kates et al., 1981; Krecic-Shepard, Barnas, et al., 2000). However, in 2005 a detailed analysis of duodenal punch biopsies from 48 men and 45 women found no clinically

meaningful sex difference in intestinal CYP3A4 content (Paine et al., 2005). To study intestinal CYP3A4 Krecic-Shepard *et al.* observed that oral verapamil is cleared more quickly in men than women with no significant difference after IV administration, suggesting some differences in intestinal metabolism exist (Krecic-Shepard, C. R. Barnas, et al., 2000) which could affect those anticholinergic medications that are substrates of CYP3A4. In females the CYP3A4 content in the intestine has been shown to decrease by approximately 20% after menopause (Paine et al., 2005) which may reduce CYP3A4 metabolism and affect the sex-difference in CYP3A4 pharmacokinetics in older women. This decrease in intestinal CYP3A4 in postmenopausal women has not been shown to be clinically meaningful to date. Similarly, differences in the drug efflux pump p-glycoprotein in the intestinal lumen have been hypothesized as a contributor to differences in drug absorption between sexes (Paine et al., 2005) but this too has not been demonstrated to be clinically meaningful in studies to date.

The second component of pharmacokinetics to consider is *distribution*. In general, males are larger than females, even at advanced age, with increased height, body mass index and waist circumference. Comparatively, women have increased adiposity (López-Ortega & Arroyo, 2016). This difference in body composition has failed to show much difference in actual drug distribution and any differences attributable to this can largely be explained by differences in total body mass (J. Schwartz, 2003). Distribution of drugs to the brain is dependent upon the nature of the blood-brain barrier. The blood-brain barrier is composed of endothelieal cells which line the capillaries on either side of the barrier that protects the brain from systemic circulation. In addition to the blood-brain barrier there is a second barrier called the blood-cerebrospinal fluid barrier and a third barrier the avascular arachnoid epithelium all of which protect the central nervous system. All three of these barriers use a combination of physical barriers (tight junctions between cells), transport barriers (specific transport mechanisms), and metabolic barriers (enzymes metabolizing molecules) (Abbott et al., 2010). The blood-brain barrier favours passage and accumulation of lipophilic drugs which are often able to diffuse across the bood-brain barrier passively. The blood-brain barrier limits transfer of macromolecules and most polar molecules via tight junctions between the cerebral endothelial cells, the

choroid plexus epithelial cells and the cells of the arachnoid epithelium. Times of inflammation, or other neurodegenerative disease can induce a leakiness to the tight junctions permitting solute, including drugs, entry to the central nervous system. In addition to passive diffusion or escape of the tight junctions there are a series of transporters that aid transport of specific solutes (Abbott et al., 2010). At this time, no statistically significant difference has been found between similarly aged women and men with respect to albumin permeability of the blood brain barrier (Pakulski et al., 2000) which likely can be extrapolated to at least some medications. The brain is also protected by p-glycoprotein, which prevents drugs from accumulating in the brain by pumping them from brain capillary endothelial cells to the blood (Roberts & Goralski, 2008). These mechanisms have not demonstrated any sex difference.

The next component to consider is *hepatic CYP-mediated drug metabolism (phase 1 metabolism)*. Several studies support that hepatic CYP metabolism varies between men and women although the clinical significance has been a challenge to understand fully. The most abundant hepatic CYP enzyme is CYP3A4 and it is involved in the metabolism of some anticholinergic medications. In humans CYP3A4 has a higher level of protein expression in the female liver than in males (Parkinson et al., 2004). Consistent with expression data, CYP3A4 oxidation was reported to be more efficient in women (Gorski et al., 1998; Greenblatt, Divoll, et al., 1980) with a two-fold higher CYP3A4 hepatic content and 50% increase in the metabolizing capacity (Wolbold et al., 2003) but this finding has not been replicated in other scientific investigations (George et al., 1995; Schmucker et al., 1990). An *in vitro* study from samples of 43 healthy livers in subjects between the ages of 27 and 83 showed a 24% increase in CYP3A4 activity identified by erythromycin N-demethylation in females in comparison to males (Hunt et al., 1992). An increase in CYP3A4 activity measured as a greater clearance of CYP3A4 substrates in women has been demonstrated. This includes the weakly anticholinergic antihypertensive medication nifedipine (Krecic-Shepard, Park, et al., 2000) and the weakly anticholinergic sedative alprazolam (Greenblatt, Allen, et al., 1980). On average, the weight-normalized clearance of alprazolam and nifedipine is mainly due to CYP3A4 and is 20% to 30% higher in young women than in young men. This difference applies to both parenteral and

oral administration and is not explained away by p-glycoprotein activity (Greenblatt & von Moltke, 2008). CYP3A4 activity has been studied regarding midazolam metabolism, which is not an anticholinergic agent however, meta-analysis suggests that women exhibit a 16% higher weight-corrected oral clearance of midazolam ($p < 0.001$) and 20% higher systemic clearance ($p = 0.002$) than men. No significant difference in the area under the curve (AUC) after oral dosing of midazolam is found but after intravenous (IV) administration women showed lower AUC than men ($p = 0.02$). No sex-dependent differences were observed in midazolam bioavailability (Hu & Zhao, 2010). Clindamycin is also metabolized by CYP3A4 and while not anticholinergic in nature it does not show any sex difference in its oral pharmacokinetics (del Carmen Carrasco-Portugal et al., 2008). These studies confirm variability in CYP3A4 metabolism with respect to sex but have failed to demonstrate any consistent clinical significance in sex-differences. To investigate sex-differences in in CYP2C19 activity 4-hydroxymephenytoin was used to measure CYP2C19 activity and failed to show any sex-differences in 4-hydroxymephenytoin recovery in a study that excluded poor metabolizers of CYP2C19 (Bebia et al., 2004). Study of CYP2C19 pharmacokinetics using zonisamide failed to show any effect of sex on clearance (Okada et al., 2008). Some evidence suggests CYP2D6 activity was increased in a sample of Spanish women (Sinues et al., 2008).

Sex differences in the glucuronidation of some medications (acetaminophen,) but not others (zidovudine) (Bock et al., 1994; Court et al., 2001; Pacifici et al., 1996) have been demonstrated suggesting that sex differences exist in *drug conjugation (phase 2 metabolism)* exist and are drug-dependent. No anticholinergic agents have been explored with respect to glucuronidation at the time this report was written. Clearance of some non-anticholinergic drugs by glucuronidation have been shown to be increased in men in comparison to women including oxazepam (Greenblatt, Divoll, et al., 1980), temazepam (Divoll et al., 1981) and acetaminophen (Miners et al., 1983) which may be able to be extrapolated to anticholinergic drugs with similar structures or that follow similar metabolic pathways. With regard to catechol-O-methyltransferase activity, liver tissue from female subjects exhibited significantly lower (about 25 %) activity than male subjects (Boudikova et al., 1990). There is a two-fold greater expression of hepatic p-

glycoprotein in men compared to women (Schuetz et al., 1995) with unclear clinical relevance.

Kidney function is integral to *drug elimination*. Glomerular filtration is related to body mass. Males typically have a greater body weight than females (López-Ortega & Arroyo, 2016), so generally glomerular filtration is greater in males than females. Body size is also influenced by ethnicity. African-American women, on average, weigh more than Caucasian women and have weights similar to men. Hispanic women, on average, have weights similar to those of Caucasian women (J. B. Schwartz, 2007). Body size likely explains the majority of sex-differences in renal drug clearance but, this has not been found for all drugs. Some kidney function calculations advocate for inclusion of race to modify for race-associated factors in kidney function (J. B. Schwartz, 2007). Race-associated factors on kidney function are currently under investigation in a large multi-center study (Norris et al., 2019). Sex has been found to be a significant factor in methotrexate clearance, and female sex was associated with a 17% reduction in methotrexate clearance after standardizing doses for body weight (Godfrey et al., 1998). Some authors have reasoned that for narrow therapeutic index drugs the sex-related effect on kidney function may be clinically relevant (Franconi et al., 2007; Godfrey et al., 1998). Pharmacokinetic studies have confirmed sex-differences in renal clearance for many drugs including the weakly anticholinergic drug digoxin, which has slower clearance in females (Yukawa et al., 1992) and the moderately anticholinergic drug amantadine, which has been shown to have significantly higher renal clearance in men due to putative sex differences in renal tubule secretion by organic cation transporters (Gaudry et al., 1993).

2.5.1 Clinical Studies Exploring Sex-Differences: Quinidine

The most commonly reported anticholinergic medication with a focus on sex-related differences was quinidine, exploring drug induced QT interval prolongation (table 3) (Benton et al., 2000; El-Eraky & Thomas, 2003; Vicente et al., 2015). The findings of both Benton and Vicente (Benton et al., 2000; Vicente et al., 2015) suggest that women clear quinidine at a faster rate than men. The challenging finding is that women have

Table 2: Details of study population, study objectives, methodology and results of trials identified to have a primary objective of exploring sex-differences in pharmacokinetic parameters for anticholinergic medications

Study Author & Design	**Study Population**	**Study Objective**	**Methodology**	**Results**
Vicente et al (Vicente et al., 2015) Randomized single blind controlled trial	24 healthy non-smoking volunteers (12 women and 12 men), 18-35 years old	To determine if quinidine induced prolongation of the time from the peak to the end of the T-wave is greater in women than men	Subjects received either 4 mg/kg of quinidine IV or a matching placebo solution over 20 min with 28 blood samples and simultaneous ECGs collected after drug/placebo infusion for each subject at predetermined time points over the following 12 h	- Quinidine causes QTc prolongation and T-wave morphology changes in both women and men - Quinidine-induced maximum QTc (541 ± 40 versus 510 ± 38 ms; p = 0.07) or maximum T_{peak}-T_{end} (216 ±60 versus 222 ± 37 ms; p = 0.76) was similar for men and women - There was a trend toward a lower maximum serum quinidine concentration in women compared to men (2.9 ± 0.7 versus 3.7 ± 1.2 μg/mL; p = 0.07) - The slope describing serum quinidine concentration versus QTc prolongation was greater in women than in men (38 ± 10 ms/μg/mL vs. 28 ± 9 ms/μg/mL; p = 0.02) - Differences between women and men occurred primarily in the first 20 min after quinidine infusion, when serum quinidine concentrations were higher in men than women

Study Author & Design	Study Population	Study Objective	Methodology	Results
Benton et al (Benton et al., 2000) Randomized single-blinded controlled trial	24 healthy non-smoking volunteers (12 women and 12 men), 18-35 years old	To determine if women have larger increases in QT interval than men at equivalent serum concentrations of quinidine after intravenous administration	Subjects received either 4 mg/kg of quinidine IV or a matching placebo solution over 20 min. 28 blood samples and simultaneous ECGs were collected after drug/placebo infusion for each subject at predetermined time points over the following 48 h	- There was a trend to greater weight-adjusted clearance of quinidine in women than in men (5.2 ± 1.1 versus 4.3 ± 1.6 mL/min/kg) - There was also a trend to a higher maximal plasma concentration of quinidine in men than in women (3.67 ± 0.13 versus 2.78 ± 0.87 μg/mL; p = 0.07) - There were no sex-related differences in the ratio of the AUC_∞ of 3-hydroxyquinidine to the AUC_∞ of quinidine - The estimated volume of distribution (V_d) at steady state was not different between the men and women - There was no difference in the free fraction of quinidine in serum between men and women - The free fraction of 3-hydroxyquinidine was slightly higher in women than in men (0.53 ± 0.05 μg/mL versus 0.47 ± 0.05 μg/mL; p < .01)

Study Author & Design	Study Population	Study Objective	Methodology	Results
Winchell et al (Winchell et al., 2002) A series of open-label, three-period, randomized, crossover studies	1. 24 healthy young subjects (mean age: 25.5 years; range: 19-39 years; 16 males and 8 females 2. 18 healthy subjects (mean age: 28.7 years; range: 22-40 years; 8 males, 10 females) 3. 12 elderly subjects (mean age: 71.3 years; range: 65-79 years; 6 males, 6 females	To investigate the pharmacokinetics and bioavailability of cyclobenzaprine, including the effects of sex and age	1. Bioavailability: Subjects received 5 mg orally or 1.25 mg IV cyclobenzaprine 2. Pharmacokinetics: Subjects received a single oral dose of 2.5, 5, or 10 mg cyclobenzaprine on Day 1 then every 8 h from Days 8 through 14 with final dose on Day 15 3. Pharmacokinetics in aging: Subjects received 5 mg cyclobenzaprine orally three times daily for 7 days and a final dose on Day 8	1. Plasma concentrations increased initially, peaking at 4 h post dose, and then declined slowly - Mean plasma clearance was 689 ± 216 mL/min - Mean oral bioavailability 5 mg tablet formulations were 0.55 (90% CI[0.51, 0.60]) 2. There were no statistically significant differences between males and females for any of the pharmacokinetic parameters - $AUC_{0\text{-}8\ h}$ and C_{Max} after the last dose were marginally significantly different between sexes 3. The population-by-sex effect was marginally significant for $AUC_{0\text{-}8\ h}$ ($p = 0.056$) but not for C_{Max}

Study Author & Design	Study Population	Study Objective	Methodology	Results
El-Eraky et al (El-Eraky & Thomas, 2003) Open trial	48 healthy volunteers (27 men, 21 women) aged 18-64 years	To determine why women are more susceptible to QT interval prolongation and torsade de pointes after administration of drugs that delay cardiac repolarization	All subjects took quinidine sulphate capsules 3 mg/kg orally then ECGs and blood samples for quinidine concentrations were taken over 24 h following drug administration	- There were no significant differences in quinidine concentrations between men and women or in any of the pharmacokinetic variables measured - The QT_a, and QT_c intervals were larger in females than in males - Quinidine did not affect QRS duration in women but reduced QRS duration in men
Koren et al (Koren et al., 2013) Single-centre, single dose open-label, reference replicate bioavailability study	12 healthy males and 12 healthy females, 18-45 years with a body mass index between 19-30 kg/m^2	To determine the effect of sex on the pharmacokinetics of doxylamine–pyridoxine 10 mg–10 mg delayed-release tablets	Participants were given doxylamine–pyridoxine 20 mg–20 mg delayed-release tablets with 240 mL water on an empty stomach with blood sampling starting 1 h pre-dose with samples analyzed using high performance liquid chromatography-tandem mass spectrometry	- Females had significantly larger AUC_{0-t} for doxylamine compared to males - A higher C_{Max} for doxylamine was observed in females compared to males

Study Author & Design	Study Population	Study Objective	Methodology	Results
Malhotra et al (Malhotra et al., 2009) Two randomized double-blind placebo-controlled trials	1. 32 healthy males aged 18-45 years 2. 16 young men, 16 older men and 16 older women	To examine the effect of age, sex and race on the pharmacokinetics, pharmaco-dynamics and safety profiles of fesoterodine	Subjects received either 8 mg of fesoterodine extended release or placebo with blood samples drawn over 36 h after drug administration and saliva samples on cotton wool collected over 24 h after drug administration	- No apparent differences in C_{Max}, $AUC_{0-\infty}$, t_{max}, or mean residual time between males and females - Total plasma clearance was highest in young men and lowest in older women - Elderly women experienced a 1 g decrease in salivary volume and elderly men did not 5 h after dose - Elderly men experienced the greatest residual urinary volume increase 8 h after dose
Ebert et al (Ebert et al., 2000) Open label crossover study	7 men and 7 women of mean age 23 years and in good health	To identify any pharmacokinetic differences between male and female volunteers in the metabolism of scopolamine when given with grapefruit juice	Each subject received at random scopolamine 0.5 mg IV, scopolamine 0.5 mg orally, or scopolamine 0.5 mg orally mixed with 150 mL fresh grapefruit juice and blood sampling occurred over the 24 h following drug administration	- C_{Max} was significantly higher in males than females (6.61 ng/mL versus 3.93 ng/mL) after IV infusion - All other parameters were similar

Study Author & Design	Study Population	Study Objective	Methodology	Results
Macleod et al (MacLeod et al., 1979) Open label study	4 men and 5 women aged 21-30 years, and 5 older men and 5 older women aged 70-88 years	To identify age and gender differences in diazepam pharmacokinetics	10 mL blood samples were taken over 1 week after receiving 0.125 mg/kg diazepam IV over 10 minutes	- There was a significant difference in plasma clearance between men and women (male: 33.2 mL/min and women: 18.1 mL/min) - The $t_{1/2}$ in men (32 h) was significantly shorter than in women (46.2 h) - V_d was not significantly different between sexes
Bigos et al (Bigos et al., 2008) Naturalized prospective study	332 men and 191 women who were using olanzapine for AD or schizophrenia	To evaluate population pharmacokinetics of olanzapine and factors that contribute to variability in exposure including sex, race and smoking status	Plasma levels of olanzapine were determined and then used to calculate non-linear mixed effects modelling for pharmacokinetic analysis	- Men cleared olanzapine 38% faster than women ($p < 0.0001$, unpaired *t* test)
Hartter et al (Hartter et al., 1998) Prospective study	15 male and female participants with major depression	To assess sex differences in fluvoxamine serum concentration at two different fixed dosing regimens (50 twice daily and 100 mg twice daily)	Drug monitoring after 14 days of either treatment	- There was a significantly greater increase in fluvoxamine serum concentration in men than in women when the dose doubled (4.6-fold versus 2.4-fold increase)

ECG changes in response to drug activity much quicker than men, which is not entirely explained by increased quinidine clearance. It is possible hormonal influences contribute to the differences in quinidine pharmacokinetics and response. These studies demonstrate sex-differences in quinidine pharmacokinetics, however the mechanism of this difference is not clear (Benton et al., 2000; El-Eraky & Thomas, 2003; Vicente et al., 2015). One hypothesis is rapid distribution after IV infusion that allows the onset of activity to be much quicker in women which over time normalizes to allow other parameters to come back into equilibrium between the sexes.

2.5.2 Clinical Studies Exploring Sex-Differences: Psychoactive Medications

Many anticholinergic psychoactive medications have been investigated for sex-differences in absorption, distribution, metabolism and excretion. A study of cyclobenzaprine examined sex-differences using a series of open-label, three-period, randomized, crossover studies. The first study included 24 healthy young subjects (mean age: 25.5 years), the second 18 healthy subjects (mean age: 28.7 years), and the third 12 older subjects (mean age: 71.3 years). The primary objective was to investigate the pharmacokinetics and bioavailability of cyclobenzaprine with attention to the effects of sex, age and hepatic insufficiency. Details of the three studies are described in table 3 but to summarize there were small significant differences in the area under the curve (AUC) and C_{MAX} between sexes in the older group (Winchell et al., 2002). This is most likely due to accumulation of drug in the group of older females. A study of the benzodiazepine diazepam demonstrated a shorter $t_{1/2}$ and a greater plasma clearance in men in comparison to women (details in table 2) (MacLeod et al., 1979). In a population of men and women receiving olanzapine for Alzheimer's Disease (AD) or schizophrenia between one and six samples were analyzed from each individual to determine sex-differences in olanzapine clearance. Sex was found to be responsible for 12% of variability in olanzapine elimination. Men cleared olanzapine 38% faster than women (Bigos et al., 2008). A natural pharmacokinetic study of anticholinergic antidepressants in older adults was designed to look for sex-differences in serum concentrations. The ratio of absolute serum concentration in comparison to the dose-adjusted serum concentration was 1.1-1.5-fold higher in women than in men for clomipramine, trimipramine (both anticholinergic)

and venlafaxine (not anticholinergic). This was seen despite a dose reduction in females who received 10-30% lower dose but still achieved serum levels equivalent to the male participants (Waade et al., 2012). Findings by Mundo and Unterecker *et al.* refute these findings by suggesting that clomipramine levels are not related to sex (Mundo et al., 2002; Unterecker et al., 2013) but rather the metabolites of clomipramine accumulate contributing to the higher plasma levels seen in women. A second naturalistic study of antidepressants examined 19,870 blood samples and demonstrated venlafaxine serum concentrations differed in men and women with higher concentrations in women (215 nmol/L versus 151 nmol/L, $p < 0.001$), but failed to show a difference for clomipramine or fluvoxamine (Reis et al., 2009) which is in keeping with findings of Mundo and Unterecker (Mundo et al., 2002; Unterecker et al., 2013). However, in a study that examined dose regimens of fluvoxamine separately, the sex difference in serum fluvoxamine concentration was dose dependent. At 100 mg daily oral dose, women achieved higher serum fluvoxamine concentrations than men, but with a 200 mg daily oral dose the serum concentrations were no longer statistically significantly different (Hartter et al., 1998). This may relate to a saturable metabolizing enzyme that is in a greater concentration or more active in men. Sex was correlated to paroxetine plasma concentration in a study of 171 subjects aged 70 years of age or older, which may relate to an observed higher V_d in male subjects (461± 260 L) versus female subjects (346 ± 256 L) (Feng et al., 2006). This was similarly seen in a study of 1,677 older men and women where the serum concentration of paroxetine was 32% higher in women (86 nmol/L versus 65 nmol/L, $p<0.001$) (Reis et al., 2009). In a third study of 70 patients receiving paroxetine the plasma concentration of paroxetine was higher in women despite age (28 versus 16 ng/mL; $p=0.001$) (Gex-Fabry et al., 2008). Mean AUC and C_{Max} for bupropion, a mildly anticholinergic antidepressant, were higher in women than men, however once these parameters were standardized for body weight the statistical significance was lost (Findlay et al., 1981). For bupropion older women had a larger V_d and longer $t_{1/2}$ than young men. This does make it challenging to know how much of the affect was contributed by sex versus age (Sweet et al., 1995). Amitriptyline plasma levels were higher in women than in men in a study of 110 inpatients receiving routine doses of amitriptyline (Preskorn & Mac, 1985), but no significant sex-difference in serum

concentration of amitriptyline was noted in the study by Reis *et al.* (Reis et al., 2009). However, nortriptyline plasma levels were affected by sex with females experiencing higher plasma levels (Dahl et al., 1996). Desipramine, an anticholinergic antidepressant has been shown to have a longer elimination $t_{1/2}$ and a faster oral clearance in older men than in older women (Abernethy et al., 1985). When examining risperidone plasma concentrations in men and women the only parameter to exhibit a statistically significant difference between males and females was the plasma concentration/dose ratio. When weight was used to adjust the plasma concentration any difference was lost (Aichhorn et al., 2005). Many of these psychoactive medications are metabolized by CYP2D6 and a sex-related difference in CYP2D6 activity has not consistently been identified in the literature (McCune et al., 2001) which means there is likely other sex-dependent mechanisms contributing to these pharmacokinetics differences. In summary, while many sex-differences exist in the pharmacokinetics of psychoactive anticholinergic medications the clinical relevance is unclear and the small increases in drug exposure that are experienced (most often by women) may contribute to the increased experience of adverse events to which women are susceptible (Rademaker, 2001; Watson et al., 2019).

2.5.3 Clinical Studies Exploring Sex-Differences: Bladder Anticholinergics

Oxybutynin is the prototype bladder anticholinergic. Oxybutynin is metabolized by CYP3A4 to N-desmethyloxybutynin, which is considered to cause many of the adverse drug reactions of oxybutynin treatment. With the hypothesis that CYP3A4 activity is increased and renal elimination slowed in women this may increase exposure to the metabolite and increase the experience of adverse drug events. However, an older study of oxybutynin pharmacokinetics failed to show sex differences in the pharmacokinetics of oxybutynin or its metabolite (Lukkari et al., 1998).

Two randomized double-blind placebo-controlled trials assessed the effects of age, sex and race on the pharmacokinetics, pharmacodynamics and safety profiles of fesoterodine in 32 healthy males aged 18-45 years and 16 young men, 16 older men and 16 older women (see table 2). Total plasma clearance was highest in young men and lowest in older women but there were no apparent sex differences in C_{Max}, $AUC_{0-\infty}$, or t_{max}.

Interestingly, older women experienced a one gram decrease in salivary volume and older men did not five hours after the dose which provided some evidence that women are more likely to experience adverse effects from anticholinergic medication (Malhotra et al., 2009). Similarly, in a study of 337 individuals darifenacin clearance was about 30% lower in females (Kerbusch et al., 2003). No sex differences in pharmacokinetics have been identified for solifenacin (Doroshyenko & Fuhr, 2009) or tolterodine (Malhotra et al., 2009). Trospium demonstrates an unexplained prolonged $t_{1/2}$ in women compared to men (Diefenbach et al., 2003). These many considerations of sex differences in medication metabolism demonstrate the complex influence of sex on the pharmacokinetics of bladder anticholinergics which are PIM in older adults with dementia.

2.5.4 Clinical Studies Exploring Sex-Differences: Antihistamines

A single-centre, single dose, open-label, reference replicate, bioavailability study in 12 healthy males and 12 healthy females aged 18 to 45 years with a body mass index between 19-30 kg/m^2 was completed to determine the effect of sex on the pharmacokinetics of doxylamine–pyridoxine 10 mg–10 mg delayed-release tablets. Females had significantly larger AUC_{0-t} and a higher C_{Max}, for doxylamine compared to males (Koren et al., 2013).

2.5.5 Clinical Studies Exploring Sex-Differences: Scopolamine

An open label crossover study of 7 men and 7 women of mean age 23 years and in good health was completed to identify any pharmacokinetic differences between male and female volunteers in the metabolism of 0.5 mg scopolamine when given IV or orally with or without grapefruit juice. The C_{Max} was significantly higher in males than females (6.61 ng/mL versus 3.93 ng/mL) after IV infusion with all other parameters being similar (Ebert et al., 2000). No differences were found in urinary elimination of scopolamine for any of the three different routes of administration by sex.

2.5.6 Lessons From Non-Anticholinergic Medications

These findings regarding non-anticholinergic medications may be considered and then applied to anticholinergic agents related through structure, metabolic pathway or route of

elimination. First, mirtazapine is cleared about 15% slower in healthy adult females which would be consistent with a faster elimination $t_{1/2}$ as well as a higher weight adjusted C_{Max} in men. The difference, although significant, was not considered to be clinically relevant (Borobia et al., 2009). Mirtazapine is primarily cleared by CYP2D6 (Timmer et al., 2000) so it is possible this difference in mirtazapine elimination is related to a sex difference in CYP2D6 activity. A second medication to consider is dextromethorphan which is not itself anticholinergic, but instead acts as a marker of CYP2D6 metabolism. A study in young healthy adult volunteers demonstrated a 16% reduction in median metabolic ratio of dextromethorphan to dextrorphan in females in comparison to males (Hagg et al., 2001). Similar results were found by Tamminga *et al.* where a 20% lower metabolic ratio was reported in females for dextromethorphan (Tamminga & Ossterhuis, 1999). These findings suggest that CYP2D6 activity is somewhat reduced in females and this may be able to account for some of the sex-differences in anticholinergic medication pharmacokinetics. Venlafaxine is largely metabolized by CYP2D6, CYP3A4 and CYP2C19 like many anticholinergic medications. In a clinical study of venlafaxine, women had a 13% smaller body weight but an average 43% larger serum concentration compared to men (Wang et al., 2020) which is much larger than the difference in body size alone would account for.

2.6 Age

Changes experienced by the aging body are another potential contributor to changes in drug pharmacokinetics. Studies with a primary objective of identifying age-related differences in drug pharmacokinetics are listed in table 3. Gastric and colonic transit is significantly faster in postmenopausal women in comparison to premenopausal women (Sadik et al., 2003) which alters *absorption*. In a study of 16 healthy adults average age 81 years and 16 healthy adults average age 24 years advanced age did not influence gastric emptying or small intestinal transit but that older individuals had a slower colonic transit than young individuals (Madsen & Graff, 2004).

In humans, it is well established that total *hepatic CYP enzyme levels* decline from about age 40 onwards. This has been quantified as about a 3.5% decline in CYP enzyme

Table 3: Details of study population, study objectives, methodology and results of trials identified to have a primary objective of exploring age-related differences in pharmacokinetic parameters for anticholinergic medications

Study Author & Study Design	**Study Population**	**Study Objective**	**Methodology**	**Results**
Winchell et al (Winchell et al., 2002) A series of open-label, three-period, randomized, crossover studies	1. 24 healthy young subjects (mean age: 25.5 years; range: 19-39 years; 16 males and 8 females) 2. 18 healthy subjects (mean age: 28.7 years; range: 22-40 years; 8 males, 10 females) 3. 12 older subjects (mean age: 71.3 years; range: 65-79 years; 6 males, 6 females)	To investigate the pharmacokinetics and bioavailability of cyclobenzaprine, including the effects of age and hepatic insufficiency	1. Subjects received 5 mg orally or 1.25 mg IV cyclobenzaprine 2. Subjects received a single oral dose of 2.5, 5, or 10 mg cyclobenzaprine on Day 1 then every 8 hours from Days 8 through 14 and a final dose on Day 15 3. Subjects received 5 mg cyclobenzaprine orally three times daily for 7 days and a final dose on the 8th day	3. Cyclobenzaprine plasma concentrations after multiple dosing were significantly higher for the older compared to young subjects - After the first dose, plasma concentration profiles were similar in older and young subjects - Mean accumulation ratio was 7.9 for older subjects compared to 4.3 for young subjects, and mean effective $t_{1/2}$ was 33.4 h (range: 20.0-53.4 h) in older subjects compared to 18.4 h (range: 9.3-41.3 h) in young subjects
Malhotra et al (Malhotra et al., 2009) Two randomized double-blind placebo-controlled trials	1. 32 healthy males aged 18-45 2. 16 young men, 16 older men and 16 older women	To examine the effect of age, sex and race on the pharmacokinetics, pharmacodynamics and safety profiles of fesoterodine	Subjects received either 8 mg of fesoterodine extended release or matching placebo with blood samples drawn over 36 h after drug administration	Renal clearance was 28% lower in older men and women than younger men

content for each decade of life (George et al., 1995; Sotaniemi et al., 1997). An older study investigating the metabolic ability of CYP 450 enzymes in aging revealed that CYP3A4 and CYP2E1 were reduced in older adults. The microsomal content of CYP3A4 was found to decrease by approximately 8% per decade of life and by 5% per decade of life for CYP2E1 (George et al., 1995). This trial failed to show a difference in CYP1A2, or CYP2C based on aging. An in vitro study of healthy human liver samples obtained during surgical procedures from 43 subjects between the ages of 27 and 83 showed no variation in CYP3A4 activity in relation to age. In this study, CYP3A4 activity was quantified by measuring erythromycin N-demethylation. While erythromycin N-demethylation has been shown to decline with age, the results of this study suggests that the age-related decline in enzyme activity is not due to declining CYP3A4 activity. Rather, other patient factors such as renal blood flow, renal filtration or body composition are likely contributing (Hunt et al., 1992). In females the CYP3A4 content in the intestine has been shown to decrease by approximately 20% after menopause (Paine et al., 2005) which may reduce intestinal CYP3A4 metabolism and contribute to an age-dependent difference in CYP3A4 metabolism. Due to a lack of studies, this decrease in intestinal CYP3A4 in postmenopausal women has not been shown to be clinically meaningful to date. In total the suggestion is that CYP3A4 demonstrates some age-related changes in the clearance of via decreases in the clearance of CYP3A4 substrate drugs suggesting older subjects may experience a reduction in clearance of drugs that rely on CYP3A4 for metabolism prior to elimination (Greenblatt et al., 2004).

Drug Conjugation (Phase 2 metabolism) has been shown in several studies as remaining fairly constant with respect to age (Court, 2010). Undeniably, numerous factors such as genetics, medication use and frailty (Wynne et al., 1990, 1993) can influence glucuronidation and sulfonation but in younger and older healthy people glucuronidation and sulfonation are not statistically significantly different. In aging rat models liver sinusoidal endothelial cells undergo pseudocapillarization (S. N. Hilmer et al., 2005; Le Couteur et al., 2005) a process characterized by loss of sinusoidal fenestrations, thickening of the endothelium, perisinusoidal collagen deposition and basal lamina formation (Le Couteur et al., 2001). This process suggests that passages for drugs through

the liver are reduced in size and this in theory could prevent large molecules, in particular protein therapeutics, and extensively protein bound drugs from travelling through the liver and being cleared by it as has been shown for liposomal doxorubicin in young and aged rats (S. N. Hilmer et al., 2004). The relevance of these changes to anticholinergic drug pharmacokinetics remains to be determined

Renal elimination declines with age by all renal routes (glomerular filtration, tubular secretion, and passive reabsorption) (Cockcroft & Gault, 1976; Isah et al., 1992). Any anticholinergic agent that is renally eliminated or has a renally eliminated active metabolite is likely to accumulate in older adults in comparison to younger adults.

In men the V_d of (R)-[11C] verapamil, a known p-glycoprotein substrate increased with age in several cortical brain regions, strongly suggesting a progressive decrease in blood brain barrier p-glycoprotein function with age (van Assema et al., 2012). This could affect drug introduction to the brain which may affect efficacy or toxicity depending upon the agent used.

2.6.1 Clinical Studies Exploring Age-Related Differences: Psychoactive Medications

Risperidone is a commonly used antipsychotic agent with anticholinergic properties. Both risperidone and its 9-hydroxyrisperidone metabolite are active. In a study of 129 adults grouped by age (less than 45, 45 to 60 and more than 60 years) on risperidone maintenance therapy, the risperidone maintenance dose was lowest in the oldest age group but the unadjusted plasma risperidone concentrations did not differ significantly across age groups. However, when adjusted for subject body weight or maintenance dose the plasma risperidone concentration was significantly higher in the older group. The concentration of active drug was comprised of both the 9-hydroxyrisperidone metabolite and risperidone parent drug, with the difference driven by the 9-hydroxyrisperidone concentration (Tamminga & Ossterhuis, 1999). This supports the use of the lowest dose possible of risperidone in older adults and provides support for a “start low and go slow” approach to antipsychotic dosing in geriatric populations. In comparison, the clearance of the sedative diazepam was not found to be affected by age in a study of young (21 to 30

years) males and females in comparison to older males and females (70 to 88 years) (MacLeod et al., 1979). A naturalized study of multiple anticholinergic antidepressants showed an increase in the absolute serum concentrations to dose adjusted serum concentrations for fluvoxamine (two-fold) and amitriptyline, clomipramine, and venlafaxine (1.5-fold) in the oldest age group more than 65 years of age in comparison to controls less than 40 years. No significant age difference was observed for the dose adjusted fluoxetine and trimipramine serum concentrations. For fluoxetine and trimipramine users older adults were using 10 to 30% lower total daily doses. The concentration to dose ratio of nortriptyline was two-fold higher in adults over 65 in comparison to the controls less than 40 years old (Waade et al., 2012) and clearance was correlated with age with faster clearance at younger ages, ($p < 0.0005$). In a different investigation no significant difference was found between patients younger or older than 60 years in the mean dose-corrected serum concentration of clomipramine and N-clomipramine, which contradicts the findings of Waade (Unterecker et al., 2013). But amitriptyline plasma levels were higher in older adults than younger subjects (Preskorn & Mac, 1985) which was consistent with findings of Waade *et al.* Dawling *et al*. who showed that both amitriptyline and nortriptyline levels were higher in older adults with older women experiencing a more exaggerated effect than their male comparators (Dawling, 1982). Fluvoxamine serum concentration did not correlate with age either at 100 mg or at 200 mg orally daily (Hartter et al., 1998). There was a trend to higher serum concentrations in older female patients with the lower dosage, but this diminished when the dosage was doubled and does suggest there is an interaction between age and sex for fluvoxamine. Older subjects taking oral paroxetine had higher plasma concentrations than younger subjects (Sawamura et al., 2004). In a study that examined bupropion kinetics in older adults with depression (mean age 71.5 years) the clearance was 80% of that seen in younger adults (Sweet et al., 1995). The $t_{1/2}$ was 34 hours in comparison to most sources which report 11 to 14 hours (Goodnick, 1991; Sweet et al., 1995). Among female subjects, there was no significant difference between young and older groups in any of the pharmacokinetic variables for triazolam. Among male subjects, the $t_{1/2}$ of triazolam increased. Furthermore, when age was evaluated as a continuous variable, AUC increased significantly with age ($p = 0.02$) and clearance decreased with age ($p = 0.02$). Further

examination of cyclobenzaprine pharmacokinetics, in this case comparing $t_{1/2}$ in older adults to younger adults showed the $t_{1/2}$ of cyclobenzaprine is increased (Winchell et al., 2002).

2.6.2 Clinical Studies Exploring Age-Related Differences: Bladder Anticholinergics

The potently anticholinergic drug oxybutynin follows the trend of increasing peak plasma levels and bioavailability with increasing age and frailty (Hughes et al., 1992). This effect was so significant that study authors suggested to halve the dose of oxybutynin which would allow older adults to achieve the same plasma levels as younger adults. AUC and C_{Max} are increased 20% and 16% respectively when an older population takes the same dose of oxybutynin as a younger population. Moreover, solifenacin, a newer bladder anticholinergic, has a longer $t_{1/2}$ due to slower elimination and longer time to reach C_{Max} in older adults. This can be explained by the slowed absorption of solifenacin in older adults which increases their exposure to solifenacin by about 1.2-fold (Doroshyenko & Fuhr, 2009). Finally, details of age-related pharmacokinetics of a third bladder anticholinergic, fesoterodine, are shown in table 3. In a study of 16 young men, 16 older men and 16 older women, receiving either 8 mg of fesoterodine extended release or matching placebo the renal clearance of fesoterodine was 28% lower in older men and women than younger men (Malhotra et al., 2009). This increased exposure to fesoterodine in older adults may predict increased exposure of tolterodine in older adults as well, as fesoterodine and tolterodine are related compounds, with fesoterodine being metabolized to the same active ingredient as tolterodine.

2.6.3 Clinical Studies Exploring Age-Related Differences: Scopolamine

Healthy adult subjects were given scopolamine hydrobromide 0.5 mg IV if they were under 65 years of age and 0.3 mg if older than 65 years. These subjects then received a battery of tests of cognitive function in addition to measurement of pharmacokinetic variables. Age was associated with slowed clearance and increased exposure to scopolamine in older adults. The study showed that age-related increases in scopolamine exposure was likely the greatest contributor to the increased sensitivity to cognitive adverse effects in older adults. The study authors hypothesized that age-related changes

in CYP3A4 activity or content may have been responsible for the increased scopolamine exposure in older adults (Alvarez-Jimenez et al., 2016).

2.6.4 Clinical Studies Exploring Age-Related Differences: Non-Anticholinergic Medications

The study of the second-generation antihistamine desloratidine in older adults demonstrated a 30% increase in $t_{1/2}$ in those over 65 years of age in comparison to those 18 to 45 years of age. The study authors did not believe that this was enough difference to warrant a recommendation of a dosage adjustment for desloratadine (Koren et al., 2013). However, if one would consider other medications with a narrower therapeutic range or more serious dose-related adverse effects this finding may be relevant for other medications.

2.7 Genetics

CYP enzymes catalyze oxidation reactions to increase the water solubility of molecules to favour excretion. The concentration of these enzymes and their activity is affected by genetic differences. A study in Brazil enrolled 396 older individuals ranging from 60 to 95 years of age (mean age 72.1 years). Of these subjects, 222 were women (56.1%) and 174 were men (43.9%). The use of drugs that act on the CYP enzyme system was observed among 61.6% of the older individuals. The proportion of women using drugs that act on the CYP enzyme system was higher (67.6%) than the proportion of men. Use of more than two drugs that act on CYP enzymes was recorded among 64 individuals (16.2%). Drugs with substrate activity formed the most frequently used group (58.8%). This proportion became 66.9% when the older individuals who smoked and/or consumed daily alcoholic drinks were grouped into this category. The use of drugs with inhibitor activity on CYP enzymes was observed among 14.9% of the subjects. Only 4.3% of the subjects used drugs with inducer activity. It is important that we understand these enzymes and how genetic variation in CYP activity can influence clinical effect or toxicity as drugs that are substrates for these enzymes are frequently used by older adults (Cabrera et al., 2009).

2.7.1 CYP2D6

There are several genetic polymorphisms at CYP2D6. These variants result from point mutations, deletions or additions, gene rearrangements and deletion or duplication/multiplication of the entire gene. The distribution of these alleles in various ethnic groups is different. Functionally, these alleles of CYP2D6 can be classified into three groups: alleles resulting in increased activity, alleles resulting in decreased activity or loss of activity and alleles with normal activity. Phenotypically, a population with various CYP activity contains extensive metabolizers (EMs), intermediate metabolizers (IMs) and poor metabolizers (PMs). For CYP2D6, there is a fourth phenotype, the ultra-rapid metabolizers (UMs) that have at least one CYP2D6 gene duplication, meaning they have at least 3 copies of the active CYP2D6 gene. To date, at least 120 different CYP2D6 variant alleles (*1B through to *105) and a series of subvariants have been identified and designated by the human CYP allele nomenclature committee. There is variability in CYP2D6 allelic frequencies across geographic and ethnic groups with poor metabolizing phenotypes CYP2D6*10 happening most often in Asia, CYP2D6 *17 and *29 in African or Black populations, CYP2D6* 41 seen in the Middle East, and CYP2D6*4 most common in Europe and among Caucasians (LLerena et al., 2014). We know that there are variant alleles of CYP2D6 with 5 to 10% of the population being PM and with this variant being most common for Asians.

CYP2D6 phenotypes have been well characterized with respect to codeine pharmacokinetics and pharmacodynamics. Limited activation and effect of codeine occurs in CYP2D6 PMs and increased metabolism and toxicity has been reported in UMs (Lopes et al., 2020). There is evidence of this in older people and some investigation of the role of CYP2D6 variants on anticholinergic medication metabolism. In nursing home patients exposed to anticholinergic drugs the highest serum anticholinergic activity was found in groups of CYP2D6 PMs (H. Kersten et al., 2014). Analysis of 70 healthy volunteers' risperidone metabolism of which 82.9% were either IM or EM revealed that the polymorphisms of the CYP2D6 enzyme are much more responsible for variation in risperidone metabolism than sex. CYP2D6 phenotype explained 52% of interindividual variability in risperidone pharmacokinetics. The AUC of the active moiety was found to

be 28% higher in CYP2D6 PM compared with IM, EM and UM. No other genetic markers were found to significantly affect risperidone concentrations (Vandenberghe et al., 2015). This genetic variation in the metabolism of risperidone is of such an extent that it could alter results when conducting bioequivalence studies (Cabaleiro et al., 2015) and should be considered as a possibility for any person initiated on risperidone which further supports using the lowest doses possible at all times.

The bladder anticholinergic tolterodine is metabolized to a similarly active 5-hydroxymethyl tolterodine (5-HMT) by CYP2D6. The bioavailability of tolterodine is strictly related to the genetic polymorphism of CYP2D6 and it ranges from 10 to 74% (Brynne et al., 1997). Byeon *et al.* investigated the relationship between CYP2D6 phenotypes and tolterodine pharmacokinetics in 46 Korean subjects. The single dose and multiple dose C_{Max} and AUC_{0-24} of tolterodine was significantly higher in the PM groups than in the EMs. The ratio of clearance to bioavailability of tolterodine in the EMs was five to 18-fold higher than PM (variant dependent) in multiple dosing studies (Byeon et al., 2019). A Swedish study also found a difference in the absorption $t_{1/2}$ of tolterodine between EM (0.41 h) and PM (0.53 h) and EM were found to have a slight increase in heart rate at steady state in comparison to baseline which was thought to be related to drug exposure (Brynne et al., 1998). Interest in understanding drug induced QT interval prolongation led to study of the effect of CYP2D6 polymorphism on ECG changes in the use of bladder anticholinergic tolterodine and its active metabolite 5-HMT. In CYP2D6 PM the systemic exposure to tolterodine is higher than EM ($t_{1/2}$ of tolterodine immediate release 10 hours in PM versus 2 to 3 hours in EM) which may contribute to differences in ECG changes (Brynne et al., 1998). However, the total concentration of active moieties (tolterodine and 5-HMT) was similar for PM and EM which makes dose adjustment unhelpful for equalizing drug exposure. However, 5-HMT and tolterodine may contribute differently to QT interval prolongation risk and so this was studied as well. QT interval prolongation in CYP2D6 PM was only slightly greater for PM likely due to differences in protein binding between the two active components (Patel et al., 2018). As a further illustration of CYP2D6 genetic variation on anticholinergic pharmacokinetics 4 mg daily dosing of fesoterodine produced a C_{Max} of 3.45 ng/mL in CYP2D6 PM versus 1.89

ng/mL in CYP2D6 EM. A similar proportional result was also observed for 8 mg daily dosing of fesoterodine in PM (C_{Max} of 6.40 ng/mL) verus EM (C_{Max} 3.98 ng/mL). Fesoterodine equally follows CYP2D6 and CYP3A4 metabolism which should make it less susceptible to CYP2D6 reduced metabolism but this is not clearly demonstrated in study (Nilvebrant et al., 1997). The oral antimuscarinic agent darifenacin is metabolized by CYP3A4 and CYP2D6 with the main metabolite being inactive (Beaumont et al., 1998). The oral bioavailability of darifenacin is significantly altered by the CYP2D6 genotype in a dose-dependent fashion. In EM the bioavailability of 7.5, 15 and 30 mg CR oral doses of darifenacin are 15, 19 and 25%, respectively. In IM and PM this bioavailability becomes 40 to 90% higher. There is less impact of the CYP2D6 variants on the systemic elimination of darifenacin. In UM the $t_{1/2}$ of darifenacin is 3.12 hours, while in PM it is 3.83 hours (Kerbusch et al., 2003).

Venlafaxine has been studied in CYP2D6 PM, IM and EM 2D6. The serum concentration of the metabolite N-desmethylvenlafaxine was 5.5-fold higher in IMs ($p < 0.01$) and 22-fold higher in PMs ($p < 0.001$) than in EMs (Hermann et al., 2008). In CYP2D6 PMs, the mean concentration to dose ratio of venlafaxine was about 8-fold and 2.5-fold higher in patients more than 65 and 40 to 65 years, respectively, compared with those less than 40 years ($p \leq 0.001$) (Waade et al., 2014) suggesting the PM phenotype is magnified in elderly subjects. Nortriptyline plasma levels were mostly correlated to CYP2D6 genotype and sex (Dahl et al., 1996). All told CYP2D6 is an important contributor to variation in pharmacokinetics of medications it metabolizes. When treating adults with psychotic illness with antipsychotics knowing the CYP2D6 genotype was not able to confer clinical benefit. PM and UM did receive higher doses of medication than EM and IM including CYP2D6 dependent antipsychotics. UM would likely need higher doses to compensate for their increased metabolism, so it is reassuring to see this in practice. However higher doses being used by PM may reflect adverse drug events being misinterpreted as psychotic symptoms leading to dose increases inappropriately (Jürgens et al., 2012).

Drug monographs have not embraced dose modification based on CYP2D6 polymorphism but clinical practice guidelines do exist to guide precision medicine for the

CYP2D6 variants. Clinical practice guidelines are available at pharmgkb.org for drugs that have been studied and accepted to have variation across CYP genotype that would indicate dose modification.

2.7.2 CYP2C19

CYP2C19 is coded in a cluster of genes on chromosome 10 (Seripa et al., 2015). In the general population it is estimated that only 1.8% of individuals are PM at CYP2C19. This confirms a role for CYP2C19 as a contributor for increased exposure to anticholinergic medications metabolized by this route, but it represents a much smaller population of those affected as PM of CYP2C19 and no studies have demonstrated a role in this variation in anticholinergic medication pharmacokinetics.

2.7.3 CYP3A4

No studies that report specifically on anticholinergic medications and CYP3A4 polymorphism were identified. Previous research has failed to identify individuals with no CYP3A4 activity. Due to the lack of genetic PM of CYP3A4, other factors such as exposure to drug inducers and inhibitors, kidney function, blood flow, and possibly age and sex are the biggest considerations for variation in CYP3A4 activity (Hunt et al., 1992; Parkinson et al., 2004).

2.8 Conclusions

Anticholinergic medications pose health risks to older adults. We know that adverse drug events due to anticholinergic medications are most commonly proportional to plasma drug concentration or serum anticholinergic activity (M. Chew et al., 2005; Golinger et al., 1987; Mulsant et al., 2003) which makes sex, age, and genetic effects on drug disposition relevant for clinical decision making. Investigating the role of sex on drug pharmacokinetics confirms what observational studies show in that women often experience increased drug exposure (Degen & Phillips, 1996; Koren et al., 2013) via a number of mechanisms which likely contributes to their experience of more adverse drug reactions than men (Benton et al., 2000; Malhotra et al., 2009; Rademaker, 2001; Vicente et al., 2015; Watson et al., 2019). Increasing age increases drug exposure through a

number of mechanisms but predominantly through the effect on renal elimination and hepatic metabolism. CYP2D6 polymorphisms are the most important genetic CYP polymorphism that can alter drug metabolism and affect exposure to anticholinergic medications. Appendix 1 summarizes the common anticholinergic drugs from the ACB scale, their pharmacokinetic parameters and if sex, age or genetic CYP polymorphisms were discovered to influence their pharmacokinetics in the production of this review. While clinical practice guidelines exist to guide best practice for medication use in older adults, adoption of these recommendations is notoriously low. Prescribing that considers sex, age and is based on known CYP2D6 genotype represents an opportunity to reduce the burden of adverse drug events in older people. The take home messages should be that older women experience the greatest increase in drug exposure and a start low, go slow approach to drug dosing is the safest. Clinical practice demonstrates that even a small decrease in dose modestly decreases adverse drug reactions with negligible effect on efficacy. This should encourage clinicians to minimize anticholinergic drug dosage, if anticholinergic medications must be used at all. While the tenants of Geriatric medicine have been touting the importance of lower doses in older adults the importance of sex in dosing has been poorly translated into clinical practice. Monographs frequently provide advice for dosing in the oldest medication users but rarely offer advice for dosing in women. With increased risk of hospitalization, cognitive impairment and mortality as risks from anticholinergic drug use, improved understanding of sex, age and genomic testing of CYP isozymes may be indicated to reduce serious anticholinergic adverse events. Rigorous pharmacokinetic analysis is an important component in understanding how dosing recommendations can be modified to most safely and effectively treat older men and women. Studies that have been done in the past often look at age, sex, or CYP polymorphism alone and future work needs to account for all of these factors so that we may better approach personalized medicine for optimal outcomes.

CHAPTER 3 SEX AND GENDER DIFFERENCES IN POLYPHARMACY IN PERSONS WITH DEMENTIA: A SCOPING REVIEW

This chapter has been published in SAGE Open Medicine (Trenaman et al., 2019) and is included herein with permission (see appendix 2).

3.1 Considerations of Sex and Gender in Medication Use, Efficacy, Safety and Toxicity

Polypharmacy is a well-recognized concern for older adults (Linjakumpu et al., 2002; Thomas et al., 1999). Worldwide estimates of polypharmacy vary by country, sex, age, and accepted definition (Bushardt et al., 2008; Linjakumpu et al., 2002; Masnoon et al., 2017; Quinn & Shah, 2017; Thomas et al., 1999; Vrettos et al., 2017). At present there is not a universally accepted definition of polypharmacy. Polypharmacy was investigated in a recent systematic review (Masnoon et al., 2017) where authors identified 138 different definitions. Polypharmacy definitions included numerical definitions determined by the number of drugs used, descriptive definitions which considered co-prescribing of multiple medications, and appropriate or inappropriate polypharmacy which examined drugs used even though they are recommended to be avoided using consensus-based tools such as Beers criteria (By the American Geriatrics Society 2015 Beers Criteria Update Expert Panel, 2015) or the medication inappropriateness index (Hanlon et al., 1992). Regardless of definition polypharmacy is a problem for older adults. In the United States 30% of adults aged 65 years of age and older are taking six or more drugs daily (Bushardt et al., 2008) and in Canada estimates suggest 63% of seniors are taking more than 5 medications, and 30% of those older than 85 years are taking more than 10 medications (*Health Reports*, n.d.). Dementia increases the risk for polypharmacy (Vrettos et al., 2017) with pharmacotherapy being an exceedingly common treatment for BPSD (Davies et al., 2018; Dyer et al., 2017; Gerlach & Kales, 2018). This is despite the knowledge that drug therapy has limited beneficial effect on BPSD (Dyer et al., 2017; Scales et al., 2018).

In general, studies enroll younger populations (Banzi et al., 2016) and rarely include those with frailty or complex comorbidities with the resulting complex medication

regimen (Jongsma et al., 2016; McMurdo et al., 2005; Zulman et al., 2011). Extrapolating from younger populations to older individuals or those with dementia is not ideal given pharmacokinetic and pharmacodynamic differences in medication response between older adults and their younger and healthier counterparts (Aichhorn et al., 2005; Cabrera et al., 2009; Divoll et al., 1981; George et al., 1995; Greenblatt, Divoll, et al., 1980; Greenblatt et al., 2004; S. N. Hilmer et al., 2005; Hughes et al., 1992; Hunt et al., 1992; MacLeod et al., 1979; Madsen, 1992; Malhotra et al., 2009; Mangoni & Jackson, 2004). Pharmacokinetic changes that need to be considered include: drug elimination slowing with age due to decreasing kidney function (Cockcroft & Gault, 1976; Manjunath et al., 2001), changes in body composition with age which may significantly influence drug distribution and effect (McLean & Le Couteur, 2004), and cytochrome P450 enzyme content decreases (George et al., 1995), which alters drug metabolism. In addition, characteristics of the blood brain barrier change (Shah & Mooradian, 1997) which alters drug introduction to the central nervous system. This is especially true for those with dementia (Reeve et al., 2017). These changes associated with aging may unpredictably influence serum drug concentrations, drug effect, and toxicity. Even so, age-related changes in drug effect are recognized by clinicians in many guidelines and tools to help guide clinical decision making for drug use for older adults (By the American Geriatrics Society 2015 Beers Criteria Update Expert Panel, 2015; O'Mahony et al., 2015).

Differences in drug pharmacokinetics and pharmacodynamics are not limited to the effect of aging; there are also differences in drug metabolism between males and females. These poorly understood sex-related differences are compounded by the age-related changes and include differences in hepatic metabolism (George et al., 1995; Gorski et al., 1998; Hagg et al., 2001; Kates et al., 1981; Krecic-Shepard, Barnas, et al., 2000; Paine et al., 2005; Schuetz et al., 1995; J. Schwartz, 2003; Yukawa et al., 1992), intestinal metabolism (Paine et al., 2005), drug distribution (J. Schwartz, 2003), and renal clearance (Yukawa et al., 1992). These sex differences have been identified but have not been well delineated and their clinical significance is thus not well understood.

The lived experience of dementia also differs between men and women. Older women are more likely to develop dementia, with 38% greater risk than older men (Hurd et al., 2013). In North American populations, women with dementia live on average 6 months longer than men with dementia, and women with Alzheimer's Disease (AD) are more likely to live in a nursing home than men with AD. Additionally, North American women with dementia spend 94% of their time with dementia in a nursing home whereas men spend closer to 60% of their time with the disease in nursing homes (Hurd et al., 2013). Some of these differences likely relate to sex (biological differences, e.g. metabolism), while others relate to gender (social roles, e.g. caregiving roles and longevity in relation to a caregiving spouse) (Soldin & Mattison, 2009). Gender roles may also lead to men and women seeking treatment for different conditions and may influence prescribing practices, with drug selection being influenced by physician gender biases (Lind et al., 2017; Manteuffel et al., 2014). While investigations into gender differences in prescribing have not specifically focused on older adults with dementia, there is no reason to believe that these principles do not apply. Indeed, these differences may be even more important to understand in older adults with dementia due to their susceptibility to adverse drug reactions (Hajjar et al., 2003).

To date, randomized controlled trials designed to evaluate drug use for older adults with dementia have not investigated sex differences sufficiently to help guide practice. We can likely assume that drugs that are temporally associated with improvements in BPSD or improvements in monitoring parameters of optimal health (such as blood pressure, heart rate, or cognition) are continued, whereas therapies that do not seem to be working are discontinued. This leads to the hypothesis that due to gender and sex differences in medication prescription, use, and response, women and men with dementia will end up on different drug profiles. This is expected to be exacerbated by the differences in comorbidity expression in men and women. Comorbidity, frailty and cognitive impairment will mean that most older adults with dementia will be taking more than five medications daily and this polypharmacy profile may differ between men and women based on the many sex and gender differences discussed.

3.2 Objective

The objective of this scoping review was to understand differences in polypharmacy as determined by medication use including the number of medications or concomitant medications used by older men and women with dementia, with the aim of informing recommendations for research and guiding initiatives to improve drug use.

3.3 Methods

A systematic review was not possible as there were no studies designed with a primary objective to explore sex or gender differences in drug use in older adults with dementia. The scoping review methodology was selected for this investigation due to the ability of this approach to present a general overview of a topic area while identifying gaps in the literature base (Arksey & O'Malley, 2005; Munn et al., 2018). Arksey & O'Malley have a five-stage framework and this approach guided the present review (Arksey & O'Malley, 2005).

3.3.1 Stage 1: Identify the Research Question

What is the relationship between sex or gender and polypharmacy in older adults with dementia?

3.3.2 Stage 2: Identify Relevant Studies

A search of each of the databases Medline, Embase, Web of Science, CINAHL and Proquest was conducted in January of 2016 to identify all published research that commented on drug use in people with dementia. Each database was searched from inception to January 1, 2016. The only limit applied to the search was that the article had to be available in English.

Searches were completed for each of three concepts independently, then the three searches were combined. The search terms included 1) Sex, gender, masculinity, femininity, machismo; 2) Polypharmacy, deprescriptions, drug combinations, drug therapy combination, polypragmasy, inappropriate prescribing, mulitmedication,

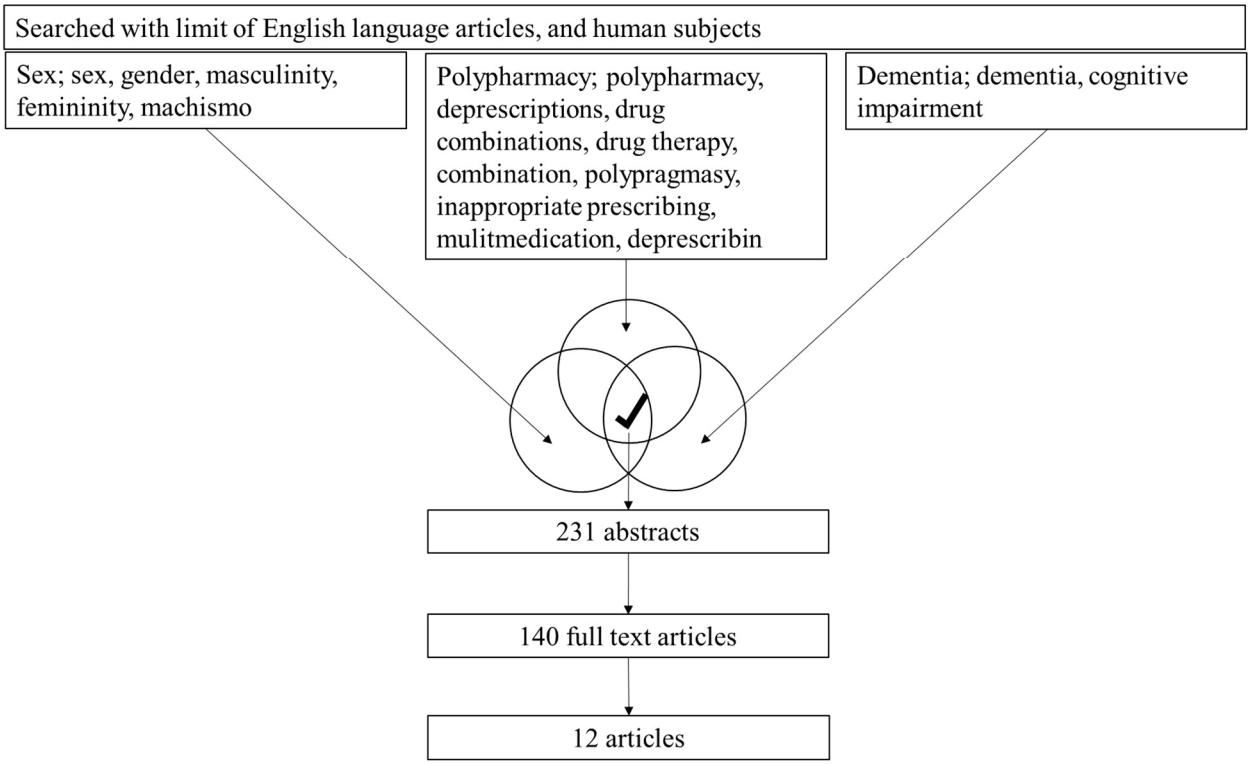


Figure 2: Search Strategy and Study Selection for Scoping Review of Sex or Gender Differences in Medication Use by Older Adults with Dementia

deprescribing; 3) Dementia, cognitive impairment. The search strategy is shown in figure 2.

3.3.3 Stage 3: Study Selection

All identified abstracts were reviewed by two reviewers with the aid of Distiller SR software©. Abstracts were selected for full text review if they; 1) were in English, 2) reported on an original study with human subjects among whom at least a subset had

cognitive impairment, and 3) reported on older adults 65 years of age or older. Articles identified from the abstract review were reviewed by two reviewers. Articles were included in the final scoping review if they; 1) were in English, 2) reported on original research, 3) if the subjects (or an identifiable subset) were 65 years old or older, 4) if there was a clear population with dementia, and 5) if those with dementia were subdivided into males and females, and 6) if some medication specific information was provided by sex or gender. Conflicts at either stage of review were resolved via consensus reached after discussion focused on the relevant selection criteria.

While study quality is not typically a component of a scoping review, quality was assessed using the National Institutes of Health (NIH) sponsored National Heart, Lung and Blood Institute's Quality Assessment for Case-Control Studies or Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies as appropriate (*Study Quality Assessment Tools*, n.d.) (and rated as good, fair or poor) or the Cochrane Collaboration's tool for assessing risk of bias for randomized controlled trials (*The Cochrane Collaboration*, n.d.) (and rated as low or high risk). The quality of studies was subjectively rated by the two reviewers and based on the criteria in the tools. This was done to explore the merits of the included studies in an effort to identify the level of attention to sex-specific or gender-specific findings regarding polypharmacy but did not impact decisions regarding inclusion/exclusion of articles in the scoping review process.

3.3.4 Stage 4: Charting the Data

Data were charted in a summary table (see table 4). Details of the studies that were of interest for the review included; Study Design, Study Purpose/Objective, Subject Population, Analytic Model, Key Findings, and an Appraisal of Evidence Quality.

3.3.5 Stage 5: Collating, Summarizing and Reporting the Results

Study findings and characteristics were considered with respect to what they revealed about the role of sex or gender on polypharmacy in older adults with dementia by each of the study authors. This led to the summary of findings and a description of the gaps in the existing literature.

Table 4: Results of scoping review search to determine what the literature can tell us about the role of sex or gender on polypharmacy in persons with dementia

	Author	Study Design	Study Purpose/ Objective	Subject Population	Analytic Model	Key Findings	Appraisal of Evidence Quality
1	(Taipale et al., 2014)	Observational cohort study	To describe prevalence and risk factors associated with antipsychotic polypharmacy among antipsychotic users with AD	9,803 community-dwelling persons with clinically verified AD residing in Finland who used antipsychotics between 2006-2009	Cox proportional hazards model	- Antipsychotic polypharmacy was associated with male sex (unadjusted HR 1.2 [1.03-1.39], adjusted HR 1.2 [1.02-1.38]) - Among antipsychotic users no sex difference for number of antipsychotic polypharmacy episodes	Good

	Author	Study Design	Study Purpose/ Objective	Subject Population	Analytic Model	Key Findings	Appraisal of Evidence Quality
2	(Stephens et al., 2014)	Retrospective longitudinal cohort study	To describe change in prescribing of antipsychotics in people with dementia treated as inpatients in England and to understand the impact of clinical and sociodemographic factors on use	63,079 adult patients over 58 years with a dementia diagnosis recorded in their clinical record between January 2010 and October 2012	Chi square test at univariate level for trends and backward stepwise logistic regression in a multivariate analysis	Male sex was associated with a 10% increase in the likelihood of antipsychotic prescribing OR 1.1 [1.06-1.15]	Fair
3	(Fiss et al., 2013)	Prospective cohort study	To analyze the occurrences of PIM in older adults and the determinants for PIM use in patients with suspicion of dementia	342 patients in primary care in Germany who screened positive for cognitive impairment	Multiple, binary logistic regression analyses	Female sex (OR=10.36 [1.28-83.87]) was a positive determinant for PIM use per the PRISCUS list	Poor

	Author	Study Design	Study Purpose/ Objective	Subject Population	Analytic Model	Key Findings	Appraisal of Evidence Quality
4	(Tjia et al., 2010)	Prospective cohort study	To examine daily medication use in advanced dementia with attention to end of life	323 nursing home residents with advanced demented living in 22 Boston area facilities recruited from February 1, 2003 and September 30, 2006	Negative binomial regression using generalized estimating equations	- Men were taking 1.36 times as many medications per day as women - Male sex was associated with a higher number of daily medications and never appropriate drug use	Good
5	(Roe et al., 2002)	Retrospective cohort study	To compare prevalence of anticholinergic drug use in a sample of patients with probable dementia to a sample of older adults without dementia	418 individuals using donepezil and 418 comparators identified from a pharmacy benefit management company in the United States	McNemar test and Chi square analysis to compare anticholinergic use and a discontinuation analysis to see if anticholinergics were stopped once donepezil was started	Use of an anticholinergic agent was not related to sex in those taking donepezil	Good

	Author	Study Design	Study Purpose/ Objective	Subject Population	Analytic Model	Key Findings	Appraisal of Evidence Quality
6	(F. Montastruc et al., 2013)	Prospective cohort study	To assess the prevalence of potentially PIM use in community-dwelling patients with mild to moderate dementia and to identify factors associated with PIM	684 subjects with mild to moderate dementia cared for by an informal caregiver in France	Binary analysis with Fisher's exact test, Pearson's X^2, student's t test or Mann-Whitney parametric test, then a backward multivariate logistic regression analysis to find factors associated with PIM use	Female sex was associated with PIM use OR 1.5 [1.1-2.2] per the Laroche list	Good

	Author	Study Design	Study Purpose/ Objective	Subject Population	Analytic Model	Key Findings	Appraisal of Evidence Quality
7	(Epstein et al., 2010)	Prospective cohort study	To characterize medication use in older adults in the ADNI study	818 participants in the ADNI cohort	ANOVA and logistic regression	- In those with AD more men were using a cholinesterase inhibitor (93.8% versus 78.4%, p=0.002) - Male sex was associated with cholinesterase inhibitor treatment in AD (OR 3.61 [1.35-9.66])	Fair
8	(Lagnaoui et al., 2003)	Cross sectional study	To assess prevalence of benzodiazepine use in AD patients and to examine patient and drug characteristics associated use	5,000 patients treated with tacrine for mild to moderate AD	Chi square analysis and multivariate regression	Benzodiazepine users were more likely to be female	Good

	Author	Study Design	Study Purpose/ Objective	Subject Population	Analytic Model	Key Findings	Appraisal of Evidence Quality
9	(Nijk et al., 2009)	Cohort study	To investigate psychotropic drug use in Dutch nursing home patients with dementia and the association between age, sex, severity of dementia, and type of neuropsychiatric symptoms	1,322 patients with dementia who had resided in a nursing home for more than 4 weeks	Binomial logistic regression	Women had an increased risk for the use of antidepressant medication (OR 1.44 and 1.49 using different methods of measuring neuropsychiatric symptoms)	Fair
10	(Wattmo et al., 2014)	Prospective open non-randomized multicenter cohort study	To describe the long term cognitive and functional abilities of solitary living individuals with AD, to compare these outcomes with those living with a family member and to identify the potential predictors of usage of community-based home-help services and nursing home placement for these two living status groups	1,258 patients recruited from memory clinics in Sweden	ANOVA, independent sample t tests, chi squared test, binary logistic regression	- Females used more antidepressant and antipsychotic medication and less lipid lowering agents - No significant sex-based differences were noted per the number of medications used at the time a cholinesterase inhibitor was initiated	Good

	Author	Study Design	Study Purpose/ Objective	Subject Population	Analytic Model	Key Findings	Appraisal of Evidence Quality
11	(Huisman et al., 2012)	Case Control	To determine if anticholinergic agents are prescribed to people on cholinesterase inhibitors	10,989 patients treated with anticholinergic bladder antispasmolytics and 32,967 controls	Regression analysis	There was no sex difference in patients receiving both cholinesterase inhibitors and anticholinergic bladder antispasmolytics	Fair

	Author	Study Design	Study Purpose/ Objective	Subject Population	Analytic Model	Key Findings	Appraisal of Evidence Quality
12	(Wills et al., 1997)	Case control	To describe the use of drugs in an older population with respect to dementia status while considering age, sex and housing type	1,810 people from Stockholm who were born in or before 1912	Logistic regression	- For many drug classes (hypnotics and sedatives, anxiolytics, potassium, minor analgesics and antipyretics, thiazides, NSAIDs, thyroid preparations, centrally acting muscle relaxants, multivitamins, psychotropic drugs) the proportion of users was larger in women - The number of medications used was similar in men and women with dementia	Good

3.4 Results

231 unique abstracts were identified for review. In addition to the search strategy, figure 2 shows the process followed for article selection. Only 140 abstracts met inclusion criteria and went on to full text review. Of the 140 full text articles reviewed, 12 were appropriate for inclusion in the final review. A summary of the 12 included papers is provided in table 4.

3.4.1 Findings for Men

In general, the included studies reported increased use of antipsychotics and cholinesterase inhibitors among men. In a Finnish cohort of community-dwelling seniors with dementia using more than one antipsychotic medication at a time was associated with male sex (Taipale et al., 2014). Men with dementia and no diagnosis of schizophrenia who were inpatients in acute care hospitals in England had a 10% increased use of antipsychotics (Stephens et al., 2014). Nursing home dwelling men near end of life were taking 1.36 times as many medications per day as women, and these men were more likely to be using a medication considered to be potentially inappropriate by the study authors at end of life (Tjia et al., 2010). In a longitudinal cohort comprised of people with cognitive impairment across 59 sites in the United States and Canada cholinesterase inhibitor use was more common in men (93.8%) compared to women (78.4%) (p=0.002) (Epstein et al., 2010). Logistic regression showed that male sex (OR 3.61; 95% CI 1.35, 9.66) was associated with increased use of cholinesterase inhibitor treatment (Epstein et al., 2010). Men received more lipid lowering therapy than women (Wattmo et al., 2014). None of the studies reported on gender specific findings for men.

3.4.2 Findings for Women

The review showed that women were generally exposed to more psychotropic medication. In a German study of community-dwelling people with dementia, female sex was associated with an increased risk of inappropriate medication use (OR = 10.36, 95% CI: 1.28–83.87) according to the PRISCUS list (Fiss et al., 2013). In community-dwelling seniors with dementia in France, female sex was associated with increased odds of PIM use according to the LaRoche list (OR1.5; 95 % CI 1.1–2.2) (F. Montastruc et al., 2013). A second study from France analyzing the cohort of the first 5000 subjects

initiated on tacrine, the first drug available for dementia treatment and a centrally acting anticholinesterase and indirect cholinergic agonist, considered their medication use 3 months prior to enrollment in the cohort showed that benzodiazepine users were more likely to be female ($p<0.001$) (Lagnaoui et al., 2003). Female residents of Dutch nursing homes had increased use of antidepressant medications in both models explored (OR 1.44 and 1.49). The first model adjusted for Neuropsychiatric Inventory Nursing Home symptoms and the second model adjusted for the Cohen Mansfield Agitation Inventory symptoms (Nijk et al., 2009). In a group of subjects with confirmed dementia from Stockholm's Kungsholmen district born in or before 1912, there was a statistically significant ($p<0.05$) association between female sex and use of a number of medication classes: hypnotics and sedatives (OR 1.70), anxiolytics (OR 1.90), potassium (OR 1.43), minor analgesics and antipyretics (OR 1.42), thiazides (1.82), NSAIDs (2.32), thyroid preparations (5.12), centrally acting muscle relaxants (2.02), multivitamins (4.95), psychotropic drugs (1.87) (Wills et al., 1997). None of the studies reported on gender specific findings for women.

3.4.3 General Sex-Specific Findings

In community-dwelling seniors in the United States with dementia, use of a drug with anticholinergic activity was not significantly related to sex ($\chi^2=1.07$; $p=0.300$) (Roe et al., 2002). In older community-dwelling adults living alone who were followed in the Swedish Alzheimer's Treatment Study, no significant sex differences were observed in drug therapy at the initiation of cholinesterase inhibitor therapy (Wattmo et al., 2014). Patients receiving cholinesterase inhibitors in the preceding year were more likely to receive anticholinergic spasmolytics (OR 5.6; 95% CI: 3.7-8.5), and this drug-drug combination did not differ between sexes (Huisman et al., 2012).

3.4.4 General Gender-Specific Findings

Surprisingly, none of the studies reported on gender specific findings.

3.5 Discussion

This scoping review identified 12 papers that provided insight into sex-related differences in polypharmacy in those with dementia, however none of the papers made any comment on gender-related differences. The identified papers highlight several findings. Most notably, among community-dwellers, women were more likely to receive PIMs (Fiss et al., 2013; F. Montastruc et al., 2013), whereas among residents of nursing homes, men received more PIMs (Tjia et al., 2010). Men with dementia in nursing homes were taking more medications overall (Tjia et al., 2010) and in particular, more antipsychotics (Stephens et al., 2014; Taipale et al., 2014). Men in the community used more cholinesterase inhibitors than women (Epstein et al., 2010). Women with dementia used more psychotropic medications than men (Lagnaoui et al., 2003; Nijk et al., 2009; Wattmo et al., 2014; Wills et al., 1997). The existence of the drug-drug interaction of a cholinesterase inhibitor combined with an anticholinergic medication did not differ by sex (Huisman et al., 2012; Roe et al., 2002).

Antipsychotic use was higher among hospitalized and institutionalized men. Taipale *et al.* showed that using more than one antipsychotic was more common in men with dementia and Stephens *et al.* found that male sex was associated with a 10% increase in the likelihood of antipsychotic use in hospitalized individuals with dementia (Stephens et al., 2014; Taipale et al., 2014). This is not be surprising, given concerns that men may be more prone to experiencing violent responsive behaviours and using antipsychotics is a culturally acceptable method to attempt to reduce BPSD despite a lack of scientific data supporting their use (Bonner et al., 2015). It follows then that in nursing home patients with advanced dementia, men are more likely to take a PIM (Tjia et al., 2010), this is likely driven by the increased use of the antipsychotics (Stephens et al., 2014) in this population. This is contrasted with the findings of Wattmo, who suggest that community-dwelling women with dementia use more antipsychotics (Wattmo et al., 2014). It is conceivable that increased antipsychotic use by community-dwelling women with dementia is simply reflective of the increased use of psychotropic medications by women with dementia in general (Wills et al., 1997).

Women with dementia's increased use of psychotropic medication is driven by an increased use of antidepressants (Nijk et al., 2009; Wattmo et al., 2014), hypnotics, sedatives, and anxiolytics (Lagnaoui et al., 2003; Wattmo et al., 2014). Antidepressants reach higher serum concentrations in women (Grossman et al., 1963) which may be mediated by gastric pH, which is higher in females, and may increase absorption of medications whose active ingredients possess basic functional groups such as many antidepressants (Grossman et al., 1963). It is worth questioning whether the reduced use of antidepressants in men with dementia is due to their reduced effect driven by lower serum concentrations being achieved.

In one study of community-dwelling seniors with AD, men were more likely to be taking a cholinesterase inhibitor (Epstein et al., 2010). This is a surprising finding as women with AD in the community are otherwise more likely to use psychoactive medication. The lower use of cholinesterase inhibitors among women might be related to their lower body weight and a reluctance by clinicians to initiate this therapy with its attendant risk of gastrointestinal upset and weight loss. It is also a consideration that as women likely achieve higher serum concentrations of cholinesterase inhibitors due to their higher gastric pH (Grossman et al., 1963) that they experience the adverse effects at a greater rate and thus are unable to tolerate and continue treatment. On the other hand, the finding that men with dementia use more lipid lowering therapies suggests that cardiac comorbidities are more common in community-dwelling men with dementia (Wattmo et al., 2014) but may also reflect known differences in cardiovascular comorbidity identification and treatment between men and women in the general population (Wills et al., 1997).

Urinary incontinence is a well-known side effect of cholinesterase inhibitors. Despite the antagonistic nature of using an anticholinergic medication to control urinary incontinence in an individual on a cholinesterase inhibitor, this strategy is attempted by some clinicians. This drug combination is generally not considered to be appropriate due to the side effect profile of bladder antispasmolytic agents and because of the counter-productive drug interaction whereby they offset the activity of the cholinesterase

inhibitor. No sex differences have been identified in the use of this combination of drugs (Huisman et al., 2012; Roe et al., 2002).

Our most startling finding was the lack of research on the topic of sex differences in drug use in older adults with dementia. None of the studies we identified were designed to focus on sex-related differences in drug use in older adults with dementia. Reported sex differences are not the primary objective of any of the studies but instead represent secondary findings. When sex differences were presented, the majority of studies commented only on the use of central nervous system active agents, but we know from prior work that frailty and many other social, economic and health-related factors influence outcomes in dementia and should influence overall medication use. The quality of the studies was variable, though the majority of the included trials were agreed to be of good quality according to the National Heart, Lung and Blood Institute's criteria for observational cohort and cross-sectional studies and case control studies (*Study Quality Assessment Tools*, n.d.). Also, no studies made any comment about participant gender or gender-related factors, which prevents any gender-based analysis of findings. Even so, our search strategy was designed to be as broad as possible, inclusive of many definitions of polypharmacy, and the scoping review methodology (as opposed to a systematic review) allowed for more detailed investigation of the existing literature. None of the studies identified were randomized controlled trials. The studies identified were only observational. Certainly, this limits the ability to draw firm conclusions based on this scoping review in isolation, but it does permit us to identify areas that require further study. It is also important to point out that none of the identified studies discussed polypharmacy from the perspective of effect on quality of life such as impact on BPSD, time to admission to nursing home or the lived experience of dementia.

3.6 Conclusions

In closing, there are many findings in this scoping review that can help characterize polypharmacy in men and women with dementia. Clinicians should be aware of the tendency toward increased psychotropic medication use and inappropriate medication use in women with dementia; ideally the goal should be to reduce or eliminate the use of

PIM. Clinicians should carefully review men and women's medications lists for anticholinergic drug and cholinesterase inhibitor drug-drug interaction and seek to discontinue the anticholinergic agents. This potentially inappropriate drug combination should be kept in mind for both men and women (Huisman et al., 2012; Roe et al., 2002). Antipsychotics continue to be used in populations with dementia. Men and women seem to use antipsychotics to greater extents dependent upon their living environment (women in the community and men in Long Term Care Facilities). Antipsychotics are also potentially inappropriate and thus clinicians still need to be vigilant for opportunities to reduce their use. Even though the literature is sparse regarding sex and gender differences in medication use in men and women with dementia, further research and knowledge translation efforts are required to understand how we can build upon and use the knowledge of these differences to improve medication use for individuals with dementia.

CHAPTER 4 TESTING OF A NOVEL CELLULAR REPORTER ASSAY FOR DETERMINING ANTICHOLINERGIC ACTIVITY AND BURDEN

4.1 Introduction

Anticholinergic drugs are notoriously problematic for older adults (Kalisch Ellett et al., 2014; Myint et al., 2015; Salahudeen et al., 2015). The anticholinergic toxidrome includes flushing, mydriasis with loss of accommodation, fever, constipation, and urinary retention (Ochs et al., 2012). In addition to these bothersome symptoms, more serious consequences of cholinergic blockade that have been verified in large observational trials (M. Chew et al., 2005; Golinger et al., 1987; Han et al., 2001; S. Hilmer et al., 2009; Mulsant et al., 2003; Myint et al., 2015) include increased risk of; cardiovascular events (Myint et al., 2015), delirium (Golinger et al., 1987; Han et al., 2001; Mulsant et al., 2003), cognitive impairment (Mulsant et al., 2003), and all-cause mortality (Myint et al., 2015). It is primarily older adults who encounter the negative effects of anticholinergic drugs and their unintended health consequences that can lead to emergency department visits and hospitalizations (M. Chew et al., 2005; Golinger et al., 1987; Han et al., 2001; S. Hilmer et al., 2009; Kalisch Ellett et al., 2014; Mulsant et al., 2003; Myint et al., 2015; Ochs et al., 2012; Salahudeen et al., 2015). Avoiding anticholinergic drugs is challenging for clinicians, in part because identifying anticholinergic drugs is not straightforward. While a small number of drugs have been developed with the express purpose of inhibiting the muscarinic acetylcholine receptor (M), such as oxybutynin and tolterodine, which are bladder antispasmolytics, most drugs with anticholinergic properties antagonize the M receptor as an undesired side effect. In addition, anticholinergic activity is reported to be additive, resulting in a cumulative anticholinergic burden; a fact that is particularly concerning in older patients who may be on multiple medications with anticholinergic activity (Carnahan et al., 2006).

To date there is no widely accepted method to measure, report, or rank the anticholinergic activity of a medication. This difficulty has led to numerous clinical scales being developed (Aizenberg et al., 2002; Ancelin et al., 2006; Buostani, 2008; Cancelli et al., 2008; Carnahan et al., 2006; M. Chew et al., 2005; Dauphinot et al., 2014; Ehrt et al., 2010; Han et al., 2001; S. Hilmer et al., 2009; Minzenberg et al., 2004; Rudolph et al.,

2008; Summers, 1978; Welsh et al., 2018; Whalley et al., 2012) to help clinicians identify anticholinergic load and to make drug therapy changes to reduce total anticholinergic burden. However, these scales are subjective in nature and have, in general, relied on the side effect profiles of medications and expert opinion to rate the level of M blockade. Therefore, a standardized, objective, and quantitative method of measuring a drug's anticholinergic activity is needed to better define a drug's potential to inhibit the M receptor. Such methodology would improve the ability to study and predict a drug's anticholinergic burden, allowing clinicians to make better informed decisions about their patients' medication.

Two common geriatric conditions, falls (Aizenberg et al., 2002; Dauphinot et al., 2014) and delirium (Golinger et al., 1987; Han et al., 2001; Tune et al., 1992), can improve with alteration of drug therapy to minimize anticholinergic burden. However, avoiding drugs that *may* have some anticholinergic activity, as defined through subjective tests, in preference of other drugs is still not without risk. For example, clinicians often avoid histamine-2 receptor blockers (H2RAs), such as ranitidine or famotidine, in favour of proton pump inhibitors (PPIs) due to the commonly accepted wisdom that H2RAs are sufficiently anticholinergic to warrant avoidance. However, long term use of PPIs has been associated with cognitive impairment, AD, functional decline, *C. difficile* infection, renal disease, and death (Chang et al., 2018; Corsonello et al., 2014; Haenisch et al., 2015; Ide et al., 2018; Kamal et al., 2018; Lazarus et al., 2016; Xie et al., 2017). An objective test to measure exactly how potent H2RAs are as anticholinergic agents would help clinicians determine whether patients are in fact better off switching to PPIs. Additionally the unrelated weakly anticholinergic beta-blocker atenolol was studied alone and in combination with PPIs in an attempt to investigate measurement of anticholinergic burden.

To measure serum anticholinergic activity, Tune and Coyle (Tune et al., 1992) developed a radioreceptor assay. This assay was able to measure anticholinergic activity in a blood serum sample. The Tune and Coyle method relied upon the high concentrations of muscarinic 1 (M1) receptors in rat forebrain for the M receptor source and employed the

potent radio-labelled anticholinergic drug quinuclidinyl benzylate (^{3}H-QNB). The test measured displacement of ^{3}H-QNB by compounds present in blood serum. This assay was limited as it was unable to identify the sources of anticholinergic activity with respect to exogenous versus endogenous contributors (Cox et al., 2009), used rat brain tissue and therefore rat (not human) M receptors, and was unable to measure a specific drugs' contribution to the overall anticholinergic activity (R. Carnahan et al., 2002).

More recently, genetically engineered cell-based bioassays have been developed to analyze agonism and antagonism of G-protein coupled receptors (GPCR) including the M receptor family. In these modified human cell lines, the GPCR is tagged with a β-galactosidase enzyme fragment. The cells co-express β-arrestin tagged with the matching β-galactosidase enzyme fragment. Activation of the GPCR results in recruitment of β-arrestin, allowing the two β-galactosidase enzyme fragments to combine and become active. The resulting functional enzyme hydrolyzes substrate to generate a chemiluminescent signal. In the case of M receptors, receptor activation by the agonist acetylcholine or blockade of the acetylcholine-mediated response by M receptor antagonist can be quantified (DiscoverX, 2016b).

4.2 Objective

The objective of this study was to determine if a M1 receptor cellular reporter assay could be used to objectively quantify the anticholinergic activity of medications with suspected anticholinergic effects. The M1 receptor is present primarily in the brain and likely plays a role in the cognitive effects of M1 receptor blockade; the M1-expressing cell reporter line was therefore chosen for this investigation as the cognitive effects of anticholinergics are often of the greatest concern to clinicians. We propose that drugs could be ranked by objectively measuring their anticholinergic activity, which represents an improvement over the consensus-driven anticholinergic scales currently in use. An empirically derived scale would give clinicians more accurate information about the

drugs they prescribe and help them to modify drug-therapy to minimize anticholinergic burden in their patients.

4.3 Methods

4.3.1 Materials

The CHRM1 U2OS β-Arrestin GPCR cells and all cell culture reagents were purchased from DiscoverX (now Eurofins, Fremont, California, United States) in a PathHunter® eXpress assay kit. Acetylcholine, ranitidine, famotidine, and atenolol were obtained from Sigma-Aldrich (Oakville, Ontario, Canada) and atropine from Selleckchem (Houston, Texas, United States).

4.3.2 Culturing of CHRM1 U2OS β-Arrestin GPCR Cells

CHRM1 U2OS β-Arrestin GPCR cells were grown according to the manufacturer's instructions (DiscoverX, 2016b, 2016a). Briefly, the cells were stored in liquid nitrogen. At the beginning of the experiment, the cell plating reagent was warmed for 15 minutes in a 37 °C water bath. Then, 500 µL of the warmed cell plating reagent was added to the vial of frozen cells with pipetting to evenly distribute. The thawed cells were added to a prepared vial containing 15 mL of warmed cell plating reagent and dispersed with pipetting. The dispersed cells were plated 100 µL per well in a 96 well plate with a translucent base and opaque (white) sides.

The plate was allowed to incubate for 24 hours in a humidified atmosphere of 5% CO_2/95% air at 37°C (standard cell culture conditions) before running the assay. Verification of the cell growth showed approximately $1.4x10^5$ cells/mL after 24 hours growth.

4.3.3 Measurement of M1 Receptor Agonism Using Acetylcholine

To verify the technique and assay efficacy, the standard acetylcholine curve was calculated using a series of dilutions of acetylcholine chloride (final concentrations of $1.0x10^{-2}$ – $5.5x10^5$ µM). Ten µL of each concentration of acetylcholine was added to individual wells of the prepared 96 well plate in triplicate and incubated for 1 hour at 37

°C. Next, 55 µL of the assay kit-provided luminescence solution was added to each well and the plates were incubated in the dark for 90 minutes. Subsequently, the plate was placed in a BioTeK Synergy HT plate reader (BioTeK, Winooski, VT, USA) and total luminescence measured. Background luminescence from blanks was subtracted from the acetylcholine treated wells.

4.3.4 Measurement of M1 Receptor Anticholinergic Response by Atropine and Test Compounds

The M1 receptor anticholinergic response was measured according to the manufacturer's instructions (DiscoverX, 2016b, 2016a). Briefly, the wells of the 96-well plate were treated with 5 µL of a series of dilutions of control (atropine [0.00006 – 0.4 µM]) or test (ranitidine [0.0238 - 608 µM], famotidine [0.0245 - 309 µM], atenolol [0.0285 - 395 µM]) antagonists. Due to limited aqueous solubility of the test agents, DMSO was used to improve dissolution. The plates were incubated in the dark for 30 minutes at 37 °C, 5 µL of acetylcholine at the EC_{80} concentration (200 µM) was added to each well (except blanks), and the plates were incubated in the dark for an additional 60 minutes. Next, 55 µL of the assay kit's luminescence solution was added to each well and the plates were allowed to rest in the dark and at room temperature for 90 minutes before reading total luminescence. When combinations of antagonists were investigated, 2.5 µL of each concentrated antagonist was added in place of 5 µL of a single antagonist. Ranitidine and atenolol were combined in two separate mixtures containing final concentrations of 709 µM (ranitidine) and 855 µM (atenolol), and 362 µM (ranitidine) and 428 µM (atenolol). Total luminescence was measured in a BioTeK Synergy HT plate reader.

4.3.5 Statistical Analysis

Each experiment was performed using more than two individual assay kits, which corresponded to separate lots of cells. The standard curve for acetylcholine and the atropine response curve were completed in duplicate experiments. EC_{80} for acetylcholine was calculated from the standard acetylcholine curve experiment and compared to the predicted value on the package insert. The IC_{50}s for atropine, ranitidine, famotidine, and atenolol were calculated from four independent experiments using non-linear regression

curve fit analyses on GraphPad Prism 5. Antagonist luminescence was standardized as percent of the baseline luminescence. Concentration of antagonist at maximum inhibition of luminescence was compared between experiments and antagonists to provide further information about anticholinergic activity. ANOVA was used to compare reagent signal inhibition to blank to explore significant inhibition of the acetylcholine signal.

4.4 Results

The M1 agonist, acetylcholine, produced a sigmoidal concentration-response with a linear response range between $1.0x10^{-2}$ to $5.5x10^{5}$ µM (figure 3) from duplicate experiments. The EC_{50} for acetylcholine was calculated to be 24.2 ± 20.3 µM, which is 9.3-fold greater than the kit's predicted EC_{50} of 2.61 µM. The EC_{80} for acetylcholine was calculated to be 200 ± 120 µM. The control M1 antagonist, atropine, inhibited the

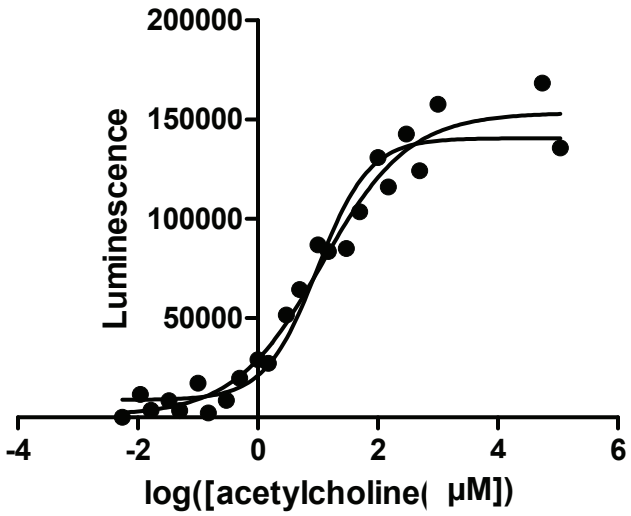


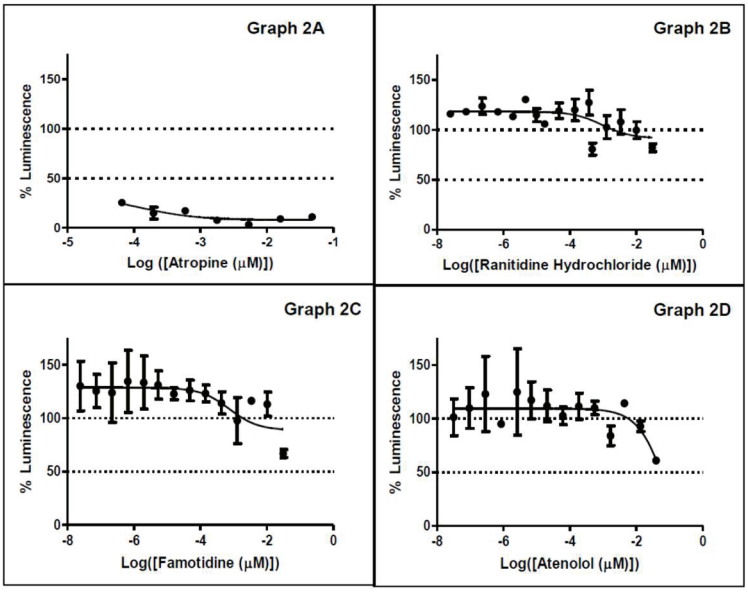
Figure 3: The standard luminescence curve caused by increasing concentrations of the control agonist, acetylcholine (n=2).

Table 5: Agents and their concentration ranges tested to initially explore anticholinergic burden as a % of acetylcholine signal measured (n=1)

Drug	Common Serum Concentration in adults*	Concentration	% of acetylcholine signal measured
Acetylcholine	-	200 ± 120 µM	-
Ranitidine	0.14 - 3.1 µM (44-977 ng/mL)*	1 447 µM	59.7
		709 µM	70.7
		362 µM	41.6
Famotidine	225 - 308 µM ($7.60x10^4$-$1.04x10^5$ ng/mL)*	1352 µM	55.9
		676 µM	59.8
		338 µM	34.8
Atenolol	2.25 µM (600 ng/mL)**	1710 µM	87.2
		855 µM	115.5
		428 µM	95.9
Ranitidine and Atenolol	-	709 µM (ranitidine) 855 µM (atenolol)	115.5
		362 µM (ranitidine) 428 µM (atenolol)	105.6

* from Micromedex Database {Micromedex]

** from Eur J Clin Pharmacol. 1980 Nov;18(5):365-74.



* $p<0.05$ for atropine, $p>0.05$ for ranitidine, famotidine and atenolol

Figure 4: Atropine (n=2), ranitidine, famotidine, and atenolol (n=4) concentration versus luminescence curves.

acetylcholine-mediated response with a calculated $IC_{50} < 1.0x10^{-2}$ μM (figure 4, graph 2A) from duplicate experiments. The three test anticholinergic agents, ranitidine, famotidine, and atenolol (figure 4, graphs 2B, 2C, and 2D), displayed less than 50% inhibition of acetylcholine activity, even at the maximum concentrations used (table 6). When tested in the absence of the acetylcholine, the three test agents gave luminescence signals that were approximately 93% of the luminescence measured for the blank. Solubility issues limited the testing of higher concentrations of ranitidine, famotidine, and atenolol; therefore, IC_{50}s could not be reliably determined for these compounds. When ranitidine and atenolol were used in combination, no inhibition of the acetylcholine signal was observed (table 1). ANOVA analyses only demonstrated a significant inhibition of the acetylcholine signal by the strong anticholinergic atropine ($p<0.05$).

4.5 Discussion

This study demonstrates that the CHRM1 U2OS β-Arrestin GPCR cells in the DiscoverX PathHunter® eXpress assay kit can be used to determine anticholinergic activity of the three weakly anticholinergic agents tested (ranitidine, famotidine, and atenolol) to some extent. Unfortunately, solubility of these test agents limited the ability to reach concentrations high enough to complete the concentration response curves required to calculate IC_{50} values. While some antagonism was observed at the highest concentrations tested, it should be noted that these concentrations exceeded what would be expected during routine therapeutic use of the three agents in patients.

The determination of the EC_{50} for acetylcholine did not provide the result predicted by the manufacturer, with the manufacturer reporting that the EC_{50} should be much lower (~10 times lower) than the calculated result. The reasons are unknown but could include difference in plate reader or minor differences in experimental technique. The EC_{80} for acetylcholine was then also calculated from the acetylcholine concentration response curve. It was this laboratory determined EC_{80} of acetylcholine that was used as a concentration for acetylcholine in agonist experiments. Atropine, the positive control M antagonist, potently and completely inhibited acetylcholine activation of the M1 receptor assay indicating that the antagonism assay was working properly.

Based on our data, some inhibition of the acetylcholine signal by ranitidine, famotidine, and atenolol was observed at the highest concentrations studied. As shown in Table 5, famotidine showed the greatest inhibition of the acetylcholine signal. This was particularly interesting because famotidine reaches relatively high levels in serum samples of treated patients (225 - 308 μM or $7.60x10^4$ - $1.04x10^5$ ng/mL (Truven Health Analytics, 2015)) which are closest to the concentrations we tested in these experiments. This suggests famotidine may be the most likely of the drugs tested to cause anticholinergic activity in patients, certainly warranting further experimentation. The level of inhibition measured seems far too low to produce any noticeable anticholinergic effects in humans taking these drugs at regular doses but it is not clear if when combined with other weakly or moderately anticholinergic medications if this could contribute enough anticholinergic activity to break a threshold and cause an anticholinergic adverse event. This is clinically relevant as there may be a preference for one H2RA over another in order to minimize anticholinergic activity exposure. Ranitidine showed some inhibition of the acetylcholine signal and atenolol showed very little. However, the concentrations of both ranitidine and atenolol used far exceed what would be expected during therapeutic use (ranitidine 0.14 - 3.1 μM or 44 - 977 ng/mL (Truven Health Analytics, 2015) and atenolol 2.25 μM or 600 ng/mL (Leonetti et al., 1980)), suggesting little to no anticholinergic activity should occur from these drugs when used in people. This contrasts with the message amongst clinicians that ranitidine is potently anticholinergic. It is possible that metabolites or byproducts of ranitidine metabolism are anticholinergic as these were not tested in the study. ANOVA analysis of the test reagents failed to show a significant inhibition of the acetylcholine signal. While there was a trend to signal inhibition at the highest concentrations of test reagents this did not reach statistical significance except for atropine our control antagonist.

Chew *et al.* examined the anticholinergic activity of 107 medications which included ranitidine, famotidine and atenolol. Our result for ranitidine does not show significant anticholinergic activity whereas Chew, *et al.* showed ranitidine had a low level of anticholinergic activity (M. L. Chew et al., 2008). It is possible that our study was unable

to show a significant anticholinergic activity for ranitidine as Chew *et al.* were able to do as they used a much higher concentration of drug. They crushed tablets or used powder from capsules at clinically relevant doses to obtain a solution to use in testing. In contrast, we used purified formulations of each reagent so it is also possible that excipients in the dosage forms used may have influenced result. In this study by Chew *et al.* the drugs in solution were exposed to rat brain homogenate as an M receptor source rather than the human M1 receptors used in the present investigation which may also account for the differences in binding between the two studies. Our result for atenolol is in agreement with Chew *et al.*, as both showed no anticholinergic activity. Given that we measured a very low level of anticholinergic activity for famotidine this differs from *Chew et al.* who identified no anticholinergic activity for famotidine (M. L. Chew et al., 2008).

Clinically, we recognize that the use of multiple anticholinergic agents is associated with increased total anticholinergic burden (Carnahan et al., 2006; Welsh et al., 2018). We had expected to find increased inhibition of the acetylcholine signal as the drugs were combined in the assay, but instead no appreciable inhibition was measured. This may have been due to the combinations of reagents blocking each other or reacting together in solution to alter the M receptor binding. This suggests that measuring anticholinergic burden *in vitro* may be more complex than previously considered; something that has been observed in previous research and requires further study. For example, Mangoni, *et al.* completed a study of serum anticholinergic activity in 71 adults taking between 0 and 5 anticholinergic drugs and failed to show any significant relationship between serum anticholinergic activity and the anticholinergic burden, which they measured multiple ways: using the anticholinergic risk scale score, the anticholinergic drug scale, the anticholinergic burden scale, and the drug burden index (Mangoni & Jackson, 2004).

In addition to Tune and Coyle (Tune & Coyle, 1980), whose methods were described previously, two other groups have attempted to develop objective methods to measure anticholinergic activity *in vitro*. The first, by Nobrega, *et al*., developed an assay that used Chinese hamster ovary cells expressing the rat M1 receptor. The Nobrega method is very similar to the original Tune and Coyle methods, in that displacement of a radio-

labelled ligand was measured to identify the anticholinergic activity (Nobrega et al., 2017). Second, Woehrling, *et al*. developed a method that uses fluorescence of human neuronal cells that express a theoretically accurate distribution of the five M receptor subtypes. It reports IC_{50} values which is meaningful for objective drug comparisons (Woehrling et al., 2015). We argue that the methods used in our study are preferable because CHRM1 U2OS β-Arrestin GPCR cells are human and therefore express human M1 receptor, which is widely expressed in the brain. In addition, our method does not require the use of radioactive materials and can be completed quickly, which is desirable when considering the potential applications in high throughput testing to identify anticholinergic agents on a large scale.

Our study has a number of limitations. For example, we were only able to complete two replicates for acetylcholine cholinergic and atropine anticholinergic characterization. We did, however, complete four replicates for each test drug. To improve solubility, we used the solvent DMSO, which may have altered the drugs' activity and produced erroneous results. Previous research groups (Mulsant et al., 2003) have suggested that dissolving drugs in DMSO can alter their binding to the muscarinic receptor and can produce a false response. We did a sensitivity analysis to verify that including or excluding DMSO as a component of the blank or the acetylcholine control did not produce any different result in luminescence, but it is still possible that the test drugs, which were first dissolved in DMSO and then in the proprietary reagents to improve solubility, reacted together or were changed slightly by the DMSO, which may have impacted the results. Third, we only studied the purified drugs in solution and not from blood samples. Considering drug distribution, binding to serum proteins, and metabolism that occur when drugs are used by human subjects, it is unclear how the results would differ if the assays were carried out using serum samples. We recognize this as a substantial limitation and have plans to complete future studies with this cell-based assay to determine serum anticholinergic activity. Fourth, as already mentioned, we focused on the M1 receptor which does not provide any information on binding to other muscarinic receptor subtypes.

In future experiments we hope to test the M1 antagonistic activity of drugs in blood samples from people taking anticholinergic agents. Furthermore, it would be informative to quantify both the serum concentrations and *in vitro* anticholinergic activity of drugs believed to be anticholinergic, as measured with this cell-based assay, and compare these results to the subjective anticholinergic effects the patient reports. In such an experiment, we may find there is a dose-response effect where more side effects are reported by the patients who have the highest measurable anticholinergic activity in their blood samples. This would suggest that our assay, as described, is a suitable method to measure and rank the objective anticholinergic activity of drugs in a manner that could be useful in the drive towards ever-personalized medicine, and therefore certainly warrants further study.

4.6 Conclusions

In conclusion, there remain significant issues in how anticholinergic activity is identified and anticholinergic burden is measured. We propose further investigation of this simple and quantitative method that allows for the measurement of drugs' anticholinergic activity. As work in this area progresses, objective measures of anticholinergic activity could ideally be completed for all drugs, thus helping guide clinician decision making.

CHAPTER 5 SEX-BASED ANALYSIS OF FOUR PRESCRIBING CASCADES IN OLDER ADULTS WITH DEMENTIA

5.1 Introduction

First reported by Rochon and Gurwitz in 1995 (P. A. Rochon & Gurwitz, 1995) the prescribing cascade refers to when an adverse drug event is misinterpreted as a new medical condition and a new medication is prescribed to treat the adverse drug event (McCarthy et al., 2019; P. A. Rochon & Gurwitz, 1995; Paula A. Rochon & Gurwitz, 2017). Older adults with dementia are more susceptible to adverse drug events than similarly aged controls without dementia (Eshetie et al., 2018; L. Kanagaratnam et al., 2016; Lukshe Kanagaratnam et al., 2014; Mullan et al., 2019; Parameswaran Nair et al., 2016) and have a higher risk of experiencing the prescribing cascade (Gill et al., 2005; Vouri et al., 2017) due to their high level of medication use. As prescribing for older adults with dementia may follow a sex-specific pattern it follows that the prescribing cascade may also be subject to sex-based differences in incidence or prevalence. The following study investigates the incidence of four prescribing cascades that were drawn from existing STOPP criteria (O'Mahony et al., 2015) in a population of Nova Scotia Seniors' Pharmacare Beneficiaries with dementia (NSSPBD) and includes a sex-based analysis.

5.1.1 Prescribing Cascade 1: Bladder Anticholinergics After Cholinesterase Inhibitors

Cholinesterase inhibitors represent a special case of the prescribing cascade for older adults with dementia as this class of medication is used almost exclusively in this population (de los Ríos, 2012; Desmidt et al., 2016). Tacrine, donepezil hydrochloride, rivastigmine tartrate, and galantamine hydrobromide are the cholinesterase inhibitors of which the latter three are currently used in Canada. Cholinesterase inhibitors bind and inhibit the activity of cholinesterase (Saxena & Dubey, 2019); an enzyme responsible for breakdown of acetylcholine (Hampel et al., 2018). In response to this drug therapy there is an increase in the concentration of acetylcholine available in the brain for neurotransmission (Håkansson, 1993; Krall et al., 1999; Kumar et al., 2015). This is how the medication is hypothesized to exert its beneficial effect in those with dementia. Cholinesterase inhibitors are not selective for the cholinesterase enzyme in the brain but

increase the concentration of acetylcholine available throughout the body. This includes acetylcholine in the urinary tract. In the urinary tract the detrusor muscle contains many muscarinic receptors (Sjögren, 1978) and activation of these muscarinic receptors causes forceful contraction of the detrusor which will force urine from the bladder (Mansfield et al., 2005; Sjögren, 1978). Muscarinic receptor subtypes M2 and M3 predominate in the detrusor, with M2 receptors comprising 71% of the muscarinic receptors and M3 receptors 22% (Mansfield et al., 2005). Increasing acetylcholine concentration during cholinesterase inhibitor treatment potentially increases detrusor contractions, causing urinary incontinence. Avoiding initiation of a bladder anticholinergic in response to adverse effects of cholinesterase inhibitor therapy is important for older adults with dementia because bladder anticholinergics can lead to worsening cognitive and functional outcomes in this population (Sink et al., 2008; Triantafylidis et al., 2018). Bladder anticholinergics are included on the Beers list and the STOPP criteria (By the 2019 American Geriatrics Society Beers Criteria® Update Expert Panel, 2019; O'Mahony et al., 2015) as PIM for older adults with dementia, and inhibit the desired effect of the cholinesterase inhibitor treatment (R. M. Carnahan et al., 2004).

Treating cholinesterase inhibitor induced urinary incontinence with a bladder anticholinergic is an example of the prescribing cascade.

5.1.2 Prescribing Cascade 2: Parkinson's Disease Medications After Metoclopramide

Parkinson's Disease refers to a progressive neurodegenerative nervous system disorder that affects movement. It is accepted that Parkinson's Disease is usually caused by degeneration of the dopaminergic neurons of the pars compacta in the substantia nigra and compaction of alpha synuclein (Balestrino & Schapira, 2020). The outcome of this neurodegeneration includes several motor (i.e. tremor, rigidity, bradykinesia) and non-motor (i.e. orthostasis, sleep disorders, restless legs) symptoms. These symptoms can be treated with supplemental dopamine (Emamzadeh & Surguchov, 2018) but, Parkinson's Disease treatment will not alter disease progression. A separate but similar disorder is caused by vascular insult to frontal lobes and other parts of the brain (Vizcarra et al., 2015). Referred to as vascular pseudoparkinsonism, this Parkinsonism is less responsive

to drug treatment but more frequently co-occurs in those with dementia, particularly those with a vascular or mixed picture of dementia (Korczyn, 2015; Rektor et al., 2018).

Metoclopramide is a seemingly unrelated medication used to treat nausea, vomiting, or loss of appetite all of which can occur in older adults and especially those older adults with dementia. Metoclopramide's mechanism of action is to antagonize the activity at D_2 receptors in the chemoreceptor trigger zone in the central nervous system which reduces the feeling of nausea. Metoclopramide is not perfectly selective for the D_2 receptors of the chemoreceptor trigger zone and can inhibit D_2 receptors in the brain inducing movement changes that mimic Parkinson's Disease. Metoclopramide-related movement symptoms can be mistaken for development of Parkinson's Disease or vascular pseudoparkinsonism and may be treated with dopaminergic medications in a prescribing cascade. Older adults with dementia who develop movement symptoms may be less likely to receive detailed neurologic work-up to diagnose the cause of the movement symptoms and receive Parkinson's Disease treatment to manage symptoms instead. Dopamine agonists and levodopa therapy are not without risk and increased dopamine concentrations can exacerbate movement symptoms or precipitate psychotic symptoms that may lead to further work-up, medical needs and care.

Treating movement symptoms caused by metoclopramide with Parkinson's Disease medications is an example of the prescribing cascade.

5.1.3 Prescribing Cascade 3: Diuretics After Calcium Channel Blockers

Calcium channel blockers are commonly used to treat hypertension. They are recommended as initial therapy as monotherapy or combination therapy for adults with either diastolic or systolic hypertension (Leung et al., 2017; Nerenberg et al., 2018). Calcium channel blockers are usually well tolerated; however, they do have several common adverse effects. One adverse effect associated with calcium channel blockers is pedal edema which is likely due to vasodilation of peripheral arterioles. The prevalence of peripheral edema is nearly 9% among people taking amlodipine and is higher in women (*Norvasc Monograph*, 2017). Treating physicians may mistake this pedal edema

for symptoms of heart failure or peripheral vascular disease and initiate a prescribing cascade by prescribing diuretics to treat the edema rather than selecting a different agent for hypertension management (Vouri et al., 2018; Woodford, 2019).

Treating pedal edema caused by calcium channel blockers with diuretics is an example of the prescribing cascade.

5.1.4 Prescribing Cascade 4: Proton Pump Inhibitor After High Anticholinergic Burden

A recently proposed prescribing cascade suggests that increased anticholinergic burden leads to prescription of proton pump inhibitors (PPI). Anticholinergic medications are known to cause gastrointestinal symptoms such as dry mouth, constipation and will decrease the pressure on the lower esophageal sphincter. In older adults with dementia who have impaired ability to explain their symptoms or perhaps recount with clarity when these gastrointestinal symptoms began it is exceedingly challenging for clinicians to recognize this potential prescribing cascade. This makes it concerning that the prescribing cascade of high anticholinergic burden leading to proton pump inhibitor prescription may occur in older adults with dementia (Rababa et al., 2016).

Treating gastrointestinal symptoms caused by a high anticholinergic burden with a PPI is an example of the prescribing cascade.

5.2 Objective

To complete a sex-based drug utilization review of medication use in older women and men with dementia with attention to four prescribing cascades:

i) Bladder anticholinergics following cholinesterase inhibitors
ii) Parkinson's Disease medications following metoclopramide
iii) Diuretics following calcium channel blockers
iv) PPI following a high anticholinergic burden

5.3 Methods

5.3.1 Data Sources

Administrative claims data was made available through Health Data Nova Scotia (HDNS). Data were extracted from provincial data sources including MSI Physician's Billings (MED), Seniors' Pharmacare (PHARM), Vital Statistics (VITAL), and the national data source the CIHI – Discharge Abstract Database (DAD). The source data for this research study from all sources was linked and was cut by HDNS on December 20, 2018. The data set included administrative data from March 1, 2005 to March 31, 2018. Databases used were housed by HDNS and data linkage was done using MSI number, which was not available to the research team but instead was replaced with a study identification number.

The data (or portions of the data) used in this report were made available by Health Data Nova Scotia of Dalhousie University. Although this research is based on data obtained from the Nova Scotia Department of Health and Wellness, the observations and opinions expressed are those of the authors and do not represent those of either Health Data Nova Scotia or the Department of Health and Wellness.

5.3.2 Data Description

Cohort entry was from the date that the Nova Scotia Seniors' Pharmacare Beneficiary (NSSPB) had at least one occurrence of any one of the International Classification of Diseases Clinical Modification (ICD) 9/10 codes that identify dementia from the MSI or DAD databases (table 6). ICD-9 and ICD-10 codes are alphanumeric codes used by physicians, health insurance companies, and public health agencies across the world to represent diagnoses. The ICD codes listed were chosen as they had been identified in the Nova Scotia Dementia Strategy (*Dementia Strategy*, 2015) as the most complete method to identify cases of dementia using administrative data.

Cohort entry was determined when a NSSPB was identified to have one of the ICD 9/10 codes within the date range of March 1, 2005 to March 31, 2015 to collect NSSPB with dementia (NSSPBD). Cohort exit was at the date of death or March 31, 2015, which was

the study end. Due to reliance on the PHARM database the cohort excluded adults less than 65 years of age with a dementia diagnosis and any adults over 65 years of age with dementia that did not participate in the Nova Scotia Seniors' Pharmacare Program (approximately 63% of adults over 65 years of age participate in the Nova Scotia Seniors' Pharmacare Program (personal communication, 2018)). The MED database provided date of dementia diagnosis, age at dementia diagnosis, and date of death.

Table 6: ICD9/10 diagnosis codes that were identified by the Nova Scotia Dementia Strategy as most likely to identify an individual with a diagnosis of dementia

Description	**ICD-9**	**ICD-10**
Alcohol-induced persisting amnestic disorder	290.x	F01.x, F05.1
Alcohol-induced persisting dementia	291.1	F10.6
Amnestic disorder in conditions classified elsewhere	291.2	F10.7
Dementia in conditions classified elsewhere	294.0	F04.x
Other cerebral degenerations ***Includes****: Alzheimer's disease; Frontotemporal dementia; Senile degeneration of the brain; Communicating hydrocephalus; Idiopathic normal pressure hydrocephalus; Cerebral degeneration in diseases classified elsewhere; dementia with Lewy's bodies; Dementia with Parkinsonism; Cerebral degeneration, unspecified.* ***Excludes****: Obstructive hydrocephalus; Reye's syndrome*	331.0-331.3, 331.5-331.7, 331.82, 331.83, 331.89, 331.9	G30.x, G31.0, G31.1, G31.8, G31.9, G32.8, G91.0, G91.2-G91.3, G91.8, G91.9, G94.x
Senility without mention of psychosis	797	R54.x

from (*Dementia Strategy*, 2015)

Once meeting cohort entry criteria, prescription drug dispensation data for drugs available through the NSSPP for requested drug classes were collected over the five year period from April 1, 2009 to March 31, 2015. Prescription data collected focused on the medications for each prescribing cascade as shown in table 7. Medication use and other patient descriptors were abstracted from the PHARM database, including, medication (ATC code), quantity dispensed, days supplied, prescription fill date, sex, and geographic

Table 7: Medications (generic name, ATC code) implicated in the four prescribing cascades studied

Prescribing Cascade	Initial Drug Class	Initial Drug	Prescribing Cascade Implicated Drug Class	Prescribing Cascade Implicated Drug
1	cholinesterase inhibitors (N06DA)	donepezil (N06DA02) rivastigmine (N06DA03) galantamine (N06DA04)	drug bladder anticholinergics (G04BD)	oxybutynin (G04BD04) tolterodine (G04BD07) solifenacin (G04BD08) trospium (G04BD09) darifenacin (G04BD10) fesoterodine (G04BD11)
2		metoclopramide (A03FA01)	Parkinson's Disease medications (N04B)	levodopa-carbidopa (N04BA02) levodopa-carbidopa-entacapone (N04BA03) amantadine (N04BB01) ropinirole (N04BC04) pramipexole (N04BC05) selegiline (N04BD01) entacapone (N04BX02)
3	calcium channel blockers (C08CA)	amlodipine (C08CA01) nifedipine (C08CA05) felodipine (C08CA02)	Diuretics (C03)	furosemide (C03CA01) spironolactone (C03DA01), hydrochlorothiazide (C03EA01) amiloride (C03DB01) ethacrynic acid (C03CC01) bumetanide (C03CA02)

Prescribing Cascade	Initial Drug Class	Initial Drug	Prescribing Cascade Implicated Drug Class	Prescribing Cascade Implicated Drug
4	drugs with high anticholinergic burden as identified as having a score of three on the anticholinergic cognitive burden scale (Buostani, 2009)	dicycloverine (A03AA07) scopolamine (hyoscine butylbromide) (A04AD01) dimenhydrinate (A04AD99) oxybutynin (G04BD04) tolterodine (G04BD07) solifenacin (G04BD08) trospium (G04BD09) darifenacin (G04BD10) fesoterodine (G04BD11) orphenadrine (M03BC01) trihexyphenidyl (N04AA01) procyclidine (N04AA04) benztropine (N04AC01) perphenazine (N05AB03) trifluoperazine (N05AB06) clozapine (N05AH02) olanzapine (N05AH03) quetiapine (N05AH04) hydroxyzine (N05BB01) desipramine (N06AA01) imipramine (N06AA02) clomipramine (N06AA04) trimipramine (N06AA06) amitriptyline (N06AA09) nortriptyline (N06AA10) doxepin (N06AA12) paroxetine (N06AB05)	Proton Pump Inhibitor (A02BC)	omeprazole (A02BC01) pantoprazole (A02BC02) lansoprazole (A02BC03) rabeprazole (A02BC04) esomeprazole (A02BC05)

location specified by the second digit of the postal code whereby 0 represents a rural location and digits 1-9 represent urban sites (*Nova Scotia Postal Codes*, 2001). Prescription data collected from April 1, 2009 to March 31, 2010 were used if needed for a look back period of one year to ensure that treatments in prescribing cascades were used in the proper sequence to meet the definition of a prescribing cascade. Exposure to a medication was defined as any dispensation according to the PHARM record, with the required assumption that dispensation was equivalent to medication use. The enrollment gap could have been as long as four years as cohort entry could be identified as early as April 1, 2005 but medication data was not collected until the period of study as much as four years later on April 1, 2009.

5.3.3 Analytic Procedures

To identify prescribing cascade (see figure 5);

Step 1. Identify cohort entry as the date of dementia diagnosis according to MED or DAD databases;

Step 2. From cohort entry or April 1, 2010 collect details of medication dispensation for initial medication (cholinesterase inhibitor, metoclopramide, calcium channel blockers, and PPI) from the PHARM database;

Step 3. Identify the first dispensation of the initial medication (cholinesterase inhibitor, metoclopramide, calcium channel blockers, PPI) between April 1, 2010 and March 31, 2015;

Step 4. Look back 365 days from the first date of dispensation of the initial medication for prescription of the associated prescribing cascade implicated medication (bladder anticholinergic, Parkinson's Disease medication, diuretic, highly anticholinergic medication). Confirm that the prescribing cascade implicated medication is started only following the initial medication by reviewing the date of dispensation;

Step 5. If the prescribing cascade implicated medication (bladder anticholinergic, Parkinson's Disease medication, diuretic, highly anticholinergic medication) was started within 180 days of the initial medication (cholinesterase inhibitor, metoclopramide, calcium channel blockers, PPI), this is identified as an instance of the prescribing cascade

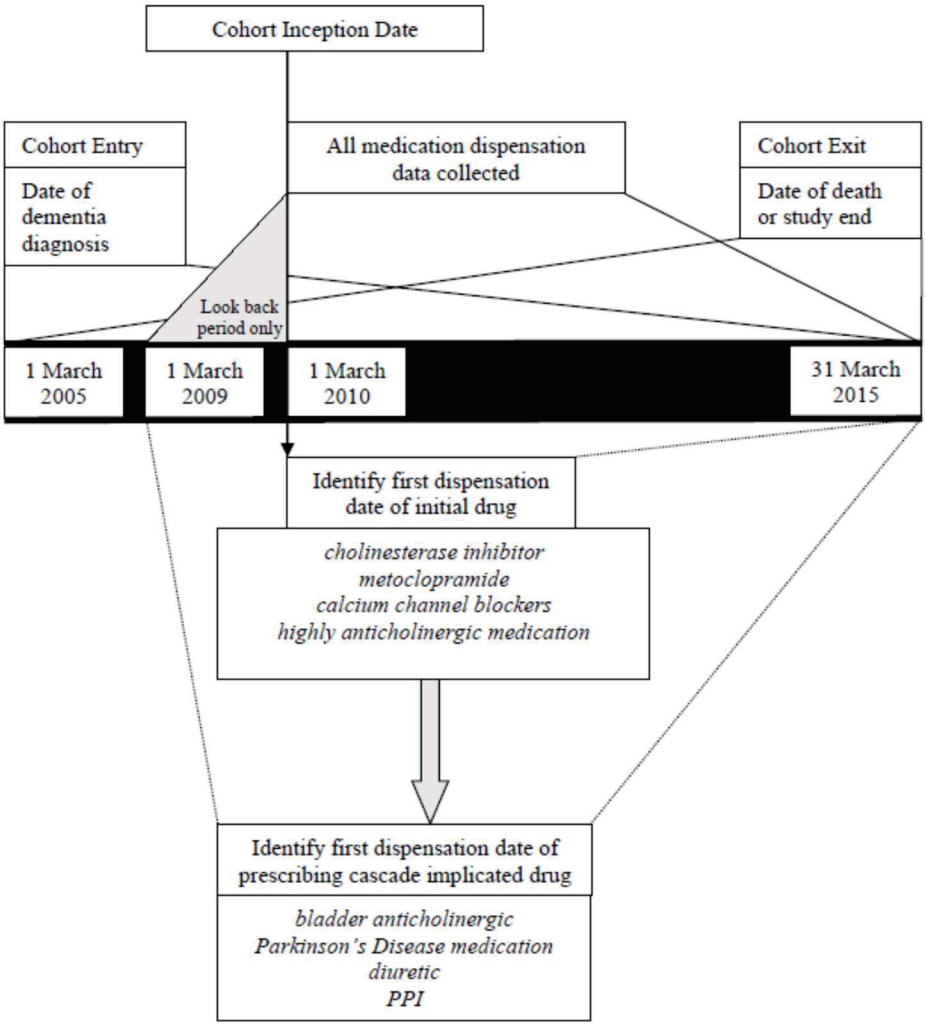


Figure 5: Study subject flow and dated data collection through the study of four prescribing cascades in Nova Scotia Seniors' Pharmacare Beneficiaries with dementia

Step 6. Robustness of each of the four prescribing cascades were tested by altering the window from 180 days to 90, 60 and 30 days;
Step 7. The number of men and women experiencing the four prescribing cascades were compared using chi square tests, the gap between both drugs in the prescribing cascade were compared using t-tests for men and women;
Step 8. The total number of prescriptions dispensed was reported as was the number of NSSPBD received at least one prescription for each medication. Percentages were calculated for men and women based on the total prescriptions or NSSPBD receiving each treatment to better demonstrate sex differences by providing a common base for male and female reporting. Duration of use for each medication was calculated by summing days supplied for consecutive prescriptions. Lag between dementia diagnosis and initiation of drug therapy was identified by the number of days from cohort entry/dementia diagnosis and date of first prescription for the medication;
Step 9. Logistic regression (adjusted) was used to identify risk factors for any prescribing cascade and for each of the four prescribing cascades.
Step 10. Patient characteristics and sex-based analysis were explored using descriptive statistics, and t-tests or chi square tests as appropriate.

Missing data were handled using case-wise deletion. Data were assessed for errors by considering ranges and examining datasets during analysis. Drug data was reported at the level of generic drug name (ATC code) and when numbers did not allow for reporting at the level of generic drug name, were collapsed to include related generic drugs into higher levels of ATC coding.

5.3.4 Statistical Software

All data analyses were completed on STATA version 15.1, StataCorp, Lakeway Drive, College Station, Texas, USA.

5.4 Results

5.4.1 Cohort Description

In the period from April 1, 2005 to March 31, 2015, a total of 37,619 NSSPB were identified with a dementia diagnosis. This included 23,241 women (61.8%) and 13,900 men (36.9%). Of this initially identified cohort 8,666 died before the study period began

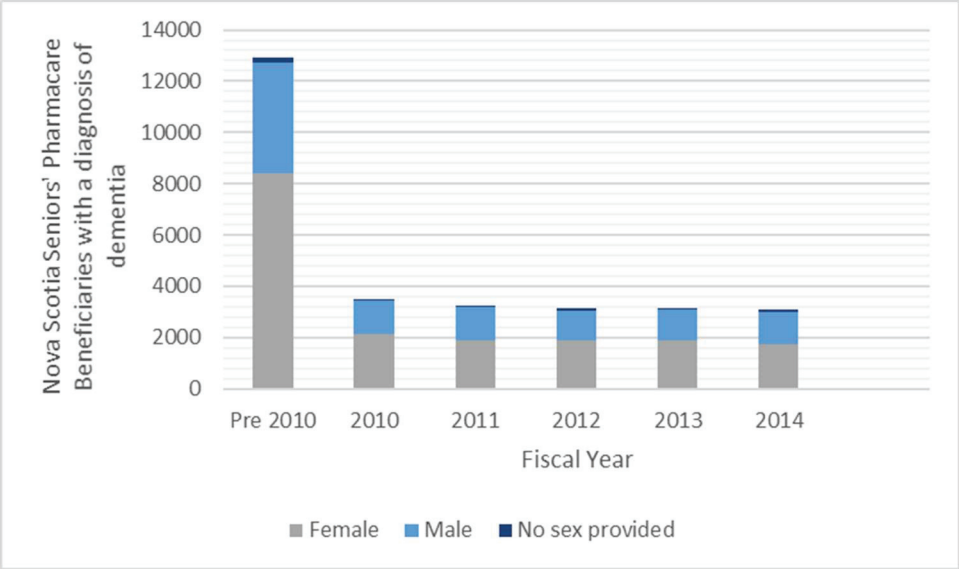


Figure 6: Number of Nova Scotia Seniors' Pharmacare Beneficiaries with a diagnosis of dementia entry to cohort by year

Table 8: Details of the cohort of Nova Scotia Seniors' Pharmacare Beneficiaries with Dementia including sex, age and rural versus urban location identified to have a dementia diagnosis and be alive between April 1, 2010 and March 31, 2015

	Total (n (%))	Women (n (%))	Men (n (%))
Number NSSPBD	28,953	17,946 (62.0%)	10,529 (36.4%)
Age at diagnosis (years (95% CI))	81.1 (81.0-81.2)	82.1 (82.0-82.2)	79.6 (79.4-79.7)
Age 65.0-74.9 (%)	6,355 (21.9%)	3,266 (11.3%)	2,922 (10.1%)
Age 75.0-84.9 (%)	12,222 (42.2%)	7,412 (25.6%)	4,637 (16.0%)
Age 85.0-94.9 (%)	8,254 (28.5%)	5,764 (19.9%)	2,385 (8.2%)
Age 95+ (%)	808 (2.8%)	637 (2.2%)	159 (0.5%)
Urban dwelling (%)	18,485 (63.8%)	11,812 (40.8%)	6,673 (23.0%)
Rural dwelling (%)	9,342 (32.3%)	5,806 (20.1%)	3,536 (12.2%)

on April 1, 2010. This left a cohort of 28,953 NSSPBD (17,946 women (62.0%) and 10,529 men (36.4%)) for study in our period of observation. During the period of observation 12,589 of the cohort died. Thus, the cohort of individuals living with dementia approaches 16,364 or 1.7% of the entire population of Nova Scotians and 8.8 % of the entire population of Nova Scotians aged over 65 years. At cohort inception date April 1, 2010 there were 12,909 living NSSPBD (8,409 women and 4,332 men). Each following year the cohort grew as shown in figure 6. The average age at dementia diagnosis was 81.1 years (95% CI: [81.0-81.2]) with women being older at diagnosis. Women were on average 82.1 years (95% CI: [82.0-82.2]) and men 79.6 years (95% CI: [79.4-79.7]) at dementia diagnosis. This difference in age at dementia diagnosis was statistically significant ($p<0.00001$).

The NSSPBD geographic locations are known with respect to rural or urban setting based on postal code. In addition to details on sex and age of NSSPBD a summary of rural versus urban locations is provided in table 8.

5.4.2 Prescribing Cascade 1: Bladder Anticholinergics After Cholinesterase Inhibitors

In total 117,416 prescriptions for a cholinesterase inhibitor (ATC N06DA) were dispensed to 5,772 NSSPBD (19.9% of NSSPBD) over the period of investigation April 1, 2010 to March 31, 2015. NSSPBD who received at least one dispensation for a cholinesterase inhibitor were on average 79.8 years of age at the time of their dementia diagnosis and 82.4 years of age at the time of their first cholinesterase inhibitor prescription. Cholinesterase inhibitors used included; donepezil (57.0%), galantamine (36.0%), and rivastigmine (7.0%). The time between dementia diagnosis and first dispensation for a cholinesterase inhibitor was on average 2.6 years (95% CI[2.5-2.6]) with women having a longer time between diagnosis and cholinesterase inhibitor treatment (2.6 versus 2.3 years, $p<0.0001$). Those NSSPBD receiving cholinesterase inhibitor treatment used these agents for on average 1.9 years (table 9) with women using cholinesterase inhibitors for a longer duration (1.9 versus 1.8 years, $p=0.0012$).

Table 9: Detailed drug utilization: Details of cohort use of cholinesterase inhibitors, bladder anticholinergics and those who experienced a prescribing cascade of bladder anticholinergics used to treat cholinesterase inhibitor induced urinary incontinence

	Total	Women	Men
Total cholinesterase inhibitor (*N06DA*) prescriptions dispensed	117,416	85,690 (73.0%)	31,515 (26.8%)
Donepezil (*N06DA02*)	66,933 (57.0%)	50,500 (43.0%)	16,293 (13.9%)
Rivastigmine (*N06DA03*)	8,270 (7.0%)	5,031 (4.3%)	3,227 (2.7%)
Galantamine (*N06DA04*)	42,213 (36.0%)	30,159 (25.7%)	11,995 (10.2%)
Number of NSSPBD receiving at least one cholinesterase inhibitor (*N06DA*) prescription	5,772	3,967 (68.7%)	1,791 (31.0%)
Average duration by patient (years, SD)	1.9 (1.5)	1.9 (1.5)	1.8 (1.4)
Donepezil (*N06DA02*)	3,439 (59.6%)	2,429 (42.1%)	999 (17.3%)
Average duration by patient (years, SD)	1.8 (1.5)	1.8 (1.5)	1.7 (1.4)
Rivastigmine (*N06DA03*)	391 (6.8%)	229 (4.0%)	161 (2.8%)
Average duration by patient (years, SD)	1.7 (1.5)	1.7 (1.5)	1.7 (1.5)
Galantamine (*N06DA04*)	1,942 (33.6%)	1,309 (22.7%)	631 (10.9%)
Average duration by patient (years, SD)	1.9 (1.5)	1.9 (1.5)	1.8 (1.5)
Age at dementia diagnosis (years, SD)	79.8 (6.8)	80.8 (6.7)	77.6 (6.5)
Age at first cholinesterase inhibitor prescription (*N06DA*) (years, SD)	82.4 (6.9)	83.5 (6.8)	79.9 (6.4)
Lag in years between dementia diagnosis and cholinesterase inhibitor treatment (years, SD)	2.5 (2.1)	2.6 (2.1)	2.3 (2.0)
Total bladder anticholinergic (*G04BD*) prescriptions dispensed	17,806	13,343 (74.9%)	4,294 (24.1%)
Oxybutynin (*G04BD04*)	11,570 (65.0%)	8,440 (47.4%)	2,908 (16.7%)
Tolterodine (*G04BD07*)	3,698 (20.8%)	3,085 (17.3%)	613 (3.4%)
Solifenacin (*G04BD08*),	1,910 (10.7%)	1,339 (7.5%)	558 (3.1%)
Trospium (*G04BD09*), Darifenacin (*G04BD10*), Fesoterodine (*G04BD11*)	628 (3.5%)	479 (2.7%)	143 (0.8%)

	Total	Women	Men
Number of NSSPBD receiving at least one bladder anticholinergic (*N06DA*) prescription	1,263	922 (73.0%)	324 (25.6%)
Average duration by patient (years, SD)	1.3 (1.3)	1.3 (1.4)	1.3 (1.2)
Oxybutynin (*G04BD04*)	925 (73.2%)	676 (53.5%)	234 (18.5%)
Average duration by patient (years, SD)	1.1 (1.2)	1.0 (1.2)	1.1 (1.2)
Tolterodine (*G04BD07*)	181 (14.3%)	138 (10.9%)	43 (3.4%)
Average duration by patient (years, SD)	1.6 (1.4)	1.7 (1.5)	1.2 (1.1)
Solifenacin (*G04BD08*)	109 (8.6%)	75 (5.9%)	32 (2.5%)
Average duration by patient (years, SD)	1.3 (1.2)	1.3 (1.2)	1.3 (1.3)
Trospium (*G04BD09*), Darifenacin (*G04BD10*), Fesoterodine (*G04BD11*)	48 (3.8%)	33 (2.6%)	15 (1.2%)
Average duration by patient (years, SD)	0.8 (0.9)	0.8 (0.9)	0.9 (1.0)
Age at dementia diagnosis (years, SD)	79.5 (7.6)	80.6 (7.7)	76.4 (6.86)
Age at first bladder anticholinergic prescription (*G04BD*) (years, SD)	81.8 (7.5)	83.0 (7.5)	78.7 (6.5)
Lag in years between dementia diagnosis and bladder anticholinergic treatment (years, SD)	2.3 (2.0)	2.3 (2.1)	2.3 (1.9)
Number of cases of the prescribing cascade in NSSPPBD	60	41 (68.3%)	19 (31.7%)
Age at diagnosis (years, SD)	79.0 (7.4)	80.9 (7.2)	74.8 (6.1)
Implicated cholinesterase inhibitor (*N06DA*)			
Donepezil (*N06DA02*)	40 (66.7%)	28 (46.7%)	12 (20.0%)
Galantamine (*N06DA04*), Rivastigmine (*N06DA03*)	20 (33.3%)	13 (21.7%)	7 (11.7%)
Implicated bladder anticholinergic (*G04BD*)			
Oxybutynin (*G04BD04*)	43 (71.7%)	27 (45.0%)	16 (26.7%)
Tolterodine (*G04BD07*), Solifenacin (*G04BD08*), Trospium (*G04BD09*), Darifenacin (*G04BD10*), Fesoterodine (*G04BD11*)	17 (28.3%)	<15	<15

In the same time period to the same population, 28,277 prescriptions for bladder anticholinergic medications were dispensed to 1,824 (6.3%) NSSPBD. NSSPBD who received at least one prescription for a bladder anticholinergic were on average 79.5 years of age at the time of their dementia diagnosis and 81.8 years at the time of their first bladder anticholinergic prescription. Bladder anticholinergics used included; oxybutynin (73.2%), tolterodine (14.3%), solifenacin (8.6%), trospium, darifenacin, and fesoterodine (combined 3.8%). The time between dementia diagnosis and first dispensation for a bladder anticholinergic was on average 2.3 years (95% CI[2.2-2.4]) which was similar for men and women (p=0.450). Those NSSPBD receiving a bladder anticholinergic used the treatment on average 1.3 years (table 9) and duration of use was similar for men and women (1.3 versus 1.3 years, p=0.4).

The accepted definition of the prescribing cascade, where cholinesterase inhibitor preceded the bladder anticholinergic by less than six months (180 days), was identified in 60 cases (41 women and 19 men, 0.2% of NSSPBD) (further details in table 9). Altering the window for the prescribing cascade to one to 90 days reduced the number of identified cases to 36 (25 women, 11 men, 0.1%) NSSPBD. Altering the window for prescribing cascade to up to 60 days reduced the number of identified cases to 32 (21 women, 11 men, 0.1%) NSSPBD. Altering the window for the prescribing cascade to up to 30 days reduced the number of identified cases to 16 (10 women, 6 men) NSSPBD.

Age and sex were significant risk factors for occurrence of the prescribing cascade of bladder anticholinergics following cholinesterase inhibitors with younger age and female sex being associated with the increased use of bladder anticholinergics following cholinesterase inhibitors (table 10).

Table 10: Logistic Regression (adjusted) for risk factors for bladder anticholinergics following cholinesterase inhibitors

Log	**Coefficient**	**Odds Ratio (95% CI)**	**P>|z|**
Age at diagnosis	-0.068	0.93 (0.90 - 0.97)	< 0.0001
Rurality	-0.089	0.92 (0.53 - 1.58)	0.750
Sex M	-0.78	0.46 (0.25 - 0.85)	0.012
Constant	-0.78	0.46 (0.03 - 6.36)	0.560

5.4.3 Prescribing Cascade 2: Parkinson's Disease Medications After Metoclopramide

In total 3,760 prescriptions for metoclopramide (ATC A03FA01) were dispensed to 1,038 NSSPBD (3.6%) over the period of follow-up. NSSPBD who received at least one dispensation for metoclopramide were on average 81.6 years of age at the time of their dementia diagnosis and 84.9 years of age at the time of their first metoclopramide prescription. The time between dementia diagnosis and first dispensation for metoclopramide was on average 3.3 years and longer for women than men (3.4 versus 2.9 years, p=0.0075). Those NSSPBD receiving metoclopramide used it for an average 0.2 years, with the shortest duration of 1 day and longest duration of 4.1 years (table 11). Duration of use did not differ between men and women (0.2 versus 0.2 years, p=0.29).

In the same time period to the same population, 25,984 prescriptions for Parkinson's Disease medications were dispensed to 997 (3.4%) NSSPBD. NSSPBD who received at least one prescription for a Parkinson's Disease medication were on average 78.6 years of age at the time of their dementia diagnosis and 81.0 years at the time of their first Parkinson's Disease medication prescription. Parkinson's Disease medications used included; levodopa-carbidopa (74.7%), pramipexole (12.2%), ropinirole (3.8%), amantadine (2.8%), levodopa-carbidopa-entacapone (1.1%), selegiline (2.0%) or entacapone (3.3%). The time between dementia diagnosis and first dispensation of a Parkinson's Disease medication was on average 2.4 years (95% CI[2.3-2.6]) with no difference between men and women (2.4 versus 2.5 years, p=0.33). Those NSSPBD receiving Parkinson's Disease treatment used it for on average 2.3 years (table 11).

The accepted definition of the prescribing cascade, where metoclopramide preceded the Parkinson's Disease medication by less than six months (180 days), was identified in 11 cases (table 11). Due to the very low number of cases of the prescribing cascade it was not possible to perform a regression analysis to identify risk factors for this prescribing cascade.

Table 11: Detailed drug utilization: Details of cohort use of metoclopramide, Parkinson's Disease medications and those who experienced a prescribing cascade of Parkinson's Disease medication used to treat metoclopramide induced movement symptoms

	Total	Women	Men
Total metoclopramide (*A03FA01*) prescriptions dispensed	3,760	2,986 (79.4%)	742 (19.7%)
Number of NSSPBD receiving at least one metoclopramide (*A03FA01*) prescription	1,038	796 (76.7%)	234 (22.5%)
Average duration by patient (years, SD)	0.2 (0.5)	0.2 (0.6)	0.2 (0.5)
Age at dementia diagnosis (years, SD)	81.6 (7.8)	82.7 (7.6)	77.8 (7.3)
Age at first metoclopramide (*A03FA01*) prescription (years, SD)	84.9 (7.8)	86.1 (7.6)	80.8 (7.3)
Lag in years between dementia diagnosis and metoclopramide treatment (years, SD)	3.3 (2.4)	3.4 (2.4)	2.9 (2.3)
Total Parkinson's Disease medication (*N04B*) prescriptions dispensed	25,984	13,643 (52.5%)	11,910 (45.8%)
Levodopa and decarboxylase inhibitor (*N04BA02*)	19,413 (74.7%)	9,782 (37.6%)	9,317 (35.9%)
Levodopa, decarboxylase inhibitor and COMT inhibitor (*N04BA03*)	280 (1.1%)	88 (0.3%)	192 (0.7%)
Amantadine (*N04BB01*)	727 (2.8%)	507 (1.9%)	198 (0.8%)
Ropinirole (*N04BC04*)	991 (3.8%)	559 (2.2%)	412 (1.6%)
Pramipexole (*N04BC05*)	3,191 (12.2%)	1,946 (7.5%)	1,171 (4.5%)
Selegiline (*N04BD01*)	529 (2.0%)	302 (1.2%)	226 (0.9%)
Entacapone (*N04BX02*)	853 (3.3%)	459 (1.8%)	394 (1.5%)
Number of NSSPBD receiving at least one Parkinson's Disease medication (*N04B*) prescription	997	536 (53.8%)	442 (44.3%)
Average duration by patient (years, SD)	2.3 (2.6)	2.2 (2.6)	2.5 (2.5)
Levodopa and decarboxylase inhibitor (*N04BA02*)	761 (76.3%)	395 (39.6%)	352 (35.3%)
Average duration by patient (years, SD)	2.2 (2.2)	2.1 (2.3)	2.3 (2.1)
Amantadine (*N04BB01*)	18 (1.8%)	12 (1.2%)	6 (0.6%)
Average duration by patient (years, SD)	3.5 (3.7)	3.2 (3.8)	3.8 (3.8)

	Total	Women	Men
Ropinirole (*N04BC04*)	42 (4.2%)	28 (2.8%)	13 (1.3%)
Average duration by patient (years, SD)	2.2 (2.6)	1.7 (2.3)	3.1 (3.0)
Pramipexole (*N04BC05*)	147 (14.7%)	93 (9.3%)	50 (5.0%)
Average duration by patient (years, SD)	2.1 (2.8)	2.0 (2.7)	2.3 (2.9)
Selegiline (*N04BD01*), Levodopa, decarboxylase inhibitor and COMT inhibitor (*N04BA03*), Entacapone (*N04BX02*)	29 (2.9%)	8 (0.8%)	21 (2.1%)
Average duration by patient (years, SD)	5.3 (4.5)	7.4 (5.6)	4.1 (3.4)
Age at dementia diagnosis (years, SD)	78.6 (7.2)	80.1 (7.4)	77.0 (6.6)
Age at first Parkinson's Disease medication (*N04B*) prescription (years, SD)	81.0 (7.1)	82.6 (7.2)	79.3 (6.4)
Lag in years between dementia diagnosis and metoclopramide Parkinson's Disease (*N04B*) treatment (years, SD)	2.4 (2.1)	2.5 (2.2)	2.4 (2.0)
Number of cases of the prescribing cascade in NSSPPBD	11	<10	<10
Age at diagnosis (years, SD)	80.9 (8.0)		
Implicated Parkinson's Disease medication (*N04B*)			
Levodopa and decarboxylase inhibitor (*N04BA02*), Ropinirole (*N04BC04*), Pramipexole (*N04BC05*),	11	<10	<10

5.4.4 Prescribing Cascade 3: Diuretics After Calcium Channel Blockers

In total 93,688 prescriptions for a calcium channel blocker (ATC C08CA) were dispensed to 4,639 NSSPBD (16.0%) over the period April 1, 2010 to March 31, 2015. NSSPBD who received at least one dispensation for a calcium channel blocker were on average 81.3 years of age at the time of their dementia diagnosis. Women were older than men at dementia diagnosis (82.6 versus 77.8 years ($p<0.0001$). Average age at first calcium channel blocker prescription was 83.5 years with women older (85.0 versus 79.9 years, $p<0.0001$). Calcium channel blockers used included; amlodipine (67.4%), felodipine (3.6%), and nifedipine (29.0%). The time between dementia diagnosis and first dispensation for a calcium channel blocker was on average 2.3 years. Women had a longer lag than men between dementia diagnosis and first calcium channel blocker prescription (2.4 versus 2.1 years, $p=0.0002$). Those NSSPBD receiving calcium channel blocker treatment used these agents for on average 1.9 years (table 12) with women using calcium channel blockers for longer durations (1.9 versus 1.8 years, $p=0.0004$).

In the same time period to the same population, 117,692 prescriptions for diuretic medications were dispensed to 6,389 (22.1%) NSSPBD. NSSPBD who received at least one prescription for a diuretic were on average 82.4 years of age at the time of their dementia diagnosis and of those who received at least one prescription for a diuretic, women were older than men at dementia diagnosis (83.5 versus 79.5 years, $p<0.0001$). NSSPBD were on average 84.8 years at the time of their first diuretic prescription with women older than men (86.1 versus 81.8 years, $p<0.0001$). Diuretics used by NSSPBD included; furosemide (86.0%), hydrochlorothiazide (6.5%), spironolactone (5.2%), amiloride, ethacrynic acid and bumetanide (0.4%). The time between dementia diagnosis and first dispensation for a diuretic was on average 2.5 years with the greatest time between diagnosis and diuretic treatment being 9.9 years. Those NSSPBD receiving a diuretic used these agents for on average 1.6 years (table 12) with women using diuretics longer than men (1.6 versis 1.5 years, $p=0.001$).

The accepted definition of the prescribing cascade, where calcium channel blocker prescription preceded the diuretic medication by less than six months (180 days), was

Table 12: Detailed drug utilization: Details of cohort use of calcium channel blockers and diuretics and those who experienced a prescribing cascade of diuretic medication used to treat calcium channel blocker induced pedal edema

	Total	Women	Men
Total calcium channel blocker (*C08CA*) prescriptions dispensed	93,688	70,873 (75.6%)	21,613 (23.1%)
Amlodipine (*C08CA01*)	60,662 (64.7%)	45,238 (48.3%)	14,618 (15.6%)
Nifedipine (*C08CA05*)	29,348 (31.3%)	22,785 (24.3%)	6,187 (6.6%)
Felodipine (*C08CA02*)	3,678 (3.9%)	2,850 (3.0%)	808 (0.9%)
Number of NSSPBD receiving at least one calcium channel blocker (*C08CA*) prescription	4,639	3,312 (71.4%)	1,266 (27.3%)
Average duration by patient (years, SD)	1.9 (1.5)	2.0 (1.5)	1.8 (1.5)
Amlodipine (*C08CA01*)	3,128 (67.4%)	2,211 (47.7%)	1,099 (23.7%)
Average duration by patient (years, SD)	1.8 (1.5)	1.9 (1.5)	1.7 (1.4)
Nifedipine (*C08CA05*)	1,343 (29.0%)	977 (21.1%)	350 (7.5%)
Average duration by patient (years, SD)	2.0 (1.7)	2.1 (1.6)	1.9 (1.7)
Felodipine (*C08CA02*)	168 (3.6%)	124 (2.7%)	59 (1.3%)
Average duration by patient (years, SD)	2.2 (1.6)	2.2 (1.6)	2.0 (1.4)
Age at dementia diagnosis (years, SD)	81.3 (7.7)	82.6 (7.5)	77.8 (7.1)
Age at first calcium channel blocker (*C08CA*) (years, SD)	83.5 (7.6)	85.0 (7.3)	79.9 (6.9)
Lag in years between dementia diagnosis and calcium channel blocker treatment (years, SD)	2.3 (2.1)	2.4 (2.1)	2.1 (2.0)
Total diuretic (*C03*) prescriptions dispensed	117,692	86,832 (73.8%)	29,719 (25.3%)
Furosemide (*C03CA01*)	101,253 (86.0%)	74,298 (63.1)	26,060 (22.1%)
Spironolactone (*C03DA01*)	9,012 (7.7%)	5,923 (5.0%)	2,929 (2.5%)
Hydrochlorothiazide (*C03EA01*)	6,915 (5.9%)	6,136 (5.2%)	693 (0.6%)
Amiloride (*C03DB01*)	408 (0.3%)	373 (0.3%)	635 (0.5%)
Ethacrynic Acid (*C03CC01*)	37 (0.03%)	<37	<37
Bumetanide (*C03CA02*)	67 (0.06%)	67 (0.06%)	0

	Total	Women	Men
Number of NSSPBD receiving at least one diuretic (*C03*) prescription	6,389	4,509 (70.6%)	1,812 (28.4%)
Average duration by patient (years, SD)	1.6 (1.6)	1.7 (1.6)	1.5 (1.6)
Furosemide (*C03CA01*) prescriptions	5,618 (87.9%)	3,915 (61.3%)	1,643 (25.7%)
Average duration by patient (years, SD)	1.5 (1.5)	1.6 (1.5)	1.4 (1.5)
Spironolactone (*C03DA01*) prescriptions	333 (5.2%)	226 (3.5%)	103 (1.6%)
Average duration by patient (years, SD)	2.4 (2.4)	2.3 (2.3)	2.7 (2.6)
Hydrochlorothiazide (*C03EA01*) prescriptions	414 (6.5%)	349 (5.5%)	61 (1.0%)
Average duration by patient (years, SD)	1.8 (1.5)	1.9 (1.5)	1.4 (1.3)
Amiloride (*C03DB01*), Bumetanide (*C03CA02*), Ethacrynic Acid (*C03CC01*)	24 (0.4%)	19 (0.3%)	5 (0.08%)
Average duration by patient (years, SD)	2.1 (2.0)	2.2 (2.1)	1.8 (1.8)
Age at dementia diagnosis (years, SD)	82.4 (7.7)	83.5 (7.5)	79.5 (7.3)
Age at first diuretic (*C03*) (years, SD)	84.8 (7.6)	86.1 (7.4)	81.8 (7.1)
Lag in years between dementia diagnosis and diuretic treatment (years, SD)	2.5 (2.2)	2.6 (2.2)	2.3 (2.1)
Number of cases of the prescribing cascade in NSSPPBD	289	191	77
Age at diagnosis (years, SD)	82.8 (7.7)	84.3 (7.4)	78.8 (7.3)
Implicated calcium channel blocker (*C08CA*)			
Amlodipine (*C08CA01*)	193	124	54
Felodipine (*C08CA02*)	10	<10	<10
Nifedipine (*C08CA05*)	86	61	20
Implicated diuretic (*C03*)			
Furosemide (*C03CA01*)	224	150	62
Hydrochlorothiazide (*C03EA01*)	41	27	8
Ethacrynic Acid (*C03CC01),* Spironolactone (*C03DA01*), Amiloride (*C03DB01*)	24	14	7

identified in 289 cases (further details in table 12). Reducing the window for the prescribing cascade to 30 days maintains 130 cases (83 women, 38 men). Logistic regression failed to identify any risk factors for this prescribing cascade (table 13).

Table 13: Logistic Regression (adjusted) for Risk Factors for Diuretics Following Calcium Channel Blockers

Log	**Coefficient**	**Odds Ratio (95% CI)**	**P>|z|**
Age at diagnosis	-0.027	0.97 (0.90 – 1.05)	0.495
Rurality	0.13	1.14 (0.30 – 4.42)	0.847
Sex M	-0.40	0.67 (0.17 – 2.62)	0.564
Constant	-5.97	0.0026 (4.1 x10^{-6} – 1.62)	0.070

5.4.5 Prescribing Cascade 4: Proton Pump Inhibitors After High Anticholinergic Loads

In total 161,791 prescriptions for a strong anticholinergic medication on the ACB scale were dispensed to 7,910 NSSPBD (27.3%) over the period of study. These NSSPBD were on average 80.3 years of age at the time of their dementia diagnosis and 83.2 years at the time of their first strong anticholinergic prescription. The variety of strongly anticholinergic medications used varied greatly. Details of use is presented in table 14. The three most commonly used strongly anticholinergic medications included; quetiapine, hyoscine butylbromide and oxybutynin which were dispensed at least once to 38.9%, 15.6% and 9.1% of NSSPBD respectively. The time between dementia diagnosis and first dispensation for a strongly anticholinergic medication was on average 2.9 years. Those NSSPBD receiving at least one dispensation for a strongly anticholinergic medication used these agents for on average 1.7 years.

In the same time period to the same population 183,225 prescriptions for PPI were dispensed to 9,072 NSSPBD (31.3%). The average age for these individuals was 80.7 years at the time of their dementia diagnosis and 83.1 years at the time of their first PPI prescription. PPI used included; rabeprazole (50.4%), omeprazole (27.8%), pantoprazole (20.0%), lansoprazole (1.7%) and esomeprazole (0.1%). The time between dementia diagnosis and first dispensation for a PPI was on average 2.5 years. Those NSSPBD receiving a PPI received the treatment on average 1.8 years (table 14).

Table 14: Detailed Drug Utilization: Details of cohort use of proton pump inhibitors and strong anticholinergic medications and those who experienced a prescribing cascade of proton pump inhibitors used to treat symptoms caused by use of strongly anticholinergic medications

	Total	Women	Men
Total strong anticholinergic prescriptions dispensed	161,791	114,418 (70.7%)	46,064 (28.5%)
Dicycloverine (*A03AA07*) and Orphenadrine (*M03BC01*)	170 (0.1%)	128 (0.08%)	42 (0.03%)
Scopolamine (hyoscine butylbromide) (*A04AD01*)	3,434 (2.1%)	2,432 (1.5%)	992 (0.6%)
Dimenhydrinate (*A04AD99*)	446 (0.3%)	339 (0.2%)	104 (0.06%)
Oxybutynin (*G04BD04*)	11,570 (7.2%)	8,440 (5.2%)	2,980 (1.8%)
Tolterodine (*G04BD07*)	3,698 (2.2%)	3,085 (1.9%)	613 (0.3%)
Solifenacin (*G04BD08*)	1,910 (1.2%)	1,339 (0.8%)	558 (0.3%)
Darifenacin (*G04BD10*)	158 (0.1%)	110 (0.07%)	45 (0.03%)
Fesoterodine (*G04BD11*) and Trospium (*G04BD09*)	470 (0.3%)	369 (0.2%)	98 (0.06%)
Trihexyphenidyl (*N04AA01*)	629 (0.4%)	384 (0.2%)	245 (0.2%)
Procyclidine (*N04AA04*), Perphenazine (*N05AB03*), Clozapine (*N05AH02*)	1,649 (1.0%)	1,266 (0.8%)	330 (0.2%)
Benztropine (*N04AC01*)	2,236 (1.4%)	1,493 (0.9%)	730 (0.5%)
Trifluoperazine (*N05AB06*)	967 (0.6%)	773 (0.5%)	194 (0.1%)
Olanzapine (*N05AH03*)	13,681 (8.5%)	9,646 (6.0%)	3,803 (2.4%)
Quetiapine (*N05AH04*)	78,171 (48.3%)	53,345 (33.0%)	24,437 (15.1%)
Hydroxyzine (*N05BB01*)	1,469 (0.9%)	1,166 (0.7%)	303 (0.2%)
Desipramine (*N06AA01*)	615 (0.4%)	521 (0.3%)	89 (0.06%)
Imipramine (*N06AA02*)	1,887 (1.2%)	535 (0.3%)	1,291 (0.8%)
Clomipramine (*N06AA04*)	938 (0.6%)	627 (0.4%)	311 (0.2%)
Trimipramine (*N06AA06*)	534 (0.3%)	441 (0.3%)	93 (0.06%)
Amitriptyline (*N06AA09*)	12,242 (7.6%)	8,893 (5.5%)	3,095 (1.9%)
Nortriptyline (*N06AA10*)	5,109 (3.2%)	4,057 (2.5%)	1,038 (0.6%)
Doxepin (*N06AA12*)	2,630 (1.6%)	1,942 (1.2%)	688 (0.4%)
Paroxetine (*N06AB05*)	17,189 (10.6%)	13,087 (8.1%)	3,985 (2.5%)

	Total	Women	Men
Number of NSSPBD receiving at least one strong anticholinergic prescription	7,910	5,559 (70.3%)	2,280 (28.8%)
Dicycloverine (*A03AA07*) and Orphenadrine (*M03BC01*)	12 (0.2%)	5 (0.06%)	7 (0.09%)
Scopolamine (hyoscine butylbromide) (*A04AD01*)	1,231 (15.6%)	929 (11.7%)	299 (3.8%)
Dimenhydrinate (*A04AD99*)	202 (2.6%)	151 (1.9%)	50 (0.6%)
Oxybutynin (*G04BD04*)	719 (9.1%)	525 (6.6%)	183 (2.3%)
Tolterodine (*G04BD07*)	148 (1.9%)	115 (1.5%)	33 (0.4%)
Solifenacin (*G04BD08*)	94 (1.2%)	62 (0.8%)	28 (0.4%)
Darifenacin (*G04BD10*)	12 (0.2%)	7 (0.09%)	5 (0.06%)
Fesoterodine (*G04BD11*), Trospium (*G04BD09*), Mirabegron (*G04BD12*)	25 (0.3%)	17 (0.2%)	8 (0.1%)
Trihexyphenidyl (*N04AA01*)	14 (0.2%)	8 (0.1%)	6 (0.08%)
Procyclidine (*N04AA04*), Perphenazine (*N05AB03*), Clozapine (*N05AH02*)	41 (0.5%)	31 (0.4%)	9 (0.1%)
Benztropine (*N04AC01*)	56 (0.7%)	38 (0.5%)	17 (0.2%)
Trifluoperazine (*N05AB06*)	17 (0.2%)	12 (0.2%)	5 (0.06%)
Olanzapine (*N05AH03*)	341 (4.3%)	217 (2.7%)	118 (1.5%)
Quetiapine (*N05AH04*)	3,074 (38.9%)	2,058 (26.0%)	997 (12.6%)
Hydroxyzine (*N05BB01*)	84 (1.1%)	63 (0.8%)	21 (0.3%)
Desipramine (*N06AA01*)	21 (0.3%)	11 (0.1%)	10 (0.1%)
Imipramine (*N06AA02*)	32 (0.4%)	22 (0.3%)	9 (0.1%)
Clomipramine (*N06AA04*)	33 (4.2%)	16 (0.2%)	6 (0.08%)
Trimipramine (*N06AA06*)	20 (0.3%)	15 (0.2%)	5 (0.06%)
Amitriptyline (*N06AA09*)	695 (8.8%)	489 (6.2%)	195 (2.5%)
Nortriptyline (*N06AA10*)	294 (3.7%)	214 (2.7%)	76 (1.0%)
Doxepin (*N06AA12*)	119 (1.5%	86 (1.1%)	33 (0.4%)
Paroxetine (*N06AB05*)	637 (8.1%)	468 (6.0%)	160 (2.0%)
Average duration by patient (years, SD)	1.7 (2.0)	1.7 (2.0)	1.6 (1.9)
Age at dementia diagnosis (years, SD)	80.3 (8.0)	81.6 (7.8)	77.3 (7.3)
Age at first strong anticholinergic medication prescription (years, SD)	83.2 (8.0)	84.6 (7.9)	80.0 (7.3)
Lag between dementia diagnosis and strong anticholinergic (years, SD)	2.9 (2.3)	3.0 (2.3)	2.6 (2.2)

	Total	Women	Men
Total proton pump inhibitor prescriptions (A02BC) dispensed	183,225	131,935 (72.0%)	49,167 (26.8%)
Omeprazole (*A02BC01*)	52,033 (28.4%)	38,549 (21.0%)	13,196 (7.2%)
Pantoprazole (*A02BC02*)	33,533 (18.3%)	23,234 (12.7%)	9,760 (5.3%)
Lansoprazole (*A02BC03*)	2,880 (1.6%)	2,054 (1.1%)	795 (0.4%)
Rabeprazole (*A02BC04*)	94,627 (51.6%)	67,972 (37.1%)	25,390 (13.9%)
Esomeprazole (*A02BC05*)	152 (0.09%)	126 (0.07%)	26 (0.01%)
Number of NSSPBD receiving at least one proton pump inhibitor prescription	9,072	6,139 (67.7%)	2,805 (30.9%)
Omeprazole (*A02BC01*)	2,526 (27.8%)	1,753 (19.3%)	748 (8.2%)
Average duration by patient (years, SD)	1.8 (1.5)	1.9 (1.5)	1.7 (1.5)
Pantoprazole (*A02BC02*)	1,810 (20.0%)	1,171 (12.9%)	605 (6.7%)
Average duration by patient (years, SD)	1.7 (1.3)	1.7 (1.4)	1.5 (1.3)
Lansoprazole (*A02BC03*)	152 (1.7%)	98 (1.1%)	52 (0.6%)
Average duration by patient (years, SD)	1.9 (1.5)	2.0 (1.5)	1.6 (1.4)
Rabeprazole (*A02BC04*)	4,575 (50.4%)	3,111 (34.3%)	1,397 (15.4%)
Average duration by patient (years, SD)	1.8(1.5)	1.9 (1.5)	1.8 (1.5)
Esomeprazole (*A02BC05*)	9 (0.1%)	<7	<7
Average duration by patient (years, SD)	1.6 (1.2)	1.8 (1.5)	1.2 (0.2)
Average duration by patient (years, SD)	1.8 (1.5)	1.9 (1.5)	1.7 (1.5)
Age at dementia diagnosis (years, SD)	80.7 (7.9)	81.9 (7.8)	78.1 (7.3)
Age at first proton pump inhibitor prescription (years, SD)	83.1 (7.8)	84.5 (7.7)	80.4 (7.1)
Lag in years between dementia diagnosis and proton pump inhibitor treatment (years, SD)	2.5 (2.2)	2.5 (2.2)	2.3 (2.1)
Number of cases of the prescribing cascade in NSSPPBD	746	490 (65.7%)	207 (27.7%)
Age at dementia diagnosis (years, SD)	82.3 (8.0)	81.4 (7.7)	78.1 (6.7)
Strong anticholinergic implicated			
Dicycloverine (*A03AA07*), Scopolamine (hyoscine butylbromide) (*A04AD01*)	94 (12.6%)	73 (9.8%)	16 (2.1%)

	Total	Women	Men
Dimenhydrinate (*A04AD99*)	15 (2.0%)	8 (1.1%)	7 (0.94%)
Oxybutynin (*G04BD04*)	99 (13.2%)	65 (8.7%)	27 (3.6%)
Tolterodine (*G04BD07*)	32 (4.2%)	20 (2.7%)	9 (1.2%)
Solifenacin (*G04BD08*), Trospium (*G04BD09*), Darifenacin (*G04BD10*), Fesoterodine (*G04BD11*), & Mirabegron (*G04BD12*)	18 (2.4%)	12 (1.6%)	<5
Benztropine (*N04AC01*), Orphenadrine (*M03BC01*), Perphenazine (*N05AB03*), Trifluperazine (*N05AB06*), Trihexyphenidyl (*N04AA01*)	11 (1.5%)	<10	<5
Olanzapine (*N05AH03*)	28 (3.8%)	17 (2.3%)	11 (1.5%)
Quetiapine (*N05AH04*)	191 (25.6%)	117 (15.7%)	67 (9.0%)
Clomipramine (*N06AA04*), Desipramine (*N06AA01*), Doxepin (*N06AA12*), Hydroxyzine (*N05BB01*), Imipramine (*N06AA02*), Trimipramine (*N06AA06*)	32 (4.3%)	23 (3.1%)	5 (0.67%)
Amitriptyline (*N06AA09*)	114 (15.3%)	75 (10.1%)	28 (3.8%)
Nortriptyline (*N06AA10*)	36 (4.8%)	23 (3.1%)	10 (1.3%)
Paroxetine (*N06AB05*)	76 (10.2%)	49 (6.6%)	21 (2.8%)
Implicated proton pump inhibitor (*A02BC*)			
Omeprazole (*A02BC01*)	234 (31.4%)	160 (21.4%)	61 (8.2%)
Pantoprazole (*A02BC02*)	123 (16.5%)	82 (11.0%)	29 (3.9%)
Rabeprazole (*A02BC04*)	376 (50.4%)	241 (32.3%)	113 (15.1%)
Lansoprazole (*A02BC03*) and Esomeprazole (*A02BC05*)	13 (1.7%)	7 (0.94%)	<5

The accepted definition of the prescribing cascade was when the strong anticholinergic drug preceded the PPI by one day to six months (180 days). 746 cases of this prescribing cascade were identified in older adult NSSPBD (2.6% of NSSPBD) (table 14). Altering the window for the prescribing cascade to one to 90 days reduced the number of identified cases to 522 (340 women, 143 men, 1.8%) NSSPBD. Altering the window for prescribing cascade to up to 60 days reduced the number of identified cases to 416 (273 women, 109 men, 1.4%) NSSPBD. Altering the window for the prescribing cascade to up to 30 days reduced the number of identified cases to 273 (181 women, 72 men) NSSPBD.

Table 15: Logistic Regression (adjusted) for Risk Factors for Proton Pump Inhibitors Following Strong Anticholinergics

Log	**Coefficient**	**Odds Ratio (95% CI)**	**P>|z|**
Age at diagnosis	-0.027	0.97 (0.96 – 0.98)	<0.0001
Rurality	-0.078	0.92 (0.79 – 1.1)	0.331
Sex M	-0.43	0.65 (0.55 – 0.77)	<0.0001
Constant	-1.52	0.22 (0.10 – 0.48)	<0.0001

Logistic regression (table 15) suggested that younger age and female sex were significant risk factors for occurrence of the prescribing cascade where the use of PPI follows highly anticholinergic medications.

5.5 Discussion

The cohort of NSSPBD included 17,946 women and 10,529 men (total of 28,593) who entered the cohort between March 1, 2005 and April 30, 2015. All Nova Scotian residents over the age of 65 are eligible to subscribe to the NSSP medication plan. Since estimates suggest 129,200 Nova Scotians (13.7%) are over 65 years of age (Senior Citizens' Secretariat, 2003) and our cohort identified approximately 16,364 NSSPBD this corresponds to 12% of the Nova Scotia population over 65 years of age having a dementia diagnosis. This exceeds the estimated 7 to 10% of older adults who live with dementia (Prince et al., 2013), but is in keeping with Nova Scotia having one of the

oldest populations in Canada. This makes it more likely that this is a good representation of the population with dementia as our aged population in Nova Scotia might be expected to have a higher prevalence of dementia.

We also see a sex distribution in our population of NSSPBD that has an increased proportion of women (62.0% women and 36.5% men). Women were also older than men at the time of their dementia diagnosis. There is a similar distribution of men and women with dementia in urban and rural settings across the province. There were more women than men with dementia at all age groups which increased as age category increased reflecting the increased life expectancy of women in general and women with dementia. This sex distribution is consistent with dementia populations in other jurisdictions (Ponjoan et al., 2020; Stocker et al., 2020).

5.5.1 Prescribing Cascade 1: Bladder Anticholinergics After Cholinesterase Inhibitors

The prescribing cascade of a bladder anticholinergic used to treat cholinesterase inhibitor induced urinary incontinence is a well-recognized prescribing cascade. Muscarinic receptors are found in the bladder in the urothelium, interstitial cells, detrusor muscle layers and nerve fibers. M2 and M3 receptor subtypes are common in the detrusor smooth muscle (Giglio & Tobin, 2009; Mukerji et al., 2006). Increasing acetylcholine concentration, as when using cholinesterase inhibitors, can overcome natural processes and increase uninhibited contractions resulting in urine being expelled from the bladder, causing urinary incontinence. Of the 5,772 NSSPBD who initiated cholinesterase inhibitor therapy during our period of observation 60 initiated a bladder anticholinergic within six months and were identified as cases of the prescribing cascade. This is only 1% of the NSSPBD who received a cholinesterase inhibitor and only 0.2% of the entire cohort. Those NSSPBD who received a cholinesterase inhibitor were initiated on the therapy an average 2.5 years after their diagnosis. More women used cholinesterase inhibitors and for longer periods of time than men with the exception of rivastigmine. In fact, rivastigmine use, as a proportion was much higher for men, with 41.1% of rivastigmine users being male compared to 32% of galantamine and 29% of donepezil users being male. This is presumably related to a higher incidence of Parkinson's Disease

dementia and dementia with Lewy Bodies in men. To date, rivastigmine has demonstrated the best evidence in the treatment of these two conditions.

Bladder anticholinergics were initiated by 1,263 NSSPBD over the period of observation. Bladder anticholinergics were more commonly used by women (75% of dispensations). For NSSPBD receiving bladder anticholinergics, these were started on average 2.3 years after their dementia diagnosis which is sooner after dementia diagnosis than cholinesterase inhibitors were started, which is an interesting finding. This may suggest that management of bladder incontinence was a greater priority early after dementia diagnosis than management of dementia specific symptoms. It likely signals that symptoms of incontinence are of concern for patients and their caregivers and this should be given significant medical attention. 4.4% of the cohort received at least one prescription for a bladder anticholinergic. While women used more bladder anticholinergics than men especially for the least expensive options (oxybutynin and tolterodine), men used proportionately more novel bladder anticholinergics (solifenacin, darifenacin, fesoterodine, and trospium).

This prescribing cascade occurred in 60 NSSPBD; 41 women and 19 men. Sex and age were associated with this prescribing cascade with the odds of the prescribing cascade for men being approximately half that for women and with each year increase in age the risk of the prescribing cascade decreasing by 7%. Donepezil was the most frequently implicated cholinesterase inhibitor and oxybutynin the most implicated bladder anticholinergic which is in keeping with general usage as the most commonly prescribed cholinesterase inhibitor and bladder anticholinergic. Altering the window of the prescribing cascade caused a reduction in the number of cases to 16 at a window of 30 days. This is a promising sign which suggests that in the short term non-pharmacological management may be attempted prior to initiation of medication.

This is not the first Canadian jurisdiction to investigate the occurrence of this prescribing cascade. An Ontario, Canada study also investigated bladder anticholinergics prescribed after cholinesterase inhibitors (Gill et al., 2005). They included individuals in the

provincial drug program who received a prescription for a cholinesterase inhibitor, and they limited the cohort to those who had a dementia diagnosis based on ICD-9 codes from physician visits. Gill *et al.* found that older adults dispensed cholinesterase inhibitors were at a higher risk of being prescribed a bladder anticholinergic than those who were not and found 916 prescribing cascade events over the 4 year period (HR 1.55; 95% CI (1.39 to 1.72)) (Gill et al., 2005). The study authors did not comment on sex differences in use of bladder anticholinergics or users of cholinesterase inhibitors but clearly identified that bladder anticholinergic use was greater in users of cholinesterase inhibitors than in those not using cholinesterase inhibitors. In our study 265 NSSPBD not receiving a cholinesterase inhibitor initiated a bladder anticholinergic. We identified 60 cases in 5,772 (1.0%) cholinesterase inhibitor users and 265 bladder anticholinergic users in 23,181cholinesterase inhibitor non-users (1.1%). This suggests that bladder anticholinergic use is not clearly increased by cholinesterase inhibitor use in our population of NSSPBD.

Similar to Gill *et al.* other researchers have analyzed bladder anticholinergic use in cholinesterase inhibitor users. Green *et al.* analyzed data from the Uniform Data Set of the National Alzheimer's Coordinating Center. While they did not assess the prescribing cascade, they examined how many people were on a bladder anticholinergic when they initiated a cholinesterase inhibitor. They found 331 cases where a bladder anticholinergic was started after already taking a cholinesterase inhibitor in this population of 10,491 older adults with dementia (Green et al., 2017). Carnahan *et al.* have investigated co-prescription of any anticholinergic medication with cholinesterase inhibitors. The prevalence of any anticholinergic being used with a cholinesterase inhibitor was 35.4% which greatly exceeds the co-prescription of bladder anticholinergics and cholinesterase inhibitors seen in our cohort (approximately 1.7%), but this is likely because we limited anticholinergics to only those used to treat urinary incontinence.

An Australian investigation into this same prescribing cascade found, over 4 years of study, in a population of 4,393 older adults with dementia, 36 cases of the prescribing cascade (0.8% of their cohort compared to 0.2% of NSSPBD). In the Australian study

nearly half of the cases of the prescribing cascade had each medication prescribed by different prescribers (Narayan et al., 2019). This points to the need for a single prescriber, ideally each person's Family Physician or Nurse Practitioner. In practice identifying strategies to reduce the occurrence of this prescribing cascade is complicated. The first issue of concern is identifying the prescribers. It is unknown in our study who prescribed each component involved in the prescribing cascade. Thus, targeting specific physician or prescriber groups with academic detailing information or resources for our Nova Scotia population of prescribers may be a challenge.

A separate significant issue to consider was the fact that in the 5-year period of study 1,263 NSSPBD were prescribed a bladder anticholinergic at all. Bladder anticholinergics are recommended to be avoided in older adults with dementia as they pose a significant risk for delirium or further cognitive decline (By the 2019 American Geriatrics Society Beers Criteria® Update Expert Panel, 2019; By the American Geriatrics Society 2015 Beers Criteria Update Expert Panel, 2015; Donnellan et al., 1997; Herbison et al., 2003; Katz et al., 1998). Surprisingly bladder anticholinergics were initiated just as quickly or even more quickly after dementia diagnosis than cholinesterase inhibitors. It is hypothesized that this reflects the fact that continence is just as important for community-dwelling adults, or their caregivers, than cognitive symptoms.

5.5.2 Prescribing Cascade 2: Parkinson's Disease Medications After Metoclopramide

We identified only 11 instances of the prescribing cascade where Parkinson's Disease medications were started after metoclopramide therapy to treat movement adverse events cause by the initial metoclopramide prescription. This was very promising suggesting that this is a very rare case of inappropriate prescribing in our population of NSSPBD. Due to the very low numbers we cannot comment on the sex distribution of this prescribing cascade but note that NSSPBD who experienced this prescribing cascade were younger than the general population of NSSPBD at the time of their diagnosis (80.9 years versus 81.1 years). In the few cases of the prescribing cascade identified, levodopa-carbidopa and ropinirole were the Parkinson's Disease medications that were most frequently implicated.

Metoclopramide use was low in the cohort with 3,760 prescriptions dispensed to 1,038 NSSPBD. Metoclopramide use was more common in women (76.7% of dispensations) compared to men (22.5% of dispensations). Duration of use was short term, likely reflecting use for temporary gastrointestinal issues or perhaps as a component of chemotherapy management. Women being dispensed metoclopramide were older than men at dementia diagnosis and at first metoclopramide dispensation.

In local clinical practice there had been a preference to using domperidone for the treatment of gastrointestinal symptoms. This was due to a favourable side effect profile and lack of extrapyramidal side effects that are associated with metoclopramide use. In 2010 domperidone was found to be associated with ventricular arrhythmia and sudden cardiac death (Berger et al., 2017; Field et al., 2019; Hondeghem, 2013; Johannes et al., 2010; Leelakanok et al., 2016). This risk of arrhythmia or QT interval prolongation was taken very seriously so domperidone was no longer considered a preferred option for the treatment of nausea for older adults with dementia locally. It might be expected that these serious side effects associated with domperidone therapy would encourage increased use of metoclopramide and thereby increase the risk of the prescribing cascade. This, however, was not the case in our population of NSSPBD.

While the low incidence of this prescribing cascade in Nova Scotia is promising, in a Korean population of adults over 60 years of age they found that those prescribed metoclopramide were about three times more likely to be prescribed levodopa than those who were not (OR 3.04; 95% CI (2.46 to 3.77) (Huh et al., 2019). They also demonstrated that as the duration of metoclopramide treatment increased the chances of levodopa prescription increased (2.82 times for days 1-19 and 4.14 times for >20 days both odds ratios were adjusted for age, sex and exposure to antipsychotic medications) (Huh et al., 2019). In a case control study of New Jersey Medicaid program patients aged 65 years or older, those taking metoclopramide were three times more likely to begin using a drug containing levodopa than patients not taking metoclopramide (OR 3.09; 95% CI (2.25 to 4.26)) (Avorn et al., 1995). We found such low levels of this prescribing

cascade it was not possible to adequately compare our population to those previously studied.

5.5.3 Prescribing Cascade 3: Diuretics After Calcium Channel Blockers

Calcium channel blockers can cause peripheral edema. Which may be mistaken for a symptom of heart failure or peripheral vascular disease. A diuretic may be initiated to treat this symptom rather than removal of the calcium channel blocker. There were 289 cases of this prescribing cascade in NSSPBD and interestingly shortening the window from 180 days to 30 days maintained 45% of the occurrences of this prescribing cascade (n=130). While management of this prescribing cascade should be discontinuation of the calcium channel blocker, it is promising that furosemide was the most frequently prescribed diuretic in this prescribing cascade as it is the most likely drug to successfully treat pedal edema. Unfortunately the primary mechanism of edema formation secondary to calcium channel blocker use is arteriolar dilatation, not fluid overload, so a loop diuretic is not likely to resolve the problem (Woodford, 2019). More concerning is the potential complications from initiation of an unneeded loop diuretic including electrolyte monitoring, causing or worsening urinary incontinence. The requirement of careful attention to hydration and possibly supplemental potassium may be far more challenging for older adults with dementia to manage than those with intact cognition and may increase caregiver burden for those reliant for support in medication management.

Women have been shown to be more likely to experience peripheral edema after treatment with calcium channel blockers (Makani et al., 2011). We did not find a statistically significant increase in this prescribing cascade in women. However, our results were supportive of previous work with 66% of cases occurring in women (191 cases in women and 77 in men). One reason women may be more sensitive to the adverse event of pedal edema may be the nature of feminine footwear which may make pedal edema easier for women to detect or more perhaps challenging for them to satisfactorally manage.

This prescribing cascade is concerning as it may lead to hypotension and falls. This is exacerbated due to evidence that nifedipine clearance is impaired in older adults and therefore can cause an increased hypotensive effect likely related to the prolonged $t_{1/2}$. This has been confirmed in older adults as five of six healthy older adults experienced a drop in systolic blood pressure exceeding 20 mmHg after receiving oral sustained release or IV nifedipine (Robertson et al., 1988).

5.5.4 Prescribing Cascade 4: Proton Pump Inhibitor After High Anticholinergic Burden

PPIs have been considered safe and as of 2014 (Canada, 2014) have been available without a prescription in Canada. Observational studies warn that PPIs may be associated with several serious adverse events, pneumonia, c. difficile infection, dementia, and kidney disease. STOPP criteria (O'Mahony et al., 2015) and the Beers list (By the 2019 American Geriatrics Society Beers Criteria® Update Expert Panel, 2019; By the American Geriatrics Society 2015 Beers Criteria Update Expert Panel, 2015) advocate for only short term use of PPIs which is the intention for making these medications available without a prescription. Of note our period of study ends in 2015 which means that any nonprescription PPI use was not captured and introduces a source of error in our reported results. PPIs were used by more than 30% of NSSPBD and use was prolonged with mean duration approaching two years. Moreover, PPI users were younger at dementia diagnosis than the average for the cohort and showed a similar sex distribution to the cohort in general.

Potent anticholinergics should be avoided in older adults with dementia (By the 2019 American Geriatrics Society Beers Criteria® Update Expert Panel, 2019; By the American Geriatrics Society 2015 Beers Criteria Update Expert Panel, 2015; O'Mahony et al., 2015). We identified a strong anticholinergic used in 7,910 (27%) of our cohort. This was more than one in four NSSPBD. Almost one third of the strongly anticholinergic medications used was quetiapine, however 25 different strongly anticholinergic medications were used by NSSPBD. Women were the predominant users of anticholinergic medications which is consistent with previous study (Chatterjee et al., 2020) and scoping review, unless the cohort is made up of adults using antipsychotics in

which case men have been shown to be the predominant anticholinergic users (François Montastruc et al., 2018). Anticholinergic medication users were younger than the cohort average and younger age increased the risk of this prescribing cascade. For every male there were nearly two females to experience this prescribing cascade. This may be related to more strong anticholinergic medication being used by women which is consistent with previous study findings.

In the original study that proposed the prescribing cascade Rababa *et al.* did not limit use of anticholinergic medication and proton pump inhibitors to the definitions of a prescribing cascade but managed to identify that increased anticholinergic burden increased the risk of proton pump inhibitor use (OR 1.066; 95% CI [1.006-1.13]) (Rababa et al., 2016). This study examined the use of PPI in 248 nursing home residents and factors associated with being prescribed a PPI. Ninety-three percent of residents taking a PPI had done so for longer than recommended durations. As anticholinergic burden, vitamin/supplement use, and number of oral products taken daily increased, residents were more likely to be taking a PPI. Higher anticholinergic burden and number of oral products taken daily were significant predictors in the final logistic regression model. Significant predictors of PPI use in the current study may be explained by the association between polypharmacy and dyspepsia and the lowering of esophageal sphincter pressure by anticholinergic drugs (Rababa et al., 2016). These described adverse drug events mimic symptoms that often lead to proton pump inhibitor prescription.

5.5.5 Limitations

Research using administrative data has a number of inherent limitations. The identification of individuals with dementia presents its own challenges, though these were mitigated by leveraging previous work by the Nova Scotia Dementia Strategy (*Dementia Strategy*, 2015). Dementia likely remains underdiagnosed in Nova Scotia which means that we were unable to capture older women and men who have dementia but have not had a diagnosis recorded in their medical record. We were unable to capture adults with dementia under the age of 65 as we lacked drug use in these cases given that the PHARM database only includes adults 65 years of age or older. We must also consider that not

everyone participates in the Nova Scotia Seniors' Pharmacare Program which limits generalizability of results. However, the majority of seniors (approximately 63% (personal communication, 2018)) in Nova Scotia subscribe to Senior's Pharmacare. We understand that Nova Scotia Seniors' Pharmacare subscribers and non-subscribers may differ in important ways. We had limited ability to describe the clinical picture of the individual patients and did not have data on medication indication, dose or directions. We were unable to identify if the subject resided in the community or in a residential care facility but were able to ascertain if they were in an urban or rural location. We assumed dispensation was equivalent to use. When examining the prescribing cascade, we did not have access to doctor provided samples, medications purchased with cash, or those purchased without a prescription. We were only able to examine fill dates by the pharmacy which does not necessarily represent when the prescriptions were used by the patients. There is, of course, limitations with respect to missing data, most importantly sex was missing for a proportion of patients. Those patients without sex specified were not included in analysis using case wise deletion. We did not have access to dose and had to rely on days supplied as a measure of duration of use. There were clearly errors in this data field as duration of use was found that exceeded study duration. There were also likely errors in the entered data. For example, there were cases that were reported with unlikely values such as age greater than 120 years. Despite these limitations, the PHARM data provided a unique and powerful opportunity to evaluate a substantial portion of the seniors living with dementia in Nova Scotia.

5.6 Conclusions

The novel prescribing cascade PPIs following potently anticholinergic medications was the most commonly identified of the four prescribing cascades studied. This is reflective of the high levels of anticholinergic medication use in the cohort. As potently anticholinergic medications represent PIM this is a concerning prescribing practice that would benefit from further investigation into understanding the types of medication used, populations using them and interventions to reduce anticholinergic medication use. Bladder anticholinergics following cholinesterase inhibitors was less common in NSSPBD than other jurisdictions which suggests that some anticholinergic medications

are being avoided in NSSPBD. Parkinson's Disease medications following metoclopramide was the least commonly identified prescribing cascade. Which is also a promising sign. Women comprised a larger portion of the cohort and were most frequently exposed to the medications and the prescribing cascades. Continuing to raise awareness of these prescribing cascades and targeting interventions to address them will be a challenge as prescribing is often shared between specialists, primary care providers and pharmacists. The province has recently consolidated prescribing information in a new Drug Information System (DIS) which should help increase knowledge of medication use for patients who see multiple prescribers or use multiple pharmacies. Incread transparency in medication use has not been studied extensively with respect to prescribing cascades but shows positive results when implemented in the management opioid use (Finley et al., 2020). But these systems are not automated and rely on clinicians consulting them regularly for updates. Encouraging each patient to have a single prescriber (Family Physician or Nurse Practitioner) and a single pharmacy is an important step to minimizing occurrence of prescribing cascades. Future work should address anticholinergic medication use, consider a sex-specific approach and proactively target older adults with dementia. It will take a collaborative approach with system-wide supports to reduce the incidence of both PIM use and prescribing cascades in NSSPBD.

CHAPTER 6 EVALUATION OF PRESCRIBING QUALITY IN OLDER ADULTS WITH DEMENTIA

6.1 Introduction

Geriatric medicine is a challenging sub-specialty of Internal Medicine which deals with the interplay of multiple chronic diseases, age-related changes in drug pharmacokinetics, drug interactions secondary to increased medication use, frailty, socio-economic challenges, and social vulnerability. To support clinicians caring for older adults respected authorities have developed tools to identify PIMs. The most commonly referenced tools in Geriatric Medicine are the Beers list criteria (By the 2019 American Geriatrics Society Beers Criteria® Update Expert Panel, 2019; By the American Geriatrics Society 2015 Beers Criteria Update Expert Panel, 2015) and the STOPP/START criteria (Khodyakov et al., 2017; O'Mahony et al., 2015). Both of these tools provide guidance for drug therapies to be avoided by older adults to optimize outcomes. Both of these tools recognize that older adults with dementia a represent a special clinical case and provide specific recommendations for this patient population. Some research has been done to look at concordance with isolated STOPP criteria in Nova Scotia (Black et al., 2015; Carter et al., 2019; Rigby et al., 2017; S. C. Trenaman et al., 2018) but this has not been a comprehensive program of prescription evaluation. Nova Scotia does not employ an active monitoring program of prescribing agreement with accepted guidelines for older adults or the sub-population of older adults with dementia. In order to understand what medication use practices need improvement in a specific population, a survey of medication use using specific and validated or widely accepted quality indicators is crucial for benchmarking purposes. An organized approach to prescription evaluation allows a focused approach to professional education, and development of disease management programs. This large-scale observational retrospective pharmacoepidemiological study of drug utilization was completed to compare concordance with quality indicators of medication use as stated in the Beer's list and STOPP/START criteria to identify the knowledge gap with special attention to sex-differences.

6.2 Objective

The objective was to complete a sex-based drug utilization review of medication use in older women and men with dementia with attention to STOPP criteria and Beers list criteria that are often of relevance to those with dementia.

Objective one was to examine prevalence of duplicate drug prescriptions from the classes of non-steroidal anti-inflammatory drugs (NSAIDs), selective serotonin reuptake inhibitors (SSRIs), loop diuretics, ACE-inhibitors, anticoagulants as recommended in the STOPP criteria.

Objective two was to examine the prevalence of classes of drugs that should be avoided by older adults with dementia including anticholinergics (STOPP criteria and Beers list) including bladder anticholinergics, and tricyclic antidepressants, antipsychotics (STOPP criteria and Beers list), benzodiazepines and zopiclone (Beers list), and H2 receptor antagonists (Beers list).

Objective three was to examine the prevalence of use of antipsychotics (i.e. other than quetiapine or clozapine) in those with parkinsonism or Lewy Body Dementia (STOPP criteria).

6.3 Methods

6.3.1 Data Sources

Administrative claims data were obtained through HDNS. Data were extracted from MED, PHARM, VITAL, and CIHI – DAD databases. The source data for this research study was cut by HDNS on December 20, 2018. The data set included administrative data from April 1, 2005 to March 31, 2018. Databases used were housed by HDNS and data linkage was done via MSI number which was not available to the research team but instead was replaced with a study identification number.

The data (or portions of the data) used in this report were made available by Health Data Nova Scotia of Dalhousie University. Although this research is based on data obtained from the Nova Scotia Department of Health and Wellness, the observations and opinions

expressed are those of the authors and do not represent those of either Health Data Nova Scotia or the Department of Health and Wellness.

6.3.2 Data Description

Cohort entry was from the date that a NSSPBD had at least one occurrence of any one of the ICD 9/10 codes that identify dementia from the MED or DAD databases (see table 6). ICD-9, ICD-10 codes were examined from March 1, 2005 to March 31, 2015 for cohort entry. Cohort exit was at the date of death or at March 31, 2015 which was the end of the period of study. Once meeting cohort entry criteria, prescription drug dispensation for requested drug classes was collected over a 5-year period from the PHARM database from April 1, 2010 to March 31, 2015. Drug data was collected at the level of the ATC code which corresponds to the generic drug name. Exposure to a medication was defined as any dispensation according to the PHARM record, with the required assumption that dispensation was equivalent to medication use. The enrollment gap was at the greatest 5 years, as cohort entry could be identified as early as April 1, 2005 but medication data was not collected until 5 years later. Figure 5 shows the movement of subjects through the cohort and study period data collection.

Medication use was abstracted from the PHARM database including ATC code, prescription fill date, and days supplied, along with sociodemographic characteristics including age at dementia diagnosis, date of dementia diagnosis, sex, geographic location specified by the second digit of the postal code whereby 0 represents a rural location and digits 1-9 represent urban sites (*Nova Scotia Postal Codes*, 2001), and date of death if it occurred during the period of observation.

6.3.3 Analytic Procedures

5.3.3.1 Objective 1: Describe Prevalence of Duplicate Drug Class Prescriptions

To examine drug class duplication, we limited the dataset to that of the prescription data of the particular drug class identified as inappropriate for duplication (NSAIDs, SSRIs, loop diuretics, ACE-inhibitors, anticoagulants) in each analysis. For each subject, the

ATC code/generic drug data was examined for the prescription claim date and days supplied which were used to create overall use for each unique ATC code. With data for each coded generic drug consecutive fills of different drugs were compared for each subject based on dispensing dates to identify overlapping drug use from the same class. Reporting included the number of NSSPBD receiving at least one prescription for each of the drugs in the classes explored, total number of prescriptions dispensed for each of the drugs in the classes explored, the drug classes duplicated in overlapping prescriptions, mean duration of overlap, mean age at dementia diagnosis and age at duplication for those receiving duplicate drug class prescriptions. All reporting was completed with stratification for sex.

6.3.3.2 Objective 2: Describe Prevalence of Medications Which Should be Avoided by Older Adults With Dementia

To give a full analysis of prevalence of PIM for older adults with dementia, prescription data was reported at the level of the ATC code/generic name and included dispensation date and days supplied. Drugs to be avoided included anticholinergic medications (Beers list and STOPP criteria) which included all drugs on the anticholinergic cognitive burden scale (Buostani, 2009) broken down by strong, moderate and weak anticholinergic medications. In addition, details for bladder anticholinergics and tricyclic anticholinergics were reported. We reported antipsychotic use by generation (first generation or conventional antipsychotics and second generation or atypical antipsychotics) (Beers list and STOPP criteria). We also reported benzodiazepine, zopiclone, H2-receptor blockers, (H2RAs) and PPI use to explore more classes of drugs to avoid as recommended by Beers list.

We reported number of NSSPBD receiving at least one prescription medication at the level of the ATC code/generic names, total number of prescriptions for each medication, duration of use, and mean age at dementia diagnosis with all parameters reported by sex.

6.3.3.3 Objective 3: Examine the Prevalence of Antipsychotic Use (i.e. Other Than Quetiapine or Clozapine) in Those With Parkinsonism or Lewy Body Dementia

In addition, details for antipsychotic medications used in combination with medications for Parkinsonism or Lewy Body Dementia were examined. We identified consecutive fills of an antipsychotic and a drug to treat parkinsonism based on dispensing date and days supplied by adding days supplied to the fill date for the first medication initiated in the pair then comparing to the fill date of the second medication. When comparing the pair of medications we assessed if the fill date for the second medication in the pair was dispensed before the first prescription ended. We were able to determine duration of overlap by assessing the dates and duration of supply of each drug in the pair. We reported drugs involved in overlapping prescriptions, number of NSSPBD receiving each prescription medication, total number of prescriptions for each medication, mean duration of overlap and mean age of those involved. All reporting was completed with stratification for sex. Because it was possible that Parkinson's Disease medications can precipitate psychotic symptoms due to dopaminergic excess, we examined which medication was initiated first in the pair to further help us determine the context of antipsychotic and Parkinson's medication co-prescription.

6.3.4 Statistical Software

All data analysis was completed on STATA version 15.1, StataCorp, Lakeway Drive, College Station, Texas, USA.

6.4 Results

6.4.1 Cohort Description

The cohort was described in chapter 5 in table 8 and figure 6.

6.4.2 STOPP Criteria – Duplicate Drug Class Prescription

STOPP criteria (O'Mahony et al., 2015) recommend optimization of monotherapy within a single drug class by achieving a target dose then consideration of a new agent. This recommendation is made for non-steroidal anti-inflammatory drugs (NSAIDs), selective serotonin re-uptake inhibitors (SSRIs), ACE inhibitors, and anticoagulants. Examination of NSSPBD with dementia found that prescribing was not in keeping with the

Table 16: Detailed drug utilization of NSAID use by NSSPBD over period of 1 April 2010 to 31 March 2015

NSAID			Total NSSPBD				Men				Women			
Total Rx dispensed			37,916				10,049 (26.5%)				25,244 (66.6%)			
NSSPBD receiving at least one Rx			6,119 (21.1%)				1,850 (30.2%)				3,741 (61.1%)			
Age at diagnosis (years (SD))			79.4 (7.7)				77.2 (7.2)				80.3 (7.8)			
Age at first NSAID Rx (years (SD))			80.0 (7.6)				78.0 (6.9)				81.3 (7.7)			
Duration (days (SD))			207.7 (360.4)				186.7 (334.2)				220.0 (372.4)			
Class	Generic Name	ATC code	# Rx	NSSPBD receiving at least one Rx	Age at first NSAID Rx (years (SD))	Dura-tion (days (SD))	# Rx	NSSPBD receiving at least one Rx	Age at first NSAID Rx (years (SD))	Duratio n (days (SD))	# Rx	NSSPBD receiving at least one Rx	Age at first NSAI D Rx (years (SD))	Dura-tion (days (SD))
Acetic Acid Derivatives	indometh-acin	M01AB01	1,404 (3.7%)	521 (8.5%)	80.0 (7.7)	53.7 (132.4)	659 (1.8%)	232 (3.8%)	78.6 (7.1)	55.0 (112.4)	582 (1.5%)	242 (4.0%)	81.8 (7.9)	51.9 (154.4)
	diclofenac	M01AB05	1,893 (5.0%)	312 (5.1%)	78.7 (7.8)	262.9 (430.2)	501 (1.3%)	103 (1.6%)	76.3 (6.5)	213.9 (365.9)	1,208 (3.2%)	170 (2.8%)	80.6 (8.1)	295.8 (460.8)
	diclofenac comb-inations	M01AB55	5,867 (15.5%)	851 (13.9%)	80.2 (7.3)	253.5 (378.8)	1,492 (4.0%)	236 (3.9%)	78.9 (7.1)	242.3 (360.7)	3,905 (10.4%)	546 (8.9%)	81.1 (7.4)	254.2 (377.1)
	sulindac etodolac ketorolac nabum-etone	M01AB02 M01AB08 M01AB15 M01AX01	347 (0.92%)	53 (0.87%)	80.8 (7.8)	255.7 (417.2)	37 (0.98%)	10 (0.2%)	75.9 (7.0)	165.6 (327.2)	238 (0.6%)	36 (0.6%)	81.9 (8.1)	241.8 (426.1)
Enolic Acid Derivatives	meloxi-cam	M01AC06	3,467 (9.1%)	434 (7.1%)	79.8 (7.1)	306.8 (443.1)	748 (2.0%)	121 (2.0%)	77.7 (6.4)	275.7 (417.8)	2,389 (6.4%)	271 (4.4%)	80.9 (7.3)	315.5 (451.6)
	piroxicam tenoxicam	M01AC01 M01AC02	105 (0.27%)	23 (0.04%)	81.6 (6.71)	166.1 (364.6)	28 (0.74%)	9 (0.1%)	79.6 (6.5)	71.2 (87.7)	35 (0.09%)	11 (0.2%)	82.0 (6.0)	145.9 (290.8)
Cox-2	celecoxib	M01AH01	13,315 (35.1%)	1,326 (21.7%)	81.0 (7.6)	337.3 (449.3)	2,948 (7.8%)	341 (5.6%)	78.7 (7.0)	307.0 (427.5)	9,769 (26.0%)	881 (14.4%)	82.3 (7.5)	362.2 (462.2)

NSAID			Total NSSPBD				Men				Women			
Class	Generic Name	ATC code	# Rx	NSSPBD receiving at least one Rx	Age at first NSAID Rx (years (SD))	Dura-tion (days (SD))	# Rx	NSSPBD receiving at least one Rx	Age at first NSAID Rx (years (SD))	Dura-tion (days (SD))	# Rx	NSSPBD receiving at least one Rx	Age at first NSAI D Rx (years (SD))	Dura-tion (days (SD))
Propionic Acid Derivatives	ibuprofen	M01AE01	3,535 (9.32%)	838 (13.7%)	80.4 (8.0)	108.4 (236.5)	1,159 (3.1%)	256 (4.1%)	77.7 (6.9)	129.1 (298.1)	2,217 (5.9%)	535 (8.7%)	81.9 (8.1)	99.2 (205.7)
	naproxen	M01AE02	7,433 (19.8%)	1,692 (27.7%)	79.0 (7.5)	137.8 (271.4)	2,213 (5.9%)	517 (8.4%)	77.4 (6.8)	133.7 (251.2)	4,634 (12.3%)	1,012 (16.5%)	80.3 (7.7)	140.3 (279.4)
	ketopro-fen	M01AE03	312 (0.82%)	48 (0.8%)	82.9 (7.5)	270.2 (310.5)	107 (0.28%)	14 (0.2%)	79.8 (8.8)	301.9 (337.1)	195 (0.5%)	29 (0.5%)	85.1 (6.4)	287.8 (317.7)
	flurbipro-fen tiapro-fenic acid	M01AE09 M01AE11	238 (0.63%)	21 (0.3%)	77.0 (5.9)	498.6 (523.3)	137 (0.36%)	11 (0.2%)	77.3 (5.0)	605.3 (573.5)	72 (0.19%)	8 (0.1%)	76.9 (7.9)	397.9 (500.2)

Table 17: Cases and Combinations of NSAIDs used concurrently for more than 30 days of overlap by NSSPBD

Drug 1 / **Drug 2**	indomethacin	sulindac	diclofenac	diclofenac, combinations	meloxicam	ibuprofen	naproxen	ketoprofen	tiaprofenic acid	celecoxib	**Total**
indomethacin			1	5	1		2			4	**13**
sulindac			1				1				**2**
diclofenac				3		3	6			2	**14**
diclofenac, combinations		1			2	4	2	1		11	**21**
piroxicam							1				**1**
meloxicam				1		1	4			1	**7**
ibuprofen			1	1			4	1		4	**11**
naproxen	1		1	3	4				1	11	**21**
ketoprofen									1		**1**
celecoxib			2	3	2	2	1				**10**
Total	**1**	**1**	**6**	**16**	**9**	**10**	**21**	**2**	**2**	**33**	**101**

recommendation and cases of duplicate prescribing were present for NSAIDs, SSRIs, ACE-inhibitors and anticoagulants as shown in tables (tables 16-24).

6.4.2.1 NSAIDs

It is recommended that prolonged use of NSAIDs be avoided. Despite this recommendation 6,119 (21.1%) NSSPBD received at least one prescription for an NSAID (table 16) and mean duration of use was 207.7 days. Duration of use was longer in women than in men (220.0 days versus 186.7 days, p=0.0006), though notably the duration of use for both men and women exceeded the recommendation of less than 90 days. NSAID use exceeding 90 days occurred in 2,170 NSSPBD (35.5% of NSAID users). Indomethacin which is considered a PIM (By the 2019 American Geriatrics Society Beers Criteria® Update Expert Panel, 2019; By the American Geriatrics Society 2015 Beers Criteria Update Expert Panel, 2015) was used by 521 older adults with dementia in the cohort (1.7%) with higher use in males (OR 0.46, 95% CI [0.38-0.56]).

There was concurrent use of NSAIDs in 317 NSSPBD (table 17). The overlap varied in duration from one day to 419 days with an average of 32.4 days. Given that short periods of overlap may represent drug switching, limiting overlap to more than 30 days identified 101 cases of NSAID duplication with an average period of duplication of 75.6 days. Limiting NSAID duplication to periods of overlap exceeding 90 days left 23 cases. Common drug duplicate pairs included celecoxib with naproxen, celecoxib with diclofenac, or diclofenac with naproxen. Duplicate NSAID use showed no sex difference (OR 1.01, 95% CI [0.66-1.55]).

6.4.2.2 SSRIs

SSRIs are considered a safe medication for depression or in some cases aggression in older adults with dementia (Aga, 2019; Ahmed et al., 2019; Pollock, 2019; Seitz et al., 2011). 9,091 (31.4%) NSSPBD received at least one prescription for an SSRI (table 18) and mean duration of use was 760.4 days or 2.1 years. Women represent 62% of the population of older adults with dementia and over 67% of those who receive at least one

Table 18: Detailed drug utilization of SSRI use by NSSPBD over period of 1 April 2010 to 31 March 2015

SSRI		Total NSSPBD				Male				Female			
Total Rx dispensed		209,743				51,543 (24.6%)				150,362 (71.7%)			
NSSPBD receiving at least one Rx		9,091				2,538 (27.9%)				6,158 (67.7%)			
Age (years (SD))		82.1 (7.9)				79.2 (7.1)				83.5 (7.8)			
Duration (days (SD))		760.4 (617.3)				700.3 (596.9)				784.5 (618.7)			
Generic Name	ATC code	# Rx	NSSPBD receiving at least one Rx	Age (years (SD))	Duration (days (SD))	# Rx	NSSPBD receiving at least one Rx	Age (years (SD))	Duration (days (SD))	# Rx	NSSPBD receiving at least one Rx	Age (years (SD))	Duration (days (SD))
fluoxetine	N06AB03	6,548 (3.1%)	274 (3.0%)	79.2 (7.9)	839.6 (715.2)	1,494 (0.7%)	71 (0.8%)	75.7 (6.6)	753.8 (645.4)	4,715 (2.2%)	185 (2.0%)	80.8 (8.0)	872.4 (711.3)
citalopram	N06AB04	148,647 (70.9%)	6,382 (70.2%)	82.6 (7.9)	754.1 (596.8)	36,809 (17.5%)	1,803 (20.9%)	79.8 (7.2)	695.3 (571.7)	107,231 (51.1%)	4,346 (47.8%)	84.1 (7.7)	779.1 (601.1)
paroxetine	N06AB05	24,082 (11.5%)	973 (10.7%)	80.5 (8.0)	885.8 (635.2)	5,511 (2.6%)	245 (2.7%)	78.0 (7.0)	816.7 (622.0)	17,501 (8.3%)	672 (7.4%)	81.8 (8.0)	906.1 (634.2)
sertraline	N06AB06	27,229 (13.0%)	1,338 (14.7%)	81.2 (7.6)	675.3 (658.3)	6,913 (3.3%)	386 (4.2%)	78.3 (6.8)	630.6 (666.7)	18,626 (8.9%)	869 (9.6%)	82.8 (7.5)	692.9 (651.1)
fluvoxamine	N06AB08	3,098 (1.5%)	120 (1.3%)	82.1 (7.8)	845.7 (642.0)	704 (0.3%)	31 (0.3%)	76.6 (4.8)	755.7 (615.2)	2,262 (1.1%)	84 (0.9%)	84.4 (7.9)	856.1 (658.5)

Table 19: Cases and Combinations of SSRIs used concurrently for more than 30 days of overlap by NSSPBD over period of 1 April 2010 to 31 March 2015

Drug 1 / **Drug 2**	fluoxetine	citalopram	paroxetine	sertraline	fluvoxamine	**Total**
fluoxetine		11		2	1	**14**
citalopram	4		12	45	4	**65**
paroxetine		6		4		**10**
sertraline		5	1			**6**
Total	**4**	**22**	**13**	**51**	**5**	**95**

prescription for an SSRI (table 18). Duration of use was longer in women than men (784.5 days versus 700.3 days, p<0.0001).

There was concurrent use of two SSRIs in 357 NSSPBD. The overlap varied from one day to 1,908 days with an average of 48.6 days. Given that short periods of overlap may represent drug switching, limiting overlap to more than 30 days identified 95 cases of SSRI duplication with an average period of duplication lasting 146.6 days (table 18). Limiting the period of SSRI overlap to more than 90 days left 24 cases. The most common drug duplicate pair was sertraline with citalopram (table 19). Duplicate SSRI use showed no sex difference (OR 0.67, 95% CI [0.42-1.07]).

6.4.2.3 Loop Diuretics

Loop diuretic use was common with 24.3% of NSSPBD receiving at least one prescription for a loop diuretic. Furosemide was the most commonly used loop diuretic and accounted for 99.9% of loop diuretic prescriptions (table 20). Concurrent loop diuretic use was exceedingly rare and limited to 9 NSSPBD. In the 9 cases of loop diuretic overlap the overlap was on average 298.2 days in duration. Removing cases of overlap less than 30 days in duration to account for drug switching reduced loop diuretic overlap to 5 instances with a duration of overlap on average 530.6 days or 1.5 years.

6.4.2.4 ACE-Inhibitors

9,083 (31.4%) NSSPBD received at least one prescription for an ACE-inhibitor (table 21) with a mean duration of use of 860 days or 2.4 years. Duration of use was similar in men and women (835.6 days versus 846.3 days, p=0.22). There was concurrent ACE-inhibitor use in 555 NSSPBD (table 22). The overlap varied from one to 1,787 days or 4.9 years with an average of 48.5 days. Given that short periods of overlap may represent drug switching, limiting overlap to more than 30 days identified 183 cases of ACE-inhibitor duplication with an average period of duplication of 123.9 days. Limiting ACE-inhibitor duplication to periods of overlap exceeding 90 days left 46 cases (table 22). Common drug duplicate pairs included combination products with a diuretic with the parent ACE-inhibitor presumably to increase ACE-inhibitor dose without increasing diuretic exposure

Table 20: Detailed drug utilization of loop diuretic use by NSSPBD over period of 1 April 2010 to 31 March 2015

Loop Diuretics		Total NSSPBD				Male				Female			
Total Rx dispensed		142,714				36,574 (25.6%)				99,391 (69.6%)			
NSSPBD receiving at least one Rx/SSRI		7,022				2,007 (28.6%)				4,641 (66.1%)			
Age (years (SD))		84.3 (7.7)				81.6 (7.2)				85.9 (7.5)			
Duration (days (SD))		687.6 (601.8)				652.3 (594.4)				694.34 (601.1)			
Generic Name	ATC code	# Rx	NSSPBD receiving at least one Rx	Age (years (SD))	Duration (days (SD))	# Rx	NSSPBD receiving at least one Rx	Age (years (SD))	Duration (days (SD))	# Rx	NSSPBD receiving at least one Rx	Age (years (SD))	Duration (days (SD))
furosemide	C03CA01	142,513 (99.9%)	7,004 (99.7%)	84.4 (7.7)	688.4 (601.7)	36,551 (25.6%)	2,003 (28.5%)	81.6 (7.3)	653.2 (594.6)	99,222 (69.5%)	4,628 (65.9%)	85.9 (7.5)	695.1 (600.9)
bumetanide ethacrynic acid	C03CA02 C03CC01	201 (0.1%)	18 (0.3%)	82.2 (9.5)	369.6 (549.8)								

Table 21: Detailed drug utilization of ACE-Inhibitor use by NSSPBD over period of 1 April 2010 to 31 March 2015

ACE-Inhibitors		Total NSSPBD				Male				Female			
Total Rx dispensed		194,822				56,367 (28.9%)				123,566 (63.4%)			
NSSPB receiving at least one Rx		9,083				2,955 (32.5%)				5,393 (59.4%)			
Age (years (SD))		81.7 (7.7)				79.0 (7.0)				83.6 (7.6)			
Duration (days (SD))		860.0 (615.5)				835.6 (598.1)				846.3 (610.9)			
Generic Name	ATC code	# Rx	NSSPBD receiving at least one Rx	Age (years (SD))	Duration (days (SD))	# Rx	NSSPBD receiving at least one Rx	Age (years (SD))	Duration (days (SD))	# Rx	NSSPBD receiving at least one Rx	Age (years (SD))	Duration (days (SD))
captopril	C09AA01	482 (0.2%)	32 (0.35%)	84.2 (7.4)	603.6 (482.1)	214 (0.1%)	13 (0.14%)	84.3 (8.3)	654.3 (516.2)	247 (0.13%)	16 (0.18%)	84.8 (7.4)	561.3 (474.3)
enalapril	C09AA02	22,267 (11.4%)	935 (10.3%)	83.4 (7.8)	947.0 (602.6)	4,744 (2.4%)	243 (2.7%)	81.0 (7.4)	859.9 (562.6)	16,228 (8.3%)	630 (6.9%)	84.6 (7.7)	954.0 (612.0)
lisinopril	C09AA03	13,518 (6.9%)	561 (6.2%)	82.6 (7.8)	964.0 (650.8)	3,058 (1.6%)	152 (1.7%)	79.2 (7.0)	916.0 (620.2)	9,670 (5.0%)	372 (4.1%)	84.2 (7.7)	963.0 (655.8)
perindopril	C09AA04	33,787 (17.3%)	1,825 (20.1%)	81.2 (7.6)	706.7 (563.8)	10,907 (5.6%)	647 (7.1%)	78.8 (6.8)	703.3 (552.2)	20,152 (10.3%)	1,019 (11.2%)	83.1 (7.6)	694.4 (559.6)
ramipril	C09AA05	88,677 (45.5%)	3,872 (42.6%)	81.8 (7.7)	906.2 (630.1)	27,743 (14.2%)	1,334 (14.8%)	79.1 (7.0)	896.2 (617.4)	54,395 (27.9%)	2,260 (24.9%)	83.9 (7.5)	872.5 (617.9)
quinapril	C09AA06	5,301 (2.7%)	205 (2.3%)	81.5 (7.7)	1029.9 (622.0)	1,246 (0.6%)	58 (0.64%)	79.4 (6.7)	909.5 (617.1)	3,544 (1.3%)	125 (1.4%)	82.8 (7.5)	1040.8 (622.3)
benazepril	C09AA07	177 (0.09%)	8 (0.09%)	79.2 (5.4)	1149.4 (654.2)								
cilazapril	C09AA08	2,740 (1.4%)	118 (1.3%)	82.0 (7.4)	964.1 (591.2)	698 (0.36%)	31 (0.34%)	79.0 (6.8)	1000.4 (550.4)	1,978 (1.0%)	81 (0.9%)	83.3 (6.8)	951.2 (593.2)
fosinopril	C09AA09	3,782 (1.9%)	150 (1.7%)	82.8 (7.9)	1101.0 (609.0)	910 (0.47%)	39 (0.43%)	79.7 (6.7)	1161.0 (550.1)	2,558 (1.3%)	99 (1.1%)	83.9 (8.1)	1022.6 (626.4)
trandolapril	C09AA10	6,776 (3.5%)	317 (3.5%)	80.6 (7.5)	799.1 (620.9)	2,012 (1.0%)	110 (1.2%)	78.5 (7.0)	753.1 (612.1)	4,331 (2.2%)	181 (2.0%)	82.2 (7.4)	823.3 (620.2)
enalapril + diuretic	C09BA02	720 (0.4%)	57 (0.63%)	82.7 (7.4)	584.8 (499.8)	118 (0.06%)	9 (0.1%)	77.3 (6.7)	712.8 (545.9)	528 (0.27%)	44 (0.48%)	83.2 (7.5)	525.8 (487.8)
lisinopril + diuretic	C09BA03	2,966 (1.5%)	147 (1.6%)	81.0 (8.0)	1002.9 (626.2)	635 (0.33%)	38 (0.42%)	76.3 (7.2)	849.8 (632.1)	1,766 (0.91%)	89 (0.98%)	83.2 (7.5)	946.2.1 (616.8)

ACE-Inhibitors		Total NSSPBD				Male				Female			
Generic Name	ATC code	# Rx	NSSPBD receiving at least one Rx	Age (years (SD))	Duration (days (SD))	# Rx	NSSPBD receiving at least one Rx	Age (years (SD))	Duration (days (SD))	# Rx	NSSPBD receiving at least one Rx	Age (years (SD))	Duration (days (SD))
perindopril + diuretic	C09BA04	5,631 (2.9%)	379 (4.2%)	79.8 (7.6)	664.5 (527.5)	1,825 (0.94%)	129 (1.4%)	77.4 (6.3)	703.4 (538.9)	3,062 (1.6%)	196 (2.2%)	81.6 (7.8)	655.6 (516.8)
ramipril + diuretic	C09BA05	5,853 (3.0%)	366 (4.0%)	80.5 (7.4)	765.9 (559.6)	1,749 (0.90%)	117 (1.3%)	77.5 (6.4)	784.2 (560.4)	3,508 (1.8%)	208 (2.9%)	82.4 (7.4)	732.5 (548.7)
quinapril + diuretic	C09BA06	1,597 (0.8%)	85 (0.94%)	80.5 (7.4)	906.1 (592.8)	326 (0.17%)	24 (0.26%)	78.5 (5.9)	768.3 (546.5)	1,151 (0.59%)	52 (0.57%)	82.2 (7.1)	967.2 (616.0)
cilazapril + diuretic	C09BA08	548 (0.3%)	26 (0.29%)	81.2 (8.8)	959.4 (656.8)	159 (0.08%)	9 (0.1%)	76.3 (7.4)	957.3 (774.3)	294 (0.15%)	15 (0.17%)	85.3 (7.8)	895.0 (612.7)

Table 22: Cases and Combinations of ACE-Inhibitors used concurrently for more than 30 days of overlap by NSSPBD over period of 1 April 2010 to 31 March 2015

Drug 1 / **Drug 2**	enalapril	lisinopril	perindopril	ramipril	quinapril	fosinopril	trandolapril	enalapril + diuretic	lisinopril + diuretic	perindopril + diuretic	ramipril + diuretic	quinapril + diuretic	**Total**
captopril			1										**1**
enalapril			8	2			1	***6***		2	1		**20**
lisinopril			4				1		***7***				**12**
perindopril				9		2				***46***		1	**59**
ramipril		1	9				2		1	9	***30***	1	**53**
quinapril												***2***	**2**
cilazapril			1										**1**
fosinopril										1			**1**
trandolapril			2										**2**
enalapril + diuretic	***2***										1		**3**
lisinopril + diuretic		***5***								1		1	**7**
perindopril + diuretic			***5***	1									**6**
ramipril + diuretic			1	***11***						1			**13**
quinapril + diuretic					***3***								**3**
Total	**2**	**6**	**31**	**23**	**3**	**2**	**4**	**6**	**8**	**60**	**32**	**5**	**183**

which represents 115 of the 183 cases (62.8%). Duplicate ACE-inhibitor use showed no sex difference (OR 1.19, 95% CI [0.86-1.63]).

6.4.2.5 Anticoagulants

There were 4,511 NSSPBD who received at least one prescription for an anticoagulant (table 23) with a mean duration of use of 683.7 days or 1.9 years. Duration of use was use was longer in men than women (706.3 days versus 659.6 days, p=0.02). There were 461 instances of duplication of anticoagulants among NSSPBD (table 24). The overlap varied from one to 233 days with an average of 30.53 days. Given that short periods of overlap may represent drug switching, limiting overlap to more than 30 days identified 160 cases of anticoagulant duplication with an average period of duplication of 63.6 days. Limiting anticoagulant duplication to periods of overlap exceeding 90 days leaves 29 cases remaining. Duplicate anticoagulant use showed no sex difference (OR 1.17, 95% CI [0.84-1.62]).

6.4.3 STOPP Criteria and Beers List Criteria - Avoid Anticholinergics

Both Beers List and the STOPP criteria recommend avoiding anticholinergic medications in older adults with dementia. Anticholinergics were approached three ways 1) the anticholinergic cognitive burden list, 2) bladder anticholinergics, and 3) tricyclic antidepressants (By the 2019 American Geriatrics Society Beers Criteria® Update Expert Panel, 2019; O'Mahony et al., 2015). 811,553 prescriptions for an anticholinergic from the ACB scale medication were dispensed to 18,552 NSSPBD (64.1%) (11, 970 women and 5,449 men).

6.4.3.1 Anticholinergic Cognitive Burden Scale Score 3 - Strong Anticholinergic

Over the period of study 12,935 (44.7%) of NSSPBD (8,689 women and 3,615 men) received at least one prescription for a score 3 or strong anticholinergic medication (table 25). The most common strong anticholinergic was quetiapine for both men and women NSSPBD and included 40.9% of all strong anticholinergic dispensations to 29.9% of NSSPBD. Paroxetine was the second most commonly dispensed strong anticholinergic; 11.4% of dispensations distributed to 7.5% of NSSPBD. Third was amitriptyline,

Table 23: Detailed drug utilization of anticoagulants as used by NSSPBD over period of 1 April 2010 to 31 March 2015

Anticoagulants		Total NSSPBD				Male				Female			
Total Rx dispensed		91,653				28,776 (31.4%)				57,513 (62.8%)			
NSSPB receiving at least one Rx		4,511				1,486 (32.9%)				2,713 (60.1%)			
Age (years (SD))		82.9 (7.2)				80.7 (6.6)				84.5 (7.1)			
Duration (days (SD))		683.7 (735.7)				706.3 (733.2)				659.6 (730.1)			
Generic Name	ATC code	# Rx	NSSPBD receiving at least one Rx	Age (years (SD))	Duration (days (SD))	# Rx	NSSPBD receiving at least one Rx	Age (years (SD))	Duration (days (SD))	# Rx	NSSPBD receiving at least one Rx	Age (years (SD))	Duration (days (SD))
warfarin	B01AA03	85,359 (93.1%)	3,120 (69.2%)	83.1 (7.1)	935.6 (744.4)	26,982 (29.4%)	1,084 (24.0%)	80.8 (6.5)	922.9 (737.3)	53,474 (58.3%)	1,818 (40.3%)	84.8 (7.0)	928.6 (742.9)
acenocou-marol	B01AA07	45 (0.05%)	<5	83.6 (9.8)	626.3 (754.5)								
heparin	B01AB01	70 (0.08%)	33 (0.7%)	82.5 (8.0)	30.3 (47.3)	21 (0.2%)	13 (0.3%)	79.9 (8.0)	30.8 (50.6)	49 (0.05%)	20 (0.4%)	84.1 (13.8)	30.0 (46.3)
dalteparin	B01AB04	2,037 (2.2%)	896 (19.9%)	82.7 (7.5)	30.7 (77.3)	652 (0.7%)	245 (5.4%)	80.0 (7.0)	34.6 (110.2)	1,278 (1.4%)	602 (13.3%)	84.1 (7.4)	30.7 (62.6)
enoxaparin	B01AB05	151 (0.2%)	60 (1.3%)	82.0 (8.7)	47.2 (155.6)	41 (0.04%)	14 (0.3%)	78.8 (7.4)	24.9 (29.0)	109 (0.1%)	45 (1.0%)	82.9 (9.0)	55.0 (178.7)
dabigatran etexilate	B01AE07	3,138 (3.4%)	209 (4.6%)	82.7 (6.1)	494.8 (333.6)	809 (0.9%)	66 (1.5%)	81.3 (5.8)	464.3 (356.0)	2,071 (2.3%)	123 (2.7%)	83.6 (5.9)	509.3 (328.2)
rivarox-aban	B01AF01	569 (0.6%)	154 (3.5%)	82.2 (7.0)	126.0 (56.2)	215 (0.2%)	55 (1.2%)	80.7 (5.8)	133.8 (56.5)	294 (0.3%)	82 (1.8%)	83.7 (7.4)	115.6 (54.5)
apixaban	B01AF02	284 (0.3%)	36 (0.8%)	82.7 (7.3)	245.4 (151.3)	53 (0.06%)	8 (0.2%)	80.3 (6.5)	192.5 (84.8)	196 (0.2%)	21 (0.5%)	83.9 (8.1)	281.4 (172.5)

Table 24: Combinations of anticoagulants used concurrently for more than 30 days by NSSPBD from 1 April 2010 to 31 March 2015

Drug	warfarin	heparin	dalteparin	enoxaparin	dabigatran etexilate	rivaroxaban	**Total**
warfarin		1	62	5	11	4	**89**
dalteparin	68						**68**
enoxaparin	3						**3**
Total	**71**	**1**	**62**	**5**	**11**	**4**	**160**

comprising 10.4% of strong anticholinergic dispensations to 11.4% of NSSPBD. This shows that amitriptyline was dispensed less often but to more individuals compared to paroxetine which was used for longer duration by NSSPBD. Oxybutynin and olanzapine represented the third and fourth most commonly dispensed strong anticholinergics with just over 8% of dispensations for each. However, olanzapine was used by only 3.5% of NSSPBD and oxybutynin by11.9% of NSSPBD. This reflects long-term use of olanzapine and shorter-term use by more NSSPBD of oxybutynin.

6.4.3.2 Anticholinergic Cognitive Burden Scale Score 2 - Moderate Anticholinergic

Over the period of study 958 (3.3%) of NSSPBD (578 women and 332 men) received at least one prescription for a score 2 moderate anticholinergic (table 26). These are the most infrequently used class of anticholinergics.

6.4.3.3 Anticholinergic Cognitive Burden Scale Score 1 - Weak Anticholinergic

Over the period of study at least one prescription for a weakly anticholinergic medication were dispensed to 17,274 (59.7%) NSSPBD (11,154 women and 5,088 men) (table 27). Some NSSPBD were receiving prescriptions for more than one of these agents. Risperidone, a potent antipsychotic, had the third greatest number of dispensations, but prednisone had the third greatest number of NSSPBD receiving it. This reflects longer term use of risperidone amongst fewer NSSPBD and short-term use of prednisone amongst more NSSPBD.

It is promising that metoprolol, which is indicated in numerous chronic medical conditions, was the most dispensed weak anticholinergic (26% of weak anticholinergic dispensations to 15.3% of NSSPBD). Unfortunately, trazodone a sedating antidepressant often used for sleep or BPSD in older adults with dementia represents the second most dispensed weak anticholinergic. Trazodone was used by 16.1% of NSSPBD.

For weak anticholinergics we see expected use of metoprolol and prednisone equally distributed between men and women and this was confirmed with approximately double the NSSPBD receiving both being women; consistent with the composition of the cohort.

Table 25: Detailed drug utilization of Anticholinergic Cognitive Burden Scale Score 3 - Strong Anticholinergic as used by NSSPBD over period of 1 April 2010 to 31 March 2015

Score 3 - Strong Anticholinergic		Total Population				Men				Women			
Total Rx dispensed		210,450				58,436 (27.8%)				143,498 (68.2%)			
NSSPBD receiving at least one Rx		12,935				3,615 (27.9%)				8,689 (67.2%)			
Age (years (SD))		82.2 (8.1)				79.4 (7.3)				83.8 (8.1)			
Duration (days (SD))		510.2 (619.2)				487.6 (601.7)				515.7 (623.4)			
Generic Name	ATC code	# Rx	NSSPBD receiving at least one Rx	Age (years (SD))	Duration (days (SD))	# Rx	NSSPBD receiving at least one Rx	Age (years (SD))	Duration (days (SD))	# Rx	NSSPBD receiving at least one Rx	Age (years (SD))	Duration (days (SD))
dicycloverine	A03AA07	190 (0.1%)	43 (0.3%)	79.8 (6.9)	144.6 (299.7)	78 (0.04%)	17 (0.1%)	77.6 (5.9)	197.2 (327.0)	108 (0.5%)	23 (0.2%)	81.1 (7.5)	123.0 (297.9)
scopolamine	A04AD01	4,328 (2.1%)	2,029 (15.7%)	86.0 (7.9)	34.5 (157.7)	1,194 (0.6%)	530 (4.1%)	82.6 (7.3)	37.3 (167.9)	2,977 (1.4%)	1,455 (11.2%)	87.5 (7.6)	30.9 (147.7)
dimenhydrinate	A04AD99	492 (0.2%)	379 (2.9%)	85.5 (7.8)	9.3 (13.5)	114 (0.05%)	96 (0.7%)	81.5 (7.5)	9.1 (11.0)	373 (0.2%)	279 (2.2%)	87.0 (7.4)	9.3 (14.2)
oxybutynin	G04BD04	18,663 (8.9%)	1,543 (11.9%)	81.2 (7.6)	441.1 (501.3)	4,582 (2.2%)	387 (3.0%)	78.6 (6.8)	428.0 (482.1)	13,098 (6.2%)	1,044 (8.1%)	82.5 (7.6)	450.3 (508.3)
tolterodine	G04BD07	5,705 (2.7%)	324 (2.5%)	81.3 (7.9)	668.1 (558.0)	1,103 (0.5%)	74 (0.6%)	77.8 (6.3)	548.1 (459.6)	4,266 (2.0%)	227 (1.8%)	82.7 (7.8)	702.7 (573.1)
solifenacin	G04BD08	2,918 (1.4%)	223 (1.7%)	80.2 (7.4)	497.9 (470.0)	836 (0.4%)	50 (0.4%)	77.7 (5.7)	580.1 (546.7)	1,848 (0.9%)	146 (1.1%)	81.4 (7.9)	476.2 (451.4)
trospium	G04BD09	550 (0.3%)	40 (0.3%)	79.4 (6.6)	493.4 (557.7)	97 (0.05%)	10 (0.08%)	77.1 (6.5)	386.6 (375.2)	348 (0.2%)	24 (0.2%)	80.4 (6.5)	495.0 (536.2)
darifenacin	G04BD10	219 (0.1%)	33 (0.3%)	78.7 (7.8)	282.7 (357.7)	65 (0.03%)	11 (0.09%)	79.1 (5.3)	376.0 (415.4)	151 (0.07%)	21 (0.2%)	78.9 (8.9)	243.3 (331.7)
fesoterodine	G04BD11	222 (0.1%)	35 (0.3%)	81.5 (8.9)	196.5 (175.5)	42 (0.02%)	7 (0.05%)	76.2 (7.1)	205.7 (147.6)	173 (0.08%)	24 (0.2%)	83.8 (9.2)	213.3 (191.2)
trihexyphenidyl	N04AA01	1,066 (0.5%)	28 (0.2%)	78.6 (6.7)	1134.6 (685.4)	324 (0.2%)	10 (0.08%)	76.2 (6.0)	954.9 (650.8)	600 (0.3%)	15 (0.1%)	79.8 (7.3)	1168.7 (726.0)
benztropine	N04AC01	3,581 (1.7%)	146 (1.1%)	75.6 (7.2)	631.7 (688.2)	1,094 (0.5%)	55 (0.4%)	74.6 (6.9)	574.0 (622.1)	2,316 (1.1%)	86 (0.7%)	76.4 (7.3)	649.3 (725.5)

Score 3 - Strong Anticholinergic		Total Population				Men				Women			
Generic Name	ATC code	# Rx	NSSPBD receiving at least one Rx	Age (years (SD))	Duration (days (SD))	# Rx	NSSPBD receiving at least one Rx	Age (years (SD))	Duration (days (SD))	# Rx	NSSPBD receiving at least one Rx	Age (years (SD))	Duration (days (SD))
perphenazine	N05AB03	2,231 (1.1%)	82 (0.6%)	79.8 (7.6)	923.7 (693.9)	207 (0.1%)	10 (0.08%)	81.7 (9.1)	891.8 (630.2)	1,822 (0.9%)	62 (0.5%)	80.4 (7.2)	944.4 (716.6)
trifluoperazine	N05AB06	1,644 (0.8%)	44 (0.3%)	78.9 (8.5)	1251.3 (783.9)	358 (0.2%)	11 (0.09%)	76.0 (9.5)	1137.4 (636.4)	1,196 (0.6%)	32 (0.2%)	79.7 (8.1)	1245.8 (807.0)
olanzapine	N05AH03	17,656 (8.4%)	456 (3.5%)	78.8 (7.8)	991.3 (813.8)	5,307 (2.5%)	158 (1.2%)	76.6 (6.7)	874.2 (778.4)	11,869 (5.6%)	287 (2.2%)	80.2 (8.0)	1039.4 (827.7)
quetiapine	N05AH04	85,996 (40.9%)	3,871 (29.9%)	83.0 (7.9)	632.6 (645.6)	27,157 (12.9%)	1,248 (9.6%)	79.9 (7.2)	615.8 (644.4)	57,457 (27.3%)	2,533 (19.6%)	84.7 (7.7)	645.7 (646.7)
hydroxyzine	N05BB01	1,868 (0.9%)	140 (1.1%)	82.9 (8.1)	396.6 (397.3)	461 (0.2%)	39 (0.3%)	78.6 (7.4)	314.9 (402.7)	1,392 (0.7%)	99 (0.8%)	84.6 (7.8)	426.2 (396.1)
desipramine	N06AA01	751 (0.4%)	55 (0.4%)	81.8 (8.3)	343.7 (532.7)	111 (0.05%)	18 (0.1%)	78.9 (8.4)	225.7 (427.4)	625 (0.3%)	32 (0.2%)	84.3 (7.7)	445.0 (604.9)
imipramine	N06AA02	2,378 (1.1%)	76 (0.6%)	80.1 (7.9)	719.3 (676.4)	1,414 (0.7%)	18 (0.1%)	76.6 (7.2)	876.8 (767.0)	799 (0.4%)	50 (0.4%)	82.0 (7.7)	621.6 (616.3)
clomipramine	N06AA04	1,321 (0.6%)	45 (0.3%)	77.2 (8.0)	957.9 (716.9)	416 (0.2%)	14 (0.1%)	72.7 (6.9)	898.2 (627.3)	803 (0.4%)	26 (0.2%)	80.4 (7.2)	1004.6 (788.9)
trimipramine	N06AA06	827 (0.4%)	31 (0.2%)	80.7 (9.7)	1096.6 (807.7)	141 (0.07%)	6 (0.05%)	74.6 (5.5)	1391.2 (1243.1)	666 (0.3%)	23 (0.2%)	83.0 (9.9)	1042.1 (668.0)
amitriptyline	N06AA09	21,853 (10.4%)	1,481 (11.4%)	79.9 (7.9)	561.9 (608.9)	5,221 (2.5%)	381 (2.9%)	77.8 (7.2)	472.4 (543.1)	14,609 (6.9%)	959 (7.4%)	81.1 (7.7)	588.9 (618.6)
nortriptyline	N06AA10	7,187 (3.4%)	608 (4.7%)	81.1 (7.8)	407.2 (504.7)	1,456 (0.7%)	154 (1.2%)	78.4 (7.1)	357.7 (460.5)	5,327 (2.5%)	403 (3.1%)	82.5 (7.7)	434.7 (518.8)
doxepin	N06AA12	4,271 (2.0%)	234 (1.8%)	82.5 (8.1)	668.2 (628.4)	857 (0.4%)	58 (0.4%)	80.2 (7.8)	457.9 (522.7)	3,034 (1.4%)	160 (1.2%)	83.9 (8.0)	705.3 (624.3)
paroxetine	N06AB05	24,082 (11.4%)	973 (7.5%)	80.5 (7.9)	885.8 (635.2)	5,511 (2.6%)	245 (1.9%)	77.8 (7.0)	816.7 (622.0)	17,501 (8.3%)	672 (5.2%)	81.8 (7.9)	906.0 (634.2)
orphenadrine procyclidine clozapine	M03BC1 N04AA04 N05AH02	449 (0.2%)	16 (0.1%)	77.7 (8.6)	1028.5 (726.1)	290 (0.1%)	8 (0.06%)	75.6 (6.0)	1267.5 (726.4)	140 (0.07%)	7 (0.05%)	81.4 (10.4)	632.3 (565.1)

Table 26: Detailed drug utilization of Anticholinergic Cognitive Burden Scale Score 2 - Moderate Anticholinergic as used by NSSPBD over period of 1 April 2010 to 31 March 2015

Score 2 - Moderate Anticholinergic		Total Population				Men				Women			
Total Rx dispensed		16,537				6,618 (40.0%)				9,145 (55.4%)			
NSSPBD receiving at least one Rx		958				332 (34.7%)				578 (60.3%)			
Age (years (SD))		80.2 (8.7)				77.8 (7.8)				82.0 (8.8)			
Duration (days (SD))		493.7 (643.9)				5145 (649.6)				465.0 (632.2)			
Generic Name	ATC code	# Rx	NSSPBD receiving at least one Rx	Age (years (SD))	Duration (days (SD))	# Rx	NSSPBD receiving at least one Rx	Age (years (SD))	Duration (days (SD))	# Rx	NSSPBD receiving at least one Rx	Age (years (SD))	Duration (days (SD))
carbamazepine	N03AF01	8,404 (50.8%)	307 (32.0%)	79.1 (8.4)	837.3 (706.8)	3,060 (18.5%)	103 (10.8%)	76.3 (7.8)	847.5 (697.5)	4,965 (30.0%)	185 (19.3%)	81.1 (8.3)	817.7 (708.3)
amantadine	N04BB01	1,438 (8.7%)	74 (7.7%)	73.8 (5.4)	679.7 (582.8)	408 (2.5%)	31 (3.2%)	73.6 (5.0)	537.3 (463.3)	785 (4.7%)	26 (2.7%)	74.7 (5.7)	926.5 (600.0)
levomepromazine	N05AA02	3,990 (24.1%)	445 (46.5%)	82.7 (8.7)	189.9 (400.6)	1,954 (11.8%)	145 (15.1%)	80.3 (8.0)	228.4 (437.9)	1,934 (11.7%)	292 (30.5%)	84.1 (8.6)	165.1 (374.1)
loxapine	N05AH01	2,217 (13.4%)	109 (11.4%)	78.6 (8.2)	591.1 (694.9)	960 (5.8%)	43 (4.5%)	77.4 (6.5)	583.4 (768.8)	1,210 (7.3%)	63 (6.6%)	79.5 (9.1)	590.8 (645.6)
pethidine pimozide	N02AB02 N05AG02	488 (3.0%)	23 (2.4%)	74.5 (7.5)	723.5 (787.4)	236 (1.4%)	10 (1.0%)	73.3 (5.3)	866.1 (845.2)	251 (1.5%)	12 (1.3%)	75.9 (9.1)	664.8 (765.5)

Table 27: Detailed drug utilization of Anticholinergic Cognitive Burden Scale Score 1 - Weak Anticholinergic as used by NSSPBD over period of 1 April 2010 to 31 March 2015

Score 1 - Weak Anticholinergic		Total Population				Men				Women			
Total Rx dispensed		584,566				157,339 (26.9%)				398,239 (68.1%)			
NSSPBD receiving at least one Rx		38,031				11,180 (29.4%)				24,815 (65.2%)			
Age (years (SD))		83.0 (7.9)				80.1 (7.2)				84.7 (7.7)			
Duration (days (SD))		500.2 (616.1)				478.5 (596.2)				500.8 (614.1)			
Generic Name	ATC code	# Rx	NSSPBD receiving at least one Rx	Age (years (SD))	Duration (days (SD))	# Rx	NSSPBD receiving at least one Rx	Age (years (SD))	Duration (days (SD))	# Rx	NSSPBD receiving at least one Rx	Age (years (SD))	Duration (days (SD))
cimetidine	A02BA01	421 (0.07%)	39 (0.1%)	81.0 (6.9)	455.6 (440.2)	93 (0.02%)	13 (0.03%)	80.7 (5.4)	341.9 (305.7)	328 (0.06%)	26 (0.07%)	81.2 (7.6)	512.5 (489.6)
loperamide	A07DA03	5,462 (0.9%)	1,157 (3.0%)	83.9 (8.1)	111.2 (265.3)	1,101 (0.2%)	274 (0.7%)	80.0 (7.6)	105.9 (252.4)	4,169 (0.7%)	849 (2.2%)	85.3 (7.8)	109.8 (261.9)
digoxin	C01AA05	24,426 (4.2%)	1,094 (2.9%)	84.0 (7.2)	809.2 (601.9)	7,091 (1.2%)	365 (1.0%)	81.2 (6.5)	764.2 (566.3)	16,107 (2.8%)	674 (1.8%)	85.7 (7.0)	803.2 (600.4)
isosorbide dinitrate	C01DA08	1,699 (0.3%)	99 (0.3%)	83.7 (8.1)	629.1 (558.7)	267 (0.05%)	28 (0.07%)	81.0 (8.3)	449.2 (452.5)	1,243 (0.2%)	62 (0.2%)	85.8 (7.4)	707.6 (574.4)
isosorbide mononitrate	C01DA14	5,894 (1.0%)	262 (0.7%)	83.1 (7.7)	840.9 (644.0)	1,813 (0.3%)	91 (0.2%)	79.7 (7.4)	798.4 (634.3)	3,839 (0.7%)	157 (0.4%)	85.5 (7.1)	861.4 (643.1)
metoprolol	C07AB02	152,221 (26.0%)	5,804 (15.3%)	82.8 (7.7)	975.9 (637.6)	43,788 (7.5%)	1,831 (4.8%)	80.1 (7.0)	940.9 (623.7)	97,829 (16.7%)	3,543 (9.3%)	84.6 (7.5)	970.8 (638.5)
atenolol & atenolol + diuretic	C07AB03 C07CB03	44,609 (7.6%)	1,818 (4.7%)	82.7 (7.9)	986.4 (630.2)	9,938 (1.7%)	466 (1.2%)	79.4 (7.3)	935.7 (642.3)	31,680 (5.4%)	1,213 (3.2%)	84.4 (7.7)	981.5 (616.1)
nifedipine	C08CA05	48,033 (8.2%)	1,941 (5.1%)	82.5 (7.6)	973.5 (684.1)	10,487 (1.8%)	508 (1.3%)	79.2 (6.9)	891.2 (677.4)	33,838 (5.8%)	1,289 (3.4%)	84.2 (7.3)	970.3 (669.1)
captopril	C09AA01	482 (0.08%)	32 (0.08%)	84.5 (7.4)	603.6 (482.1)	214 (0.04%)	13 (0.03%)	84.9 (8.4)	654.3 (516.2)	247 (0.04%)	16 (0.04%)	84.9 (7.4)	561.3 (474.3)
prednisone	H02AB07	31,286 (5.4%)	4,137 (10.9%)	82.2 (7.7)	208.0 (425.2)	8,105 (1.4%)	1,270 (3.3%)	80.2 (7.0)	180.4 (385.3)	21,206 (3.6%)	2,565 (6.7%)	83.5 (7.8)	223.5 (446.9)
colchicine	M04AC01	5,826 (1.0%)	914 (2.4%)	82.1 (7.6)	195.4 (365.4)	2,711 (0.5%)	378 (1.0%)	80.1 (7.0)	219.8 (367.1)	2,612 (0.4%)	447 (1.2%)	84.2 (7.7)	181.4 (375.1)

Score 1 - Weak Anticholinergic		Total Population				Men				Women			
Generic Name	ATC code	# Rx	NSSPBD receiving at least one Rx	Age (years (SD))	Duration (days (SD))	# Rx	NSSPBD receiving at least one Rx	Age (years (SD))	Duration (days (SD))	# Rx	NSSPBD receiving at least one Rx	Age (years (SD))	Duration (days (SD))
fentanyl	N01AH01 N02AB03	7,457 (1.3%)	364 (1.0%)	84.2 (7.7)	561.3 (728.1)	1,222 (0.2%)	83 (0.2%)	79.0 (7.8)	415.3 (476.1)	6014 (1.0%)	272 (0.7%)	85.8 (7.0)	595.0 (783.6)
morphine	N02AA01	17,950 (3.1%)	3,602 (9.5%)	86.0 (7.9)	100.0 (322.6)	4,032 (0.7%)	911 (2.4%)	82.2 (7.4)	91.7 (311.4)	13,598 (23.2%)	2,641 (6.9%)	87.5 (7.6)	100.6 (318.2)
codeine	N02AA59	17,328 (3.0%)	3,438 (9.0%)	80.9 (7.8)	99.8 (241.9)	5,641 (1.0%)	1,079 (2.8%)	78.6 (6.9)	97.2 (255.7)	10,504 (1.8%)	2,069 (5.4%)	82.6 (7.7)	103.5 (237.6)
acetaminophen, combinations	N02BE51	10,622 (1.0%)	1,680 (4.4%)	82.1 (8.0)	125.3 (268.6)	2,538 (0.4%)	450 (1.2%)	78.9 (7.1)	119.5 (266.6)	7,707 (1.3%)	1,107 (2.9%)	83.8 (7.9)	135.3 (278.0)
risperidone	N05AX08	60,646 (10.4%)	3,283 (8.6%)	83.7 (7.7)	532.0 (559.0)	16,747 (2.9%)	980 (2.6%)	80.4 (7.0)	505.8 (578.2)	42,965 (7.3%)	2,259 (5.9%)	85.3 (7.5)	540.9 (546.1)
diazepam	N05BA01	6,455 (1.1%)	446 (1.2%)	78.9 (7.4)	418.5 (551.7)	2,451 (0.4%)	152 (0.4%)	77.2 (6.8)	406.9 (546.2)	3,463 (0.6%)	260 (0.7%)	80.4 (7.4)	407.5 (535.4)
alprazolam	N05BA12	8,295 (1.4%)	369 (1.0%)	80.7 (7.8)	758.4 (675.2)	1,771 (0.3%)	88 (0.2%)	79.1 (6.6)	693.4 (725.7)	5,703 (1.0%)	240 (0.6%)	81.6 (8.1)	767.0 (660.3)
trazodone	N06AX05	117,888 (20.2%)	6,115 (16.1%)	83.9 (7.8)	566.8 (566.5)	31,629 (5.4%)	1,794 (4.7%)	81.0 (7.1)	535.1 (539.2)	83,901 (14.4%)	4,167 (11.0%)	85.3 (7.7)	583.0 (576.0)
bupropion	N06AX12	9,109 (1.6%)	412 (1.1%)	78.0 (7.6)	624.3 (602.5)	3,745 (0.6%)	156 (0.4%)	75.4 (7.2)	641.2 (591.5)	5,095 (0.9%)	231 (0.6%)	80.2 (7.3)	643.0 (612.2)
theophylline theophylline, combinations	R03DA04 R03DA54	1,992 (0.3%)	123 (0.3%)	79.2 (8.2)	643.6 (612.3)	750 (0.1%)	46 (0.1%)	79.5 (7.3)	695.3 (605.9)	1,195 (0.2%)	72 (0.2%)	79.2 (8.8)	616.7 (621.1)
codeine cough suppressant	R05DA04	5,551 (0.9%)	842 (2.2%)	83.2 (8.0)	158.8 (337.4)	1,120 (0.2%)	194 (0.5%)	80.2 (7.4)	143.7 (271.2)	4,234 (0.7%)	609 (1.6%)	84.5 (7.8)	163.2 (357.4)
dipyridamole chlorthalidone potassium clorazepate	B01AC07 C03BA04 N05BA05	914 (0.2%)	60 (0.2%)	82.9 (8.6)	619.5 (547.3)	85 (0.01%)	10 (0.01%)	75.4 (6.8)	423.0 (407.5)	762 (0.1%)	47 (0.1%)	84.5 (8.0)	654.6 (555.5)

Risperidone use was increased in men and trazodone use exceeded expected use in women. There were sex-specific differences in medication use in NSSPBD.

6.4.3.4 Bladder Anticholinergics

Over the period of study 2,198 (7.7%) NSSPBD (1,486 women and 539 men) received at least one prescription for a bladder anticholinergic. There were 28,277 bladder anticholinergic prescriptions dispensed in the study period (table 28). Duration of use was on average 475 days (1.3 years) with oxybutynin prescriptions predominating (66.0%). Sex distribution of bladder anticholinergic prescription represent fairly similar use by men and women NSSPBD.

6.4.3.5 Tricyclic Antidepressants

Over the period of study 2,530 NSSPBD (1,653 women and 649 men) received at least one prescription for a tricyclic antidepressant. There were 38,588 tricyclic antidepressant prescriptions dispensed to NSSPBD during the study period (table 29). Amitriptyline was the most commonly dispensed tricyclic antidepressant and was used by the greatest number of NSSPBD, followed by nortriptyline and doxepin. There seemed to be greater use of tricyclic antidepressants by women (65.3% of users women versus 25.7% men). Use was also longer by women with duration of use on average 573.6 days by women and 466.0 days in men. This is clearly limited in its interpretation by the fact that women have a longer life expectancy in general than men, but it is still noteworthy.

6.4.4 Antipsychotics

First generation antipsychotics comprised 11.6% of antipsychotic prescriptions (table 30). Second generation antipsychotics represent 88.4% of antipsychotic prescriptions (table 30). Women were older than men at initiation of antipsychotics (either first or second generation). Distribution of use and duration of use is similar for men and women, but use was much longer for second generation antipsychotics than first generation antipsychotics.

Table 28: Detailed drug utilization of bladder anticholinergics (all strongly anticholinergic) as used by NSSPBD over period of 1 April 2010 to 31 March 2015

Bladder Anticholinergics		Total Population				Men				Women			
Total Rx dispensed		28,277				6,725 (34.4%)				19,884 (70.3%)			
NSSPBD receiving at least one Rx		2,198				539 (24.5%)				1,486 (67.6%)			
Age (years (SD))		81.1 (7.6)				78.4 (6.6)				82.4 (7.7)			
Duration (days (SD))		475.0 (510.4)				453.9 (482.3)				485.4 (517.7)			
Generic Name	ATC code	# Rx	NSSPBD receiving at least one Rx	Age (years (SD))	Duration (days (SD))	# Rx	NSSPBD receiving at least one Rx	Age (years (SD))	Duration (days (SD))	# Rx	NSSPBD receiving at least one Rx	Age (years (SD))	Duration (days (SD))
oxybutynin	G04BD04	18,663 (66.0%)	1,543 (70.2%)	81.2 (7.6)	441.1 (501.3)	4,582 (16.2%)	387 (17.6%)	78.7 (6.7)	428.1 (482.1)	13,098 (46.3%)	1,044 (47.5%)	82.5 (7.6)	450.3 (508.3)
tolterodine	G04BD07	5,705 (20.2%)	324 (14.7%)	81.3 (7.9)	668.1 (558.0)	1,103 (3.9%)	74 (3.4%)	77.8 (6.3)	548.1 (459.6)	4,266 (15.1%)	227 (10.3%)	82.7 (7.8)	702.7 (573.1)
solifenacin	G04BD08	2,918 (10.3%)	223 (10.1%)	80.2 (7.4)	497.9 (470.0)	836 (3.0%)	50 (2.3%)	77.5 (5.8)	580.1 (546.7)	1,848 (6.5%)	146 (6.6%)	81.5 (7.8)	476.2 (451.4)
trospium	G04BD09	550 (1.9%)	40 (1.8%)	79.3 (6.5)	493.4 (557.7)	97 (0.3%)	10 (0.5%)	77.2 (6.5)	386.6 (375.2)	348 (1.2%)	24 (1.1%)	80.3 (6.4)	495.0 (536.2)
darifenacin	G04BD10	219 (0.8%)	33 (1.5%)	78.9 (7.8)	282.7 (357.7)	65 (0.2%)	11 (0.5%)	79.5 (5.6)	376.0 (415.4)	151 (0.5%)	21 (1.0%)	78.9 (8.9)	243.3 (331.7)
fesoterodine	G04BD11	222 (0.8%)	35 (1.6%)	81.5 (9.0)	196.5 (175.5)	42 (0.1%)	7 (0.3%)	76.4 (7.2)	205.7 (147.6)	173 (0.6%)	24 (1.1%)	83.8 (9.2)	213.3 (191.2)

Table 29: Detailed drug utilization of tricyclic antidepressants (all strongly anticholinergic) as used by NSSPBD over period of 1 April 2010 to 31 March 2015

Tricyclic Antidepressants		Total Population				Men				Women			
Total Rx dispensed		38,588				9,616 (24.9%)				25,863 (67.0%)			
NSSPBD receiving at least one Rx		2,530				649 (25.7%)				1,653 (65.3%)			
Age (years (SD))		80.4 (7.9)				78.0 (7.3)				81.8 (7.8)			
Duration (days (SD))		548.1 (604.5)				466.0 (555.3)				573.6 (609.4)			
Generic Name	ATC code	# Rx	NSSPBD receiving at least one Rx	Age (years (SD))	Duration (days (SD))	# Rx	NSSPBD receiving at least one Rx	Age (years (SD))	Duration (days (SD))	# Rx	NSSPBD receiving at least one Rx	Age (years (SD))	Duration (days (SD))
desipramine	N06AA01	751 (1.9%)	55 (2.2%)	81.7 (8.2)	343.7 (532.7)	111 (0.3%)	18 (0.7%)	78.8 (8.4)	225.7 (427.4)	625 (1.6%)	32 (1.3%)	84.2 (7.4)	445.0 (604.9)
imipramine	N06AA02	2,378 (6.2%)	76 (3.0%)	80.2 (7.7)	719.3 (676.4)	1,414 (3.7%)	18 (0.7%)	76.8 (6.6)	876.8 (768.9)	799 (2.1%)	50 (2.0%)	82.1 (7.6)	621.6 (616.3)
clomipramine	N06AA04	1,321 (3.4%)	45 (1.8%)	77.3 (7.9)	957.9 (716.9)	416 (1.1%)	14 (0.6%)	73.1 (6.8)	898.2 (627.3)	803 (2.1%)	26 (1.0%)	80.6 (7.2)	1004.6 (788.9)
trimipramine	N06AA06	827 (2.1%)	31 (1.2%)	81.0 (9.4)	1096.6 (807.7)	141 (0.4%)	6 (0.2%)	75.5 (5.2)	1391.2 (1243.1)	666 (1.7%)	23 (0.9%)	83.2 (9.6)	1042.1 (668.0)
amitriptyline	N06AA09	21,853 (56.6%)	1,481 (58.5%)	79.9 (7.8)	561.9 (608.9)	5,221 (13.5%)	381 (15.1%)	77.7 (7.2)	472.4 (543.1)	14,609 (37.9%)	959 (37.9%)	81.0 (7.8)	588.9 (618.6)
nortriptyline	N06AA10	7,187 (18.6%)	608 (24.0%)	81.1 (7.8)	407.2 (504.7)	1,456 (3.8%)	154 (6.1%)	78.4 (7.1)	357.7 (460.5)	5,327 (13.8%)	403 (15.9%)	82.5 (7.6)	434.7 (518.8)
doxepin	N06AA12	4,271 (11.1%)	234 (9.2%)	82.4 (8.1)	668.2 (628.4)	857 (2.2%)	58 (2.3%)	80.1 (7.8)	457.9 (522.7)	3,034 (7.9%)	160 (6.3%)	83.7 (8.0)	705.3 (624.3)

Quetiapine was the most commonly used antipsychotic followed by risperidone and olanzapine (in that order). Risperidone seemed to have disproportionately greater use in women, but this may have been due to men having greater incidence of comorbidities that contraindicate risperidone use.

Of NSSPBD receiving a first generation antipsychotic, haloperidol comprised over half (57.5%) of the dispensations. While most first generation antipsychotics suggested a similar distribution between men and women, chlorpromazine and pimozide use was far more common in men and perphenazine was more commonly used by women. Perphenazine use may be representative of use for nausea so may be reflective of use outside the context of BPSD.

We were able to identify 313 NSSPBD (156 women and 144 men) using combinations of Parkinson's disease medications and antipsychotics. Duration of overlap was on average 579.8 days. Of these cases 158/313 (50.5%) were for antipsychotics that are appropriate for older adults with parkinsonism (table 30). It should be noted that for 296 cases the Parkinson's Disease medication was initiated first. For these individuals, levodopa-carbidopa was the most common (249 cases), followed by ropinirole (25 cases). For those who initiated Parkinson's Disease medications first (19 cases), quetiapine (8 cases) was the most common antipsychotic, followed by risperidone (7 cases).

6.4.5 Sedatives

Benzodiazepines were used by 8,503 NSSPBD with dementia. This represents 27.7% of the cohort. Lorazepam was the most frequently prescribed benzodiazepine (59.1% of benzodiazepine prescriptions) (table 32). The z-drug hypnotic zopiclone was used by 8.36% of the cohort (table 32).

Table 30: Detailed drug utilization of First and Second Generation Antipsychotics as used by NSSPBD over period of 1 April 2010 to 31 March 2015

Antipsychotics			Total Population				Men				Women			
Total Rx First Generation			21,640				7,576 (35.0%)				13,217 (61.1%)			
NSSPBD receiving at least one Rx			2,400				801 (33.4%)				1,544 (64.3%)			
Age (years (SD))			82.5 (8.3)				79.6 (7.3)				84.2 (8.3)			
Duration (days (SD))			237.3 (469.8)				233.3 (461.6)				227.0 (457.4)			
Total Rx Second Generation			164,862				49,476 (30.0%)				112,498 (68.2%)			
NSSPBD receiving at least one Rx			7,638				2,396 (31.4%)				5,094 (66.7%)			
Age (years (SD))			83.1 (7.9)				79.9 (7.1)				84.7 (7.7)			
Duration (days (SD))			610.5 (630.6)				588.1 (634.8)				620.8 (626.3)			
	Generic Name	ATC code	# Rx	NSSPBD receiving at least one Rx	Age (years (SD))	Duration (days (SD))	# Rx	NSSPBD receiving at least one Rx	Age (years (SD))	Duration (days (SD))	# Rx	NSSPBD receiving at least one Rx	Age (years (SD))	Duration (days (SD))
First Generation	chlorpromazine	N05AA01	1,977 (9.1%)	86 (3.6%)	78.5 (8.3)	623.6 (674.7)	851 (3.9%)	42 (1.8%)	76.6 (6.4)	637.8 (764.5)	1,082 (5.0%)	38 (1.6%)	80.6 (9.8)	617.7 (572.6)
	levopromazine	N05AA02	3,990 (18.4%)	445 (18.5%)	82.7 (8.6)	189.9 (400.6)	1,954 (9.0%)	145 (6.0%)	80.3 (8.0)	228.4 (437.9)	1,934 (8.9%)	292 (12.2%)	84.1 (8.6)	165.1 (374.1)
	perphenazine	N05AB03	2,231 (10.3%)	82 (3.4%)	79.7 (7.6)	923.7 (693.9)	207 (1.0%)	10 (0.4%)	81.2 (9.6)	891.8 (630.2)	1,822 (8.4%)	62 (2.6%)	80.3 (7.1)	944.4 (716.6)
	prochlorperazine	N05AB04	753 (3.5%)	188 (7.8%)	79.5 (8.0)	110.4 (274.9)	250 (1.2%)	57 (2.4%)	76.5 (6.9)	131.1 (320.8)	441 (2.0%)	121 (5.0%)	81.1 (8.2)	91.7 (208.4)
	trifluoperazine	N05AB06	1,644 (7.6%)	44 (1.8%)	78.8 (8.5)	1251.3 (783.9)	358 (1.7%)	11 (0.5%)	75.6 (9.2)	1137.4 (636.4)	1,196 (5.5%)	32 (1.3%)	79.9 (8.2)	1245.8 (807.0)
	haloperidol	N05AD01	7,259 (33.5%)	1,384 (57.5%)	84.0 (7.8)	119.6 (277.5)	2,361 (10.9%)	472 (19.7%)	80.6 (6.9)	114.3 (247.5)	4,699 (21.7%)	898 (37.4%)	85.8 (7.6)	115.9 (274.4)
	flupenthixol	N05AF01	410 (1.9%)	24 (1.0%)	74.8 (7.4)	617.7 (594.1)	132 (0.6%)	9 (0.4%)	75.0 (7.5)	453.1 (456.9)	273 (1.3%)	14 (0.6%)	75.4 (7.3)	762.6 (656.9)
	pimozide	N05AG02	453 (2.1%)	13 (0.5%)	73.2 (6.5)	1259.8 (647.3)	232 (1.1%)	6 (0.3%)	71.3 (2.2)	1438.0 (551.9)	221 (1.0%)	7 (0.3%)	74.8 (8.6)	1107.1 (724.8)
	loxapine	N05AH01	2,217 (10.2%)	109 (4.5%)	78.6 (8.0)	591.1 (694.9)	960 (4.4%)	43 (1.8%)	77.4 (6.4)	583.4 (768.8)	1,210 (5.6%)	63 (2.6%)	79.6 (8.7)	590.8 (645.6)
	fluphenazine periciazine zuclopenthixol	N05AB02 N05AC01 N01AF05	706 (3.3%)	25 (1.0%)	74.9 (8.2)	748.0 (681.1)	271 (1.3%)	6 (0.3%)	71.1 (5.7)	1051.3 (739.3)	339 (1.6%)	17 (0.7%)	76.3 (8.9)	563.3 (613.7)

	Generic Name	ATC code	# Rx	NSSPBD receiving at least one Rx	Age (years (SD))	Duration (days (SD))	# Rx	NSSPBD receiving at least one Rx	Age (years (SD))	Duration (days (SD))	# Rx	NSSPBD receiving at least one Rx	Age (years (SD))	Duration (days (SD))
Second Generation	olanzapine	N05AH03	17,656 (10.7%)	456 (6.0%)	78.9 (7.7)	991.3 (813.8)	5,307 (3.2%)	158 (2.1%)	76.6 (6.7)	874.2 (778.4)	11,869 (7.2%)	287 (3.8%)	80.3 (8.0)	1039.4 (827.7)
	quetiapine	N05AH04	85,996 (52.2%)	3,871 (50.7%)	83.0 (7.9)	632.6 (645.6)	27,157 (16.5%)	1,248 (16.3%)	79.9 (7.2)	615.8 (644.4)	57,457 (34.9%)	2,533 (33.2%)	84.7 (7.7)	645.7 (646.7)
	risperidone	N05AX08	60,646 (36.8%)	3,283 (43.0%)	83.7 (7.7)	532.0 (559.0)	16,747 (10.2%)	980 (12.8%)	80.4 (7.0)	505.8 (578.3)	42,965 (26.1%)	2,259 (29.6%)	85.3 (7.6)	540.9 (546.1)
	aripiprazole ziprasidone clozapine paliperidone	N05AX12 N05AE04 N05AH02 N05AX13	564 (0.3%)	28 (0.4%)	74.7 (6.3)	573.0 (567.8)	265 (0.2%)	10 (0.1%)	70.9 (3.3)	666.2 (691.1)	207 (0.1%)	15 (0.2%)	77.5 (6.4)	445.8 (452.3)

Table 31: Combinations of Antipsychotics and Parkinson's Disease Medications used concurrently by NSSPBD over period of 1 April 2010 to 31 March 2015

Drug	chlorpromazine	levomepromazine	fluphenazine	perphenazine	prochlorperazine	haloperidol	flupentixol	loxapine	olanzapine	quetiapine	risperidone	aripiprazole	**Total**
levodopa and decarboxylase inhibitor	1	2	1	1	4	9	1	3	20	156	62		**260**
levodopa, decarboxylase inhibitor and COMT inhibito										2		1	**3**
amantadine		1							2	3	2		**8**
ropinirole				1		1				3	6		**11**
pramipexole		2			1	2			1	19	5		**30**
selegiline					1								**1**
Total	**1**	**5**	**1**	**2**	**6**	**12**	**1**	**3**	**23**	**183**	**75**	**1**	**313**

Women were more likely to receive a benzodiazepine (OR 1.44; 95% CI [1.36-1.53]) or a Z-drug (OR 1.10; 95% CI [1.01-1.19]). Lorazepam was the most commonly prescribed sedative (52% of sedative users), followed by zopiclone (27% of sedative users). Sedative use (37.9% of cohort) was almost two times greater than cholinesterase inhibitor use (19.3% of cohort).

6.4.6 Gastrointestinal Agents

H2-Receptor antagonists (H2RA) were commonly prescribed, as were PPI, with 11.2% of the cohort receiving at least one prescription for an H2RA and 28.3% receiving at least one prescription for a PPI. Mean duration of use for both agents was prolonged. H2RA use exceeded 400 days and PPI use exceeded 500 days. Distribution of use was similar across sexes for H2RAs and PPIs and duration of use was similar for both agents and across sexes (table 33).

Ranitidine comprised over 97% of H2RA use and was used on average for the longest duration of H2RAs. Rabeprazole was the most commonly dispensed and least expensive formulary PPI followed by omeprazole and then pantoprazole.

6.5 Discussion

STOPP Criteria and Beers List Criteria have specific recommendations for older adults with dementia. Some of these recommendations can readily be evaluated using pharmacy claims data. By evaluating pharmacy claims data, we can better appreciate how prescribing practices in our jurisdiction are in concordance with the best practice recommendations. Due to agreement between clinicians, STOPP and Beers List do agree on a several points. Below we have combined these criteria and commented on the state of prescribing for NSSPBD over the period from April 1, 2010 to March 31, 2015.

6.5.1 Duplicate NSAIDs

Duplication of drugs from the NSAID class was not common in NSSPBD but did occur. 101 cases of NSSPBD with concurrent NSAID use of more than 30 days in length were

Table 32: Detailed drug utilization of sedatives as used by NSSPBD over period of 1 April 2010 to 31 March 2015

Sedatives		Total Population				Men				Women			
Number of Rx		174,135				42,376 (24.3%)				120,758 (69.3%)			
Number of NSSPB receiving at least 1 Rx for any sedative		13,443				3,607 (26.8%)				9,244 (68.8%)			
Age (years (SD))		82.7 (8.2)				79.7 (7.4)				84.2 (8.1)			
Duration (days (SD))		395.1 (552.5)				350.3 (511.2)				396.6 (553.5)			
Generic Name	ATC code	# Rx	NSSPBD receiving at least one Rx	Age (years (SD))	Duration (days (SD))	# Rx	NSSPBD receiving at least one Rx	Age (years (SD))	Duration (days (SD))	# Rx	NSSPBD receiving at least one Rx	Age (years (SD))	Duration (days (SD))
diazepam	N05BA01	6,455 (3.7%)	446 (3.3%)	78.9 (7.4)	418.5 (551.7)	2,451 (1.4%)	152 (1.1%)	77.2 (6.8)	406.9 (546.2)	3,463 (2.0%)	260 (1.9%)	80.4 (7.4)	407.5 (535.4)
oxazepam	N05BA04	18,807 (10.8%)	1,155 (8.6%)	83.2 (8.1)	516.0 (580.5)	4,839 (2.8%)	316 (2.4%)	80.4 (7.6)	471.4 (565.0)	12,973 (7.4%)	774 (5.8%)	84.7 (7.8)	529.6 (579.5)
lorazepam	N05BA06	75,470 (43.3%)	6,084 (45.3%)	82.7 (8.2)	365.0 (548.4)	16,376 (9.4%)	1,527 (11.4%)	79.6 (7.3)	310.9 (494.9)	55,196 (31.7%)	4,280 (31.8%)	84.2 (8.0)	370.5 (552.6)
bromazepam	N05BA08	3,626 (2.1%)	148 (1.1%)	78.5 (7.4)	812.1 (653.5)	601 (0.3%)	31 (0.2%)	76.5 (6.0)	683.2 (654.7)	2,376 (1.4%)	101 (0.8%)	79.9 (7.6)	852.4 (654.4)
clobazam	N05BA09	2,651 (1.5%)	99 (0.7%)	77.0 (7.4)	728.1 (625.4)	744 (0.4%)	36 (0.3%)	75.2 (6.4)	652.0 (635.2)	1,762 (1.0%)	60 (0.4%)	78.4 (7.8)	717.3 (584.4)
alprazolam	N05BA12	8,295 (4.8%)	369 (2.7%)	80.6 (7.8)	758.4 (675.2)	1,771 (1.0%)	88 (0.7%)	79.1 (6.6)	693.4 (725.7)	5,703 (3.3%)	240 (1.8%)	81.4 (8.0)	766.9 (660.3)
triazolam	N05CD05	607 (0.3%)	128 (1.0%)	81.0 (7.6)	170.1 (202.1)	161 (0.09%)	36 (0.3%)	78.7 (6.5)	161.9 (212.8)	416 (0.2%)	82 (0.6%)	82.3 (7.8)	176.7 (196.1)
temazepam	N05CD07	8,323 (4.8%)	444 (3.3%)	80.4 (8.0)	645.2 (604.0)	2,329 (1.3%)	137 (1.0%)	78.2 (7.5)	564.4 (568.0)	5,223 (3.0%)	275 (2.0%)	82.0 (8.0)	649.9 (584.3)
midazolam	N05CD08	1,857 (1.1%)	1,439 (10.7%)	87.4 (7.5)	5.8 (9.4)	452 (0.3%)	366 (2.7%)	83.6 (7.4)	5.3 (9.0)	1,405 (0.8%)	1,073 (8.0%)	88.7 (7.1)	5.9 (9.5)
chlordiazepoxide potassium clorazepate flurazepam	N05BA02 N05BA05 N05CD01	1,656 (1.0%)	97 (0.7%)	79.8 (8.1)	635.7 (618.1)	393 (0.2%)	33 (0.2%)	75.5 (5.8)	401.2 (557.2)	932 (0.5%)	53 (0.4%)	82.8 (8.5)	695.4 (576.4)
zopiclone	N05CF01	46,388 (26.6%)	3,144 (23.4%)	82.0 (8.1)	477.4 (541.9)	12,259 (7.0%)	885 (6.6%)	79.2 (7.3)	422.5 (492.5)	31,309 (18.0%)	2,046 (15.2%)	83.5 (8.0)	496.0 (551.8)

Table 33: Detailed drug utilization of gastrointestinal agents as used by NSSPBD over period of 1 April 2010 to 31 March 2015

			Total Population				Men				Women			
H_2RA	Number of Rx		71,897				18,225 (25.3%)				49,156 (68.4%)			
	Number of NSSPBD receiving at least 1 prescription		4,241				1,108 (26.1%)				2,858 (67.4%)			
	Age (years (SD))		82.5 (7.9)				79.8 (7.2)				83.9 (7.9)			
	Duration (days (SD))		615.8 (562.3)				616.2 (562.0)				604.4 (551.4)			
PPI	Number of prescriptions		255,704				67,167 (26.3%)				174,192 (68.1%)			
	Number of NSSPBD receiving at least 1 prescription		13,645				3,994 (29.3%)				8,747 (64.1%)			
	Age (years (SD))		82.2 (7.9)				79.8 (7.1)				83.7 (7.9)			
	Duration (days (SD))		668.5 (575.8)				636.6 (565.2)				675.0 (571.2)			
	Generic Name	ATC code	# Rx	NSSPBD receiving at least one Rx	Age (years (SD))	Duration (days (SD))	# Rx	NSSPBD receiving at least one Rx	Age (years (SD))	Duration (days (SD))	# Rx	NSSPBD receiving at least one Rx	Age (years (SD))	Duration (days (SD))
	ranitidine	A02BA02	70,385 (97.9%)	4,135 (97.5%)	82.5 (7.9)	617.6 (563.2)	18,011 (25.1%)	1,082 (25.5%)	79.8 (7.2)	621.5 (564.7)	47,986 (66.7%)	2,787 (65.7%)	83.9 (7.9)	605.3 (551.6)
	famotidine	A02BA03	748 (1.0%)	53 (1.2%)	83.8 (6.4)	552.6 (534.2)	96 (0.1%)	10 (0.2%)	78.7 (4.8)	503.0 (479.5)	541 (0.8%)	36 (0.8%)	85.8 (5.9)	507.2 (520.5)
	cimetidine nizatidine	A02BA01 A02BA04	764 (1.1%)	53 (1.2%)	81.6 (6.6)	540.7 (511.2)	118 (0.2%)	16 (0.4%)	80.5 (5.3)	326.8 (286.2)	629 (0.9%)	35 (0.8%)	82.0 (7.3)	637.6 (575.1)
PPI	omeprazole	A02BC01	74,174 (29.0%)	3,923 (28.8%)	82.3 (7.9)	681.3 (591.3)	18,495 (7.2%)	1,116 (8.2%)	79.8 (7.2)	643.7 (578.9)	51,922 (20.3%)	2,581 (18.9%)	83.7 (7.9)	685.7 (586.9)
	pantoprazole	A02BC02	46,780 (18.3%)	2,989 (21.9%)	81.6 (7.9)	549.5 (473.7)	13,140 (5.1%)	933 (6.8%)	79.3 (7.2)	519.2 (463.7)	30,689 (12.0%)	1,802 (13.2%)	83.1 (7.9)	569.0 (475.6)
	rabeprazole	A02BC04	130,059 (50.9%)	6,432 (47.1%)	82.5 (7.9)	719.9 (602.5)	34,456 (13.5%)	1,862 (13.6%)	79.9 (7.1)	696.9 (594.7)	88,367 (34.6%)	4,162 (30.5%)	84.0 (7.8)	719.5 (595.6)
	esomeprazole lansoprazole	A02BC05 A02BC03	4,691 (1.8%)	301 (2.2%)	82.9 (7.3)	584.3 (533.8)	1,076 (0.4%)	83 (0.6%)	81.1 (5.9)	508.6 (518.8)	3,214 (1.3%)	202 (1.5%)	84.1 (7.6)	567.4 (498.0)

identified. NSAID duplication was not frequently reported in the literature but was noted by Korean researchers (S.-Y. Jung et al., n.d.; Kang et al., 2016). In 21 million patient visits among people from birth to death Kang *et al.* identified 59,636,222 NSAID prescriptions with 13.3% of cases involving therapeutic duplication over 3 months (the first quarter) of 2011 (Kang et al., 2016). Similarly, in the carefully selected population of NSSPBD, over the 5 years of study, we identified 6,594,602 prescriptions of which 37,916 were NSAID prescriptions. Of these only 317 involved therapeutic duplication (or 5.2%). This shows that among NSSPBD we are more cautious of this inappropriate prescribing and we see much lower rates than in the general population of Koreans. Recent follow-up in Korea has shown NSAID therapeutic duplication fall to 5.6% (S.-Y. Jung et al., n.d.) after implementation of a nationwide drug utilization monitoring program which still exceeds the rate of NSAID duplication in our NSSPBD but does bring NSAID duplication in Korea in line with Iran (Azoulay et al., 2005) and Belgium (Leemans et al., 2003). In the Korean studies women made up 59.3% (Kang et al., 2016) and 75.3% (S.-Y. Jung et al., n.d.) of NSAID prescriptions compared to 66.6% of NSSPBD. In our population women were older than men receiving NSAID prescriptions but received the prescriptions for similar durations. Prescribing by different providers was frequent in Korea and was thought to have contributed to NSAID duplication there. Multiple prescribers may be an issue in the NSSPBD but we did not collect information on prescriber so cannot comment on this possibility. Jung *et al.* also noted that celecoxib was frequently implicated in cases of therapeutic duplication. This may have been due to expectations of additional benefit from COX-2 inhibition, which is unlikely to help with pain, but likely to increase risk of cardiovascular risk (S.-Y. Jung et al., n.d.). We also saw celecoxib implicated in NSAID duplication (43%). We were unable to report on over the counter NSAID use or aspirin use so we are likely under reporting therapeutic NSAID duplication.

It is concerning that the two diclofenac containing products were being combined. It is possible that directions in these cases were to instruct patients to use either or prescription. Or to use each preparation once a day rather than twice a day as monograph instruction recommends.

NSAID use was associated with frailty in a study of 12, 405 community dwelling adults, aged 58-73 years in France (Martinot et al., 2018). This is an interesting finding as the side effect profile of NSAIDs makes them contraindicated in those with reduced kidney function or at risk of gastrointestinal bleeding. We do not have frailty data on our cohort, but we know that our population has dementia and are likely more frail than a general population of older adults. We cannot comment on if frailty is associated with NSAID use in our cohort, but it is of note that the presence of frailty did not reduce or eliminate NSAID use substantially in other jurisdictions.

Canadian researchers have looked at the cost effectiveness of a community pharmacist-led education program for community dwelling older adults on NSAID discontinuation. They considered a population of older adults in Quebec and used decision tree and Markov state transition modeling to analyze the cost of such a program. NSAIDs did have potential adverse events, such as GI bleeding independent of NSAID duplication. The researchers found that an educational intervention by community pharmacists to encourage NSAID discontinuation was less costly and more effective than standard care (Sanyal et al., 2020) when considering adverse events prevented.

6.5.2 Duplicate SSRIs

Duplication of SSRIs was expected to occur for short periods of time due to drug switching within the class. When limiting cases of concurrent SSRI use from any duration to those more than 30 days in length there were 95 cases. This did not seem like a great number when it is considered as a percent of the total NSSPBD receiving at least one prescription for an SSRI (1.0%). However, the duration of concurrent use was concerning given that average periods of SSRI overlap was 180 days (6 months). This exceeds the duration of time needed for a typical taper and switch and is more likely to represent long term concurrent us of two SSRIs. Martinot *et al.* looked for duplicate antidepressant use in a French population and found duplication in 0.4% of the cohort (Martinot et al., 2018),which is in keeping with our findings. Although concurrent use of

SSRIs is not common, it likely does not confer any benefit and substantially increases the risk of adverse events (Sultana et al., 2015; Tham et al., 2016).

6.5.3 Duplicate Loop Diuretics

Duplication of loop diuretics was not common with only 11 cases identified over the 5 years of study of NSSPBD. Once again this is reassuring but the limited occurrences of long duration of overlap does suggest that concomitant loop diuretics may be considered a viable method for managing fluid overload by a small number of clinicians, though prescribing guidelines suggest this is not a safe practice. No reports on concurrent loop diuretics are available for comparison to other jurisdictions.

6.5.4 Duplicate ACE-Inhibitors

There were very few cases of ACE-Inhibitor duplication (only 183). This is reassuring and suggests that ACE-Inhibitor overlap may represent drug switching due to intolerance more than intentional co-therapy.

6.5.5 Duplicate Anticoagulants

Anticoagulant duplication was within expected limits. It seems that oral anticoagulants are being used appropriately in NSSPBD and overlap of anticoagulants can likely be explained by bridging with parenteral anticoagulants or switching of warfarin to dabigatran. This is expected as novel oral anticoagulants are far easier to manage for older adults who meet the criteria for their use (Amin et al., 2019; Fawzy et al., 2019; Giustozzi et al., 2019).

6.5.6 Avoid Anticholinergics

Anticholinergic use was very common in our cohort with 44.7% NSSPBD receiving at least one prescription for a drug on the ACB scale. A study of Medicare beneficiaries who were nursing home residents with dementia showed that 77% used at least one anticholinergic drug per the ACB scale (Buostani, 2009; Palmer et al., 2015). In our cohort which is most likely predominantly community dwelling we saw much lower anticholinergic drug exposure. But this level of anticholinergic use still far exceeds

recommendations and may contribute to further cognitive decline. There is evidence to suggest that anticholinergic drug exposure increases risk of dementia. A recent study that compared incidence of dementia in Canadian adults starting either a bladder anticholinergic or a beta-3 agonist for urinary incontinence showed that over eight years of follow-up there were more cases of dementia in the bladder anticholinergic group that in the beta-3 agonist group (HR 1.23 94% CI (1.12-1.35)). Men and those over 75 years of age had the greatest risk of dementia (Welk & McArthur, 2020). Previous studies investigating anticholinergic medications and a risk of dementia have been subject to protopathic bias as urinary incontinence is condition that often co-occurs with dementia so identifying controls is challenging. By using controls that also were seeking treatment for urinary incontinence this helped control for this bias. Activation of M1 and M3 receptors in the brain increases the non-amyloidogenic activity of beta and gamma secretases. So by inhibiting these receptors it encourages plaque formation secondary to cleavage of amyloid precursor protein by beta and gamma secretases to amyloidogenic products (Siegler & Reidenberg, 2004). This fairly theoretical idea was confirmed in autopsy study of the subpopulation of patients with Parkinson's Disease who had long term anticholinergic use who had higher rates of amyloid plaque and neurofibrillary tangle formation (Perry et al., 2003).

In our cohort 4.8% received at least one prescription for a bladder anticholinergic. The EPIC study which occurred in Canada, Germany, Italy and the UK in 2006 identified an overall prevalence of overactive bladder of 11.8% (Irwin et al., 2006). It is anticipated that with an aging population the prevalence of urinary incontinence increased over time (Irwin et al., 2011). This meant it was not surprising incontinence was being treated in NSSPBD. The concern with pharmacologic treatment of urinary incontinence with bladder anticholinergics is that these medications antagonize an already impaired cholinergic system in those with cognitive impairment. Additionally, these medications can cause dry mouth, headache, constipation, abnormal and blurred vision all of which may be challenging for older adults with dementia or their caregiver to manage. More concerning though is the risk of cardiac or CNS disturbance (Pagoria et al., 2011). NSSPBD had relatively low use which compared favorably with results of the National

Alzheimer's Coordinating center, where from 2005 to 2015 data from annual visits for dementia care for community-dwelling adults 65 years of age or older found 5.2% of their cohort was receiving a bladder anticholinergic. As in our Nova Scotia cohort, oxybutynin was the most commonly used bladder anticholinergic (Green et al., 2017). Our NSSPBD cohort had less bladder anticholinergic use than an Australian population of older adults with dementia, where bladder anticholinergic use was reported in 8.7% of the cohort (Narayan et al., 2019). On the other hand, our bladder anticholinergic use exceeded that of a cohort of 12,405 community dwelling adults aged 58-73 years in France, where 0.9% were using bladder anticholinergics (Martinot et al., 2018). Interestingly in an Ontario, Canada study that examined bladder anticholinergic users from 2010-1018 tolterodine (39.7%) was the most common bladder anticholinergic followed by oxybutynin (28.7%), solifenacin (26.2%), then fesoterodine, trospium and darifenacin (5.4%) (Welk & McArthur, 2020).

Bladder anticholinergics have been studied using the United Kingdom's Clinical Practice Research Data link. All patients newly prescribed bladder anticholinergic medications from January 1, 2004 to December 31, 2012 were assessed. Mean age of bladder anticholinergic users were 62 years, 70% were female, and patterns of bladder anticholinergic use similar to NSSPBD with 33% oxybutynin, 31% tolterodine, 27% solifenacin over the 11,912 new users. Of these bladder anticholinergic users there were 1,126 cardiovascular and 1,007 cerebrovascular related deaths. This corresponded to an age-sex standardized hazard ratio of 19.9 for all-cause mortality. Cardiovascular events in general were increased and there was an increased risk of major adverse cardiovascular events (HR 12.19; 95% CI [11.61-12.80]). This study went on to examine each bladder anticholinergic separately and found that solifenacin was the least likely to cause cardiovascular outcomes (Arana et al., 2018).

Older adults are more likely to experience dry mouth (RR: 1.09 95% CI [1.00-1.19]), constipation (RR: 1.92 95% CI [1.52-2.43]), dizziness (RR: 2.37 95% CI [1.21-4.62]), and urinary retention (RR: 4.17 95% CI [1.76-9.89]) than younger adults related to bladder anticholinergic therapy. Headache was less common in older adults (RR: 0.58

95% CI [0.40-0.86]). These ADR may have contributed to discontinuation in older adults (RR: 1.59 95% CI [1.20-2.11]). Older adults with dementia may be unable to communicate these adverse effects which may increase the risk of these mild events contributing to BPSD. In addition older adults were 10% more likely than younger adults to experience adverse effects due to bladder anticholinergics however there have not been sex-differences in adverse effects of bladder anticholinergics (Usmani et al., 2019).

In a French study of 12,405 community dwelling adults, aged 58-73 years, 1.2% were using tricyclic antidepressants (Martinot et al., 2018), compared with 2.5% of an American cohort of community-dwelling older adults (Davidoff et al., 2015). In contrast, we found tricyclic antidepressant use to be higher at 6.1% in our cohort of NSSPBD. The more advanced age and concomitant dementia present in our cohort would suggest that tricyclic antidepressant use should be less than a younger group of community dwelling older adults.

6.5.7 Avoid Antipsychotics

In a cohort of 12,405 community dwelling adults aged 58-73 years in France, 0.4% were using antipsychotics (Martinot et al., 2018) compared to 22.9% in our cohort. Importantly, the French data were collected at two points in time versus our assessment of five continuous years of prescription data, which may inflate our numbers, but this is still a striking difference that begs consideration between prescribing practices in France and Nova Scotia.

Quetiapine use remained high and comprised 46.1% of all antipsychotic prescriptions in our cohort. Established prescribing guidelines consistently give the message that antipsychotics and benzodiazepines are dangerous to older adults with dementia. Regardless, quetiapine seems to maintain a perception of relative safety amongst prescribers which may contribute to its high level of use (Kelly et al., 2018).

An evaluation of prescribing in Taiwan reviewed discharge medications of those aged 65 years and older being discharged from medical wards. Antipsychotics were used by 5.6%

of these older adults which still is far less than use in our cohort of NSSPBD (34.7%) (Liu et al., 2012). In a prospective study of PIM use in eight European countries (England, Estonia, Finland, France, Germany, the Netherlands, Spain, and Sweden) risperidone use exceeding six weeks duration was the second most common PIM (Renom-Guiteras et al., 2018).

Women are at a greater risk of weight gain, diabetes and cardiovascular adverse effects of antipsychotics (Meaney et al., 2004). Women and men experience increased prolactin secretion secondary to the dopamine inhibition caused by antipsychotics. Risperidone and conventional antipsychotics are the most common antipsychotics to increase prolactin levels and can increase prolactin level 10-fold above pretreatment levels. Because women start at a higher baseline prolactin, they are more likely to experience symptoms of gynecomastia, galactorrhea, and atrophy of urethral and vaginal mucosa, the latter of which can further exacerbate urinary incontinence. There is conflicting evidence but women may also suffer greater reductions in bone mineral density after long term antipsychotic use than men (D.-U. Jung et al., 2006; Meaney et al., 2004). This means that because women may have more osteoporotic fractures than men at baseline, the risk of fracture is heightened for women upon chronic antipsychotic use.

Female sex is also a risk factor for clozapine related agranulocytosis (Alvir et al., 1993; Hiltgen et al., 2006). Other blood dyscrasias seem to be similarly distributed between men and women (Stübner et al., 2004). Our population of NSSPBD had very low clozapine use but other blood dyscrasias remain a potential concern among both men and women with dementia using other antipsychotics. Also cardiovascular death is higher in women treated with antipsychotic than men which is opposite of the general population (Mahmoodi et al., 2007) and may be a relevant consideration in choosing pharmacologic management strategies for BPSD for men and women.

A population based cohort in patients with dementia were examined to determine the relative frequency of parkinsonism after starting risperidone, olanzapine or quetiapine (Marras et al., 2012). Those included were more than 65 years of age without known

parkinsonism and not previously treated with antipsychotics in the year prior. Dementia was defined similarly to this study via ICD-9 or 10 codes from hospital discharge or physician outpatient service claim or if they received a prescription for a cholinesterase inhibitor. They included prescriptions for Parkinson's Disease medications or ICD-9 or 10 codes as evidence of parkinsonism. This is different from the current study that relied on prescriptions as evidence of parkinsonism. They calculated the risk of Parkinson's Disease dependent on antipsychotic used. They included risperidone, quetiapine and olanzapine in analysis with risperidone as the comparator. Over the seven years of case identification they identified 51,878 older adults with dementia who received risperidone, olanzapine or quetiapine. Those treated with quetiapine were more likely to receive a cholinesterase inhibitor. 421 of the cohort developed parkinsonism. 65% of women used antipsychotic in the groups of those both with and without parkinsonism. Parkinsonism occurred in men twice as often in women (HR 2.29 95% CI[1.88-2.79]) but the hazard ratios for men versus women were similar within each drug and dose subgroup suggesting that the higher risk in of parkinsonism was not influenced by medication induced phenomena. Olanzapine users had a greater risk of parkinsonism than those using risperidone (Marras et al., 2012).

6.5.8 Avoid Sedatives

Benzodiazepines were used by 9.3% of community-dwelling older adults in the United States Medication Expenditure Panel Study (Davidoff et al., 2015). Among older adults with dementia, sedatives are more commonly prescribed than cholinesterase inhibitors. Sedatives are more often used by women, suggesting that targeted interventions toward reducing sedative use in women is needed. This pattern of sedative use is not in accordance with prescribing guidelines for older adults with dementia.

Review of inpatient and outpatient records at a Taiwanese hospital that included over 15,000 geriatric inpatient and outpatient visits annually showed that 151 of the 308 (49%) individuals with dementia assessed received at least one prescription for a benzodiazepine (Tien et al., 2020). In this population over 60% of the benzodiazepine users received the medication for more than 180 days. In NSSPBD the average duration

of sedative use exceeded 1 year in keeping with the Taiwanese study however they did not identify any association with sex and benzodiazepine use, which differed from our study.

6.5.9 Avoid Unnecessary Gastrointestinal Agents

PPIs were cited as the most frequent PIM in a prospective study of medication use in eight European countries (England, Estonia, Finland, France, Germany, the Netherlands, Spain, and Sweden). PPIS comprised 19.1% of the PIM in that study (Renom-Guiteras et al., 2018). In NSSPBD PPIs were used by 34.7% of the cohort. H2RAs are also considered PIM on prescribing guidelines and were used by 13.7% of the cohort. Both PPIs and H2RAs were available without a prescription so use of these agents was likely under-reported.

PPIs are of great interest as the impact of PPI use on survival in older adults with dementia has been investigated. 28,428 people with dementia on a PPI compared to two controls matched on sex, age and residence showed that PPI exposure was associated with an increased mortality risk in adults with dementia unadjusted HR 1.07 95% CI (1.03-1.12) and adjusted HR 1.47 95% CI (1.31-1.64) (Cetin et al., 2020). PPIs have been used in favour of H2RAs as H2RAs have been considered PIM but in addition to a negative effect on survival PPIs are associated with hypomagnesiemia, infections, fracture and may be associated with an increased risk of dementia or dementia progression (Ortiz-Guerrero et al., 2018). H2RAs have been considered anticholinergic for many years but this has been debated in recent years and even have been removed as PIM from some prescribing guidelines. Regardless avoiding unnecessary gastrointestinal agents is a wise clinical practice and a challenging one for older adults with dementia.

6.5.9 Limitations

This study relied on the same cohort that was compiled for the study of prescribing cascades (chapter 5). This makes it susceptible to the same limitations as listed previously. We had limited ability to describe the clinical picture of the individual patients (e.g. severity of symptoms, resistance to other treatment options, co-morbid

conditions, and support for non-pharmacologic treatment) and did not have data on medication indication or dose. This makes it challenging to assess any clinical considerations that may have made the prescribing choices appropriate contrary to clinical practice guidelines for older adults. For drug duplication, the presence of prescriptions for two drugs from the same class does not mean that they were being used simultaneously despite the assumptions.

6.6 Conclusions

Given that there are many well respected guidelines that guide prescribing for older adults with dementia the hypothesis was that PIM would be present but rare in the NSSPBD. These represent a subgroup of the most vulnerable and frail of the older adults in Nova Scotia who were anticipated to be protected from PIM by careful prescribing. Instead there were PIM in each of the categories investigated. NSAID, SSRI, loop diuretics and ACE-inhibitors were all used with overlap that was likely representative of duplication. This is concerning as duplication of these classes of medication does not increase therapeutic effect but most likely increases risk of adverse drug events. Anticholinergic medications are a diverse category of medication and older women experience increased exposure to many of these drugs due to sex and age and their effects on pharmacokinetics which increase risks of adverse events. Despite these concerns, levels of anticholinergic medication use in NSSPBD were quite high, especially for psychoactive agents in women NSSPBD. Antipsychotics carry risks for older adults with dementia. It is promising to see lower levels of first generation antipsychotic use but concerning that second generation antipsychotics are used and are used for longer durations. There are high levels of sedative use in NSSPBD. There are no settings where sedatives have been shown to be beneficial for older adults with dementia so the high levels of use for long durations are concerning and an excellent place to initiate practice changes. Due to the concerns of multiple prescribers or multiple pharmacies a collaborative team approach to prescribing and deprescribing is worth developing to protect older adults with dementia from potential harms from PIMs (Clark et al., 2020; Finley et al., 2020).

CHAPTER 7 A COLLABORATIVE INTERVENTION FOR DEPRESCRIBING: THE ROLE OF STAKEHOLDER AND PATIENT ENGAGEMENT

This chapter has been published in Research in Social and Administrative Pharmacy (Shanna Trenaman et al., 2019) and is included herein with permission (see appendix 2).

7.1 Introduction

The Canadian population is aging; as of 2014, over 15.6 percent of Canada's population is aged 65 years or older. Estimates suggest that by 2030 approximately 23 percent of Canadians will be over the age of 65 (*Government of Canada - Action for Seniors Report*, 2018). With increased life expectancy comes the accumulation of medical conditions, which contribute to frailty (Song et al., 2010). As frailty and medical comorbidity increases, the number of medications used also increases (Andrew et al., 2017; Mannucci et al., 2014). A 2011 study found that 30% of Canadian seniors aged 65 to 79 took at least five prescription medications concurrently (Rotermann et al., 2014). These medications are used with the intention of improving health, but they also come with downsides, including that polypharmacy (more than 3 medications) is associated with increased hospitalization (OR 3.79, 95% CI {1.33, 10.90}) and increased mortality (OR 1.27, 95% CI {1.04, 1.56}) (Fried et al., 2014; Nossaman et al., 2017; Schottker et al., 2017).

There are numerous tools designed to support reduction of medication use in clinical practice (By the American Geriatrics Society 2015 Beers Criteria Update Expert Panel, 2015; Carnahan et al., 2006; Hanlon et al., 1992; Hilmer et al., 2007; Holt et al., 2010; Laroche et al., 2007; O'Mahony et al., 2015; Wills et al., 1997). *Deprescribing* is the process of withdrawal of an inappropriate medication, supervised by a healthcare professional with the goal of managing polypharmacy and improving outcomes (Reeve et al., 2015). Previous work suggests that including pharmacists or nurses in the healthcare team increase deprescribing success (Steinman, 2016). Pharmacists have extensive training that positions them well to support patients and prescribers in deprescribing (Johansson et al., 2016).

Even with ideally resourced teams, patient buy-in is critical for the success of deprescribing efforts. Thompson et al. call for greater patient engagement in deprescribing research (Thompson, Reeve, et al., 2018) as patients must be willing to consider deprescribing, take an active role in the decisions surrounding deprescribing, and then complete the deprescribing plan for it to be successful. This aligns well with the observation that patient engagement in health research supports more relevant research that better addresses patient needs and concerns (Forsythe et al., 2019; Thompson, Reeve, et al., 2018). Canadian data suggests 63% of adults aged 65 years or older would like to reduce the number of medications they are taking (Sirois et al., 2017), and previous work has suggested that patients are open to pharmacist involvement in deprescribing (Reeve et al., 2013, 2014).

Given the challenges of implementing deprescribing interventions, and the critical need for patient engagement in making medication changes, it is particularly important to include the patient voice in the design of a deprescribing intervention. The Canadian Deprescribing Network has used a well-organized strategy of patient engagement in their work (Thompson, Reeve, et al., 2018) which has allowed patient and caregiver representatives to participate as equal members of the research team, joining clinicians, researchers, policy makers and other stakeholders. This approach is recognized as a model in the incorporation of the patient voice in health research (Brett et al., 2017). The present paper will describe the methods used to engage patient and caregiver representatives in a project aiming to develop a deprescribing intervention for collaborative primary care practices that have a team pharmacist.

7.2 Objective

The overarching goal of this project is to develop and evaluate a practical, feasible, and well-tolerated intervention that can be implemented by pharmacists in integrated healthcare teams to safely initiate and monitor deprescribing. The objective of this paper is to highlight the approach to patient engagement used to refine the deprescribing intervention.

7.3 Methods

This project engaged pharmacists, geriatricians, primary care physicians, nurses, researchers, a patient advocate, and health policymakers from New Brunswick (NB) and Nova Scotia (NS) to create a core research team with extensive and varied expertise. As part of this core planning team, a patient advocate who had expressed interest in working with the Dalhousie University Geriatric Medicine Research Unit on research projects provided the patient viewpoint for the grant writing stage. The project objective was to develop and implement a pharmacist-led deprescribing intervention in collaborative primary care sites (two sites in NS and one in NB), including nursing home sites (three sites in NB).

In order to ensure that a diversity of patient and public voices were heard, a facilitated meeting was planned in conjunction with the Maritime Strategy for Patient Oriented Research (SPOR) Support Unit (MSSU) who were engaged to provide facilitation services for the event. The MSSU reached out to a contact list of potential patient representatives who had expressed interest in participating in research that examined the healthcare of older adults about the intended project. Five respondents from different home addresses were invited on a first-come, first-served basis to join the facilitated meeting. Patient representatives were provided with an honorarium and expenses for their time and expertise ($100 for participation in the facilitated meeting, reimbursement of mileage for travel, and meals over the two days).

The research team was aware that this environment could be intimidating for patient and public representatives finding themselves amongst an established group of clinicians and academics. The MSSU planned the meeting facilitation and acted as a neutral party to mitigate this potential issue. In addition to the meeting facilitator, the MSSU provided facilitators to lead small group discussion. These small group facilitators monitored conversation and actively encouraged input from quieter group members. Before the event, a list of medical and research related jargon that researchers anticipated might be used was compiled for review at the facilitated meeting. In addition, when new or unfamiliar words were used, these were clarified for the larger group. The event was

designed to provide a welcoming environment for all participants; discussion groups ensured a mix of clinical, research and patient voice, and facilitators focused on engaging all voices equally.

Sixteen members of the research team met with the five patient representatives at an in-person facilitated meeting. This meeting was held over two days to engage the research team and set the objectives, aims, and methods that would be most meaningful for a deprescribing intervention in collaborative primary healthcare settings. The facilitator chose seven focus areas, which were informed by the original grant proposal: 1) ways to identify a patient appropriate for deprescribing which included frailty assessment, 2) ways to identify potentially inappropriate medications, 3) ways to prioritize medications for deprescribing, 4) ways to discuss deprescribing with patients using a patient-centered process (Reeve et al., 2014), 5) ways to communicate effectively with prescribers, 6) an intervention for deprescribing in the project, and 7) a communication method for documenting and communicating progress with prescribers.

The first day of meetings included introductions from the lead principal investigator, facilitators, content experts, a government representative and the original patient advocate. The facilitator set the tone of the event by reminding the group that each participant was an expert in their own right and had valuable contributions to make to the project. Then the group was broken into four working groups organized by the facilitator. Each group rotated through four topics (shown in table 34) in fifteen-minute sessions. These groups were provided with large flipcharts to document their discussion and findings. When the fifteen minutes had passed, groups moved to the next station and were able to review the prior groups' notes to help further develop ideas. Once all groups rotated through the four stations, there was a period of large group discussion to summarize findings of the day. At the end of the first day, everyone was invited to a social dinner at a local restaurant.

Table 34: Discussion Points Used to Develop Deprescribing Intervention at Stakeholder Engagement Meeting

Four Topics for Discussion to Develop Deprescribing Intervention	
Topic A: Medications - When creating a tool to help pharmacists deprescribe medications: - How can we identify potentially inappropriate medications for seniors? - How can we choose and prioritize the medications to reduce or stop?	**Topic B: Patient Selection** - When creating a tool to help pharmacists deprescribe medications: - How can we identify a patient appropriate for deprescribing? - How can we include a frailty assessment in this process?
Topic C: Process - When creating a tool to help pharmacists deprescribe medications: - How is the tool used? - How can we discuss deprescribing with patients in a patient-centered way? - How can we communicate effectively back to prescribers (e.g., family physicians)?	**Topic D: Evaluation** - How will we know we were successful? - How do we measure satisfaction? - What do different groups want the tool to achieve? - How can the tool be used to communicate information back to patients? Caregivers? Providers?

The second day of facilitated meetings shuffled participants into new working groups to take ideas from the previous day and develop the intervention in greater detail. The facilitator instructed the group to accept consensus. Consensus was defined as everyone being committed to finding a solution with which everyone could agree, even if their official position was not in unanimous agreement. Consensus was used as it allows the group to move the project forward in order to reach common ground that they could "live with". After the preliminary findings were collected, three rounds of remote revisions including invited stakeholder feedback was planned to complete the framework and communication tool. The details of framework development and communication tool are outside the scope of this publication and will be reported separately.

7.4 Results

The response to the MSSU call to potential patient representatives exceeded expectations. Seven individuals responded with interest in the project. This was in addition to the original patient advocate. The first five respondents to the MSSU call who resided at separate home addresses were invited to participate in the facilitated meeting. Results of the facilitated meeting are shared here and organized to reflect the three main ways that patient and caregiver representatives' input directed intervention development differently than the research team's original intention.

7.4.1 Eligibility

The research team had intended to limit the study participants eligible for the deprescribing intervention to adults 65 years of age or older. This was in keeping with a geriatric medicine population. The patient and caregiver representatives raised concerns with the age limit, and the appropriateness of withholding the deprescribing intervention from a younger person who was interested in it. They were concerned that it went against the goal of the project to exclude those who could benefit from deprescribing based solely on their age. Given that polypharmacy becomes more prevalent as people age, it is likely that more often potential study participants would be older adults, but the team agreed that there was no reason to limit participation based on age. The entire research team agreed that adults 18 years of age and older should be eligible for study inclusion.

7.4.2 Toolbox

The patient and caregiver representatives clearly recognized the benefits of deprescribing but expressed concern that the success of deprescribing would depend upon the patients being supported through the process. In general, the clinician perspective for deprescribing a medication that is no longer needed or that has risks exceeding its benefits is straightforward. The patient and caregiver representatives identified that it would likely be more challenging for patients to accept a deprescribing intervention. Patient and caregiver representatives discussed the need for substitute supports or resources to replace the discontinued medications. The idea that grew out of this observation was development of a resource toolbox which would include a series of

mostly non-pharmacological options to substitute and enable successful deprescribing. The example was if the clinician recommendation was to discontinue a sedative due to concerns of over-sedation and risk of falls, the patient would benefit from other non-drug supportive advice that could help the patient continue to have acceptable sleep. This soon developed further into a collection of resources that could support healthcare professionals during deprescribing and support patients as they participate in deprescribing. This toolbox would be available both as a hardcopy of brochures and resources to be distributed by the pharmacist or other healthcare professionals at the healthcare site and as a website that could be accessed online by healthcare professionals or at home by patients or caregivers.

7.4.3 Continued Engagement

Patient and caregiver representatives' satisfaction with the stakeholder meetings was not measured aside from a general feedback survey that was given to all participants. Even so, one measure of satisfaction and feelings of meaningful participation is that all patient caregiver representatives continue to be involved with the project. Some patient and caregiver representatives offered their specific talents. One patient representative with graphic design experience has developed the posters to be used to raise awareness of the intervention study at the sites. Another patient representative shared resources they have used in previous work for survey development that will be used to track success of the intervention amongst healthcare professionals. The deprescribing intervention which includes a framework, communication tool and resource toolbox has received feedback from all the patient and caregiver representatives in addition to the research team. There have been three subsequent rounds of review and the intervention and has been approved by the entire research team.

7.5 Discussion

The present paper reports experience with patient engagement in developing a deprescribing intervention. Patient input refined the intervention, identifying a need for supportive resources and encouraging the research team to open the study to include any adult interested in deprescribing irrespective of age. This experience with patient and

caregiver engagement was positive. Patient and caregiver representatives provided crucial feedback and ongoing involvement, which it is hoped will improve the relevance and quality of the study (Sirois et al., 2017; Young et al., 2019).

Patient engagement is a priority area for large funding agencies such as the Canadian Institutes of Health Research (Government of Canada, 2012). This dovetails well with the need to engage patients in deprescribing efforts. A world café style meeting to discuss priorities for deprescribing (Thompson, Reeve, et al., 2018) confirmed the need for deprescribing studies that explored topics of importance to patients and how best to achieve shared decision making between patients and healthcare providers. There are recently published strategies to promote public engagement around deprescribing (Turner et al., 2018). In agreement with these strategies, the present study included patient and caregiver representatives from the beginning, with a single patient representative involved in preparing the grant proposal. This has grown to six engaged patient and caregiver representatives who have been involved in the design of the intervention.

Few published studies of deprescribing have included patient engagement (14 hits on PubMed). These papers were heterogeneous and did not demonstrate patient engagement in deprescribing research. Two of the papers reported findings from surveys of general practitioners on their views on deprescribing (Carrier et al., 2019; Wallis et al., 2017). These studies found that general practitioners were generally supportive of deprescribing but were infrequently able to incorporate deprescribing into regular practice (Carrier et al., 2019; Wallis et al., 2017). Three papers reported on deprescribing of specific drug classes (Ostrow et al., 2017; Janice B. Schwartz et al., 2019; Thompson, Black, et al., 2018). Some of the remaining papers reported on reviews of patient engagement in deprescribing and offered best practice recommendations (Linsky et al., 2017; Turner et al., 2018). A review article that documenting a series of meetings focused on Pharmacotherapy in Older Adults with Cardiovascular Disease that set out to identify the top priority areas for research in older adults with cardiovascular disease concluded that patient engagement was important (Janice B. Schwartz et al., 2019). Despite the call for

patient engagement, details of any patient engagement at the meetings themselves was not clear.

In contrast, some deprescribing studies have reported how patient and caregiver representatives have had an opportunity to help shape the research that affects them. A study of discontinuation of psychiatric medications employed a survey instrument that was developed with input from actual service users (Ostrow et al., 2017). This retrospective survey of participants' experience with withdrawal symptoms during the deprescribing of psychiatric medications investigated the role of supports. Allowing service users to help develop the survey increased the likelihood that all potential sources of support were included for evaluation. The authors believed this was the first study that asked participants to report the helpfulness of several deprescribing supports and resources. This observation that the patient voice had heretofore been missing is concerning given that evaluation of supports is crucial for identifying future interventions that can support deprescribing and withdrawal.

The "Patient Perceptions of Deprescribing" survey recognized patient and public engagement as an important component of deprescribing trial development (Linsky et al., 2017). This study employed extensive focus groups and semi-structured interviews with patients taking more than five medications. However, the problem to consider is that this research was being carried out *on* these subjects rather than *by* them. Patient perspective informed the survey questions but patient representation on the research team would have helped the patient voice remain heard rather than researcher voice subsuming the project.

7.5.1 Limitations

Concerted efforts were made to support patient and caregiver representatives at the facilitated meeting. Despite these efforts, it is possible the patient and caregiver representatives were not comfortable. The team overlooked the opportunity to survey them and ask them directly about their experience other than in the context of a general event evaluation. The facilitators were instructed to monitor conversation to get feedback from all group members, but it is difficult to know if they felt comfortable enough to

express all their concerns. Reassuringly, the fact that the patient and caregiver representatives have continued to be engaged suggests that they did feel welcomed and valued as members of the research team.

The agenda development at the facilitated meeting was done by the facilitator, such that there was little direct team involvement, and no direct patient involvement in the development of the facilitated meeting. Rather, the experienced facilitator developed the agenda based on the original grant proposal and some selected references[24]; patient involvement in meeting development may have further improved the patient engagement experience.

7.6 Conclusions

Overall, holding a facilitated meeting to engage with patient and caregiver representatives allowed the study team to develop a deprescribing intervention using a method that aligns well with priorities for deprescribing clinical trials.[20,24,28] While the approach described is only one method to engage with the public, these methods provide guidance for incorporating patient and public involvement in research at the stage of intervention planning and design. Patient involvement at the facilitated meeting led to improvements in study design. Continued engagement of patient and caregiver representatives as the study rolls out is encouraging and hopefully portends broader public interest in improved prescribing.

CHAPTER 8 CONCLUDING REMARKS

This dissertation provided a multi-faceted investigation into the challenges of understanding medication use and effect in older men and women with dementia. This thesis has taken an interdisciplinary approach to understanding how age, sex, and genetic polymorphisms of cytochrome P450 (CYP) enzymes all play a role in anticholinergic medication effect and toxicity, identifying trends in anticholinergic medication use, investigating improved pharmacological methods to identify and quantify the anticholinergic activity of medications, a pharmacoepidemiological evaluation of medication use in older adults with dementia in Nova Scotia that included review of four prescribing cascades and a series of prescribing indicators and stakeholder engagement on the pathway to developing and implementing appropriate deprescribing interventions to facilitate deprescribing of PIM in the community.

The initial literature review showed that drug effect and toxicity may be affected by the influence of age, sex and genetic polymorphisms of the CYP enzymes on the pharmacokinetics of anticholinergic medications. The review identified that women have slowed gastric and colonic emptying, catechol-O-methyl transferase activity, glucuronidation and renal clearance. Differences in drug metabolism were inconsistent and tended to show increased CYP activity in women but the presence of active metabolites made the outcome of these differences in metabolism difficult to apply to medications without specific study of each medication. Naturalistic study of anticholinergic medication exposure in older women consistently demonstrated a higher medication exposure in women. With increased exposure in women it was hoped that women would have reduced use of anticholinergic medications. This was not the case. Study of medication use in NSSPBD showed increased anticholinergic medication use in women and particularly psychoactive medications with anticholinergic activity.

The literature also shows that CYP2D6 PM are at risk of increased exposure to many anticholinergic medications. Currently tests exist to identify CYP2D6 PM but these are not used routinely, but CYP2D6 substrates are. We have high levels of risperidone and amitriptyline use in the population. Given that serious adverse events can occur with

anticholinergic medication use (especially in older adults with dementia) it may be beneficial to carry out genetic testing to identify poor metabolizers (PM). This would permit a more personalized approach to medications use. It may also identify those at greatest risk of not tolerating specific medications which would allow us to choose medications and organize dosing strategies that would be most appropriate for CYP2D6 PMs when they were identified.

The scoping review had limited findings and they were challenging to contextualize in the Nova Scotia experience. Similar to the observational studies assessed in the scoping review, in Nova Scotia there was increased psychotropic medication use by women. Cholinesterase inhibitors were more commonly used in men in the studies reviewed but we saw similar rates of cholinesterase inhibitor use in men and women in our study. A recent study in Australia using the Pharmaceutical Benefits Scheme selected a 10% sample of pharmacy claims data to examine prescribing patterns in older adults with dementia compared to controls without dementia. Those with dementia were considered older adults who had received at least one prescription for a cholinesterase inhibitor. This investigation likely severely underestimated cases of Alzheimer's Disease in the population, as we found that only 19.9% of NSSPBD with dementia received at least one prescription for a cholinesterase inhibitor. This only is likely to bias against the null in the Australian study as it would fail to identify cases who would potentially be incorporated into the controls. The Australian cohort composed of 8,280 older adults with dementia had 36.6% male and 63.4% female older adults of an average age 83 years. They identified antidepressant use by 48%, antihypertensive use by 44%, gastrointestinal drugs by 43%, statin use by 41%, benzodiazepine use by 17.5%, antipsychotic use by 39%, and Parkinson's Disease drug use by 6.8% (Eshetie et al., 2019). The cohort of NSSPBD had a similar sex distribution in cholinesterase inhibitor users (68.7% women and 31.0% men). NSSPBD had similar rates of use of gastrointestinal drugs (39.5% of NSSPBD) and antipsychotics (34.7% of NSSPBD). There was less use of Parkinson's Disease medications with only 3.4% of NSSPBD receiving at least one prescription for these medications. Benzodiazepines were used by 27.7% of in comparison to only 17.5% in the Australian cohort. This is of note as the Nova Scotia context showed similar prescribing

with the exception of benzodiazepines. The Australian study included only adults being treated with cholinesterase inhibitors so may have represented a group of older adults more receptive to pharmacologic treatment for dementia and may have been less likely to use off-label treatments for BPSD.

PIM use was common in NSSPBD and previous findings confirm this finding in other jurisdictions. PIM was used by one in every four community-dwelling older adults (Barton et al., 2008; Mort & Aparasu, 2000) and by one in every two care home dwelling adults (Somers et al., 2010). One in every four NSSPBD with dementia was using an anticholinergic medication which reiterates the prevalence of these medications in regular use in Nova Scotia. A high prevalence of PIM use has significant ramifications. 1,429 community-dwelling women over 75 years of age were studied over five years at four clinical sites in the United States to identify predictors of PIM use, ACB and impairment based on six different cognitive tests. PIM use was significantly associated with one or more new IADL impairments (unadjusted OR:1.33, 95% CI [1.05-1.70]) as was increased ACB (unadjusted OR:1.11 95% CI[1.05-1.75]). There were reductions in category fluency and recall as PIM use or ACB increased (Koyama et al., 2014). Women using PIM at baseline had poorer performance on cognitive tests than non-users, test included CVLT-II, tests of words recalled, immediate recall and Trails B. PIM users took longer to complete a category fluency test. Higher ACB score was associated with fewer words recalled and impaired category fluency. PIM and ACB use did not affect backwards digit span test result. All testing was after five years of follow-up and PIM and ACB increases were associated with increasing functional impairment (Koyama et al., 2014). Discontinuing or deprescribing anticholinergic medications seems to be a wise approach for older women based on this study. In a Canadian study using different cognitive tests 102 older adults 60 years of age and older followed for one year if anticholinergic burden increased over the year of follow-up the cognitive performance on the Trail making test B and cued delayed recall performance decreased (OR:2.9 95% CI [1.1-8.0] and OR:4.2 95% CI [1.8-15.4]) (Kashyap et al., 2014) which suggests men also suffer reduced cognition in response to use of anticholinergic medications.

Unfortunately improving anticholinergic burden has not led to global improvement in cognitive impairment. In a randomized single blind pharmacist intervention study of 87 care home residents that used a pharmcist-led medication review to reduce ADS (Carnahan et al., 2006). ADS did decrease from 4 to 2 ($p<0.0001$) but there was no change in the four functional scales investigated which included the MMSE and three CERAD memory subscales over eight weeks of follow-up (Hege Kersten et al., 2013). In a study of 67 adults with dementia in a Veteran Home who were given access to a primary care team with recent education in a program encouraging a reduction in anticholinergic burden. ACB was reduced according to the Clinician-Rated Anticholinergic Score in intervention group versus a reference group. (0.5 ± 1.1 versus 1.1 ± 1.3, $p=0.021$), but MMSE and Barthel Indices were similar after 12 weeks of follow-up (Yeh et al., 2013). This shows that reducing ACB does not lead to a quick recovery in cognition and avoiding these agents altogether is a better approach.

While cognitive outcomes have not demonstrated improvement as ACB decreases improving MAI and reducing PIM use in 400 older hospitalized adults in Sweden demonstrated a decrease in drug-related hospital readmissions in 12 months of follow-up (Gillespie et al., 2009, 2013). These improvements in prescribing were achieved using hospital pharmacists. This was an important finding that pharmacist interventions demonstrated a benefit in MAI and the clinically relevant outcome of reduced hospitalization or rehospitalization.

Improvements in prescribing can be recommended by prescribers or pharmacists but they need to be welcomed and implemented by patients and caregivers for them to be successful. Perceived effectiveness was the primary factor related to medication value in a study of older patients and caregivers in Pepper Geriatric Research Registry (patients) and the Pitt+Me Registry (caregivers) maintained by the University of Pittsburgh. The possibility of adverse drug events was perceived as low value in the overall value of medications and did not motivate patients to change their medications. Also of note, the prescriber relationship was of greater importance in perceived medication value than the training level of the prescriber (Pickering et al., 2020). This does suggest that pharmacists

with well-established patient relationships should be able to provide care acceptable to patients during the deprescribing process.

Comparison to other jurisdictions suggested that we can improve our prescribing by coordinated drug-utilization monitoring and limiting prescribing to one prescriber (family physician or nurse practitioner). Pharmacists are a highly accessible healthcare provider who could provide medication management and support for older adults. In our deprescribing stakeholder and patient engagement meeting there was strong support of the pharmacists to manage the deprescribing process. In four Japan nursing homes pharmacists provided drug therapy interventions that reduced PIM use from 2.64 to 2.39 PIM per patient in six months (95% CI [2.74-2.89]) and this corresponded to a reduction in falls from a mean of 0.04 per patent in the intervention group and 0.41 per patient in the control group (Hashimoto et al., 2020). Additionally PIM use was associated with higher medication costs with 17.5% of the medication budget spent on PIM (Harrison et al., 2018). These may not be motivational for patients to choose deprescribing but should be motivational for policy makers to save costs and improve the health of the population.

Identifying the risk factors for increased anticholinergic medication exposure is important but identifying which medications have anticholinergic activity is crucial for creating prescribing guidelines. We lack an easy way to identify anticholinergic activity so the cellular reporter assay investigated in this dissertation provides a novel approach that may be able to be modified to create an objective measure of the anticholinergic activity of medications and possibly even be used to investigate serum anticholinergic activity. This study is quite a preliminary investigation and in order for future work to be of clinical relevance it will need to consider active metabolites, drug distribution and how these correlate with clinical effect.

Future work needs to develop a better understanding of the causes and motivators of PIM use and how to make discontinuing these medications desirable for older adults with dementia and their caregivers. Projects that study anticholinergic antipsychotic and sedative users with dementia to identify pharmacokinetic parameters and then understand

behaviour changes in response to discontinuation of these PIM in a controlled setting such as a geriatric day hospital or clinic. Continuing to work with patients and caregivers to discuss realistic expectations from medications as well as risks of PIM use is important. Once these are better understood, study needs to focus on what is needed to support patients and caregivers during medication changes. Development of easy to access and understand information on PIM could form one component of this support. The science of PIM exposure in older adults with dementia and clinical observation need to come together to develop a solution for PIM use in older adults with dementia.

In summation anticholinergic medications are recognized as PIM and best avoided in older adults with dementia. Prescribing guidelines, Beers list and STOPP criteria, use what we know of drug properties and adverse effect profiles to give best practice prescribing recommendations. More recent iterations provide guidance based on prescribing for older adults with specific comorbidities (like dementia), but they do not give any sex-specific guidance. We currently lack widely accepted standardized methods to identify anticholinergic medications. Despite recommendations to avoid anticholinergic medications in older adults with dementia there are still high rates of use of anticholinergic medications in older adults with dementia in Nova Scotia. Both men and women use anticholinergic medications but there are differences in the distribution of which anticholinergic medications are used by men and women. Further work is needed to better identify anticholinergic medications and how to address PIM in older adults with dementia to encourage deprescribing of these agents.

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APPENDIX 1: PHARMACOKINETIC PROPERTIES AND SEX, AGE AND GENETIC INFLUENCE ON PHARMACOKINETIC PARAMETERS ON ANTICHOLINERGIC MEDICATIONS

Generic Drug Name	ACB [1]	ARS [2]	ADME[3]	Effect of		
				Sex on ADME	Age on ADME	Genetics on ADME
Alprazolam	1		F: approximately 90% Distribution: 80%, mostly to albumin Metabolism: Liver, extensive via CYP3A Renal Clearance: 371 mL/h Renal Excretion: 80% Fecal Excretion: 7% TBC: 76 mL/min $t_{1/2}$: After oral administration to healthy adults 11.2 h	The weight-normalized clearance of alprazolam is 20% to 30% higher in young women than in young men	Renal clearance is significantly decreased in elderly men	
Amantadine	2	2	F**:** 86-94% Distribution: 59-67% bound to serum proteins V_d: 404 L or 4.9 L/kg Metabolism: Liver, extensive via CYP3A Renal Clearance: 371 mL/h Renal Excretion: 80% Fecal excretion: 0.6% TBC: 0.2-0.3 L/h/kg $t_{1/2}$: 17 (± 4) h	Amantadine has significantly higher renal clearance in men	Reduced clearance in elderly patients and reduced renal function: 22.6 to 45 h	

Generic Drug Name	ACB [1]	ARS [2]	ADME[3]	Effect of		
				Sex on ADME	Age on ADME	Genetics on ADME
Amitriptyline	3	3	F: high Metabolism: Liver, CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 $t_{1/2}$: 15 h (range: 9-25 h)	Amitriptyline plasma levels were higher in women than in men	1.5-fold higher ratio of absolute serum concentration to dose adjusted serum concentration in the oldest age group in comparison to controls < 40 years of age	
Atenolol	1		F: 46-60% Distribution: <5% bound to serum proteins, brain tissue:blood concentration ratio of 0.2:1 V_d: 50-75 L Metabolism: No liver metabolism and no active metabolites Renal Excretion: 40-50% Fecal Excretion: 50% $t_{1/2}$: 6-7 h			

Generic Drug Name	ACB [1]	ARS [2]	ADME[3]	Effect of		
				Sex on ADME	Age on ADME	Genetics on ADME
Atropine	3	3	F: high Distribution: Serum protein binding is highly variable by age: 22.5% ± 20.6% (<16 years), 14% ± 9.1% (16-58 years), 22.2% ± 16.7% (65-75 years) V_d: 3.3-3.9 L/kg $t_{1/2}$: 4 h (adults), 6.5 h (children)		Protein binding is highly variable upon age, $t_{1/2}$ varies by age	
Baclofen		2	F: 100% V_d: 59.1 L Metabolism: Liver, limited Renal Clearance: 103 mL/min Renal Excretion: 69-85% of oral dose Fecal Excretion: 10% TBC: 180 mL/min $t_{1/2}$: 3-6.8 h			
Benztropine	3	3	F: poor			
Brompheniramine	3		V_d: 11.7 L/kg Metabolism: Liver, extensive Renal Excretion: 17% $t_{1/2}$: 25 h			

Generic Drug Name	ACB [1]	ARS [2]	ADME[3]	Effect of		
				Sex on ADME	Age on ADME	Genetics on ADME
Bupropion	1		Distribution: 84% bound to serum proteins, CSF concentration 10-25 fold higher than plasma V_d: 19-21 L/kg Metabolism: Liver, extensive, primarily CYP2B6 Renal Excretion: 87% Fecal Excretion: 10% TBC: 160 mL/h (± 23%) $t_{1/2}$: 14-21 h	Mean AUC and C_{Max} for bupropion are higher in women than men however once these parameters are standardized for body weight the statistical significance is lost	In older adults (mean age 71.5 years) the clearance was 80% that seen in younger adults and the elimination $t_{1/2}$ was extended to 34 h compared to most sources which report 11-14 h	
Captopril	1		F: 70-75% Distribution: 25-30% bound to serum proteins V_d: 0.7 L/kg Metabolism: Liver, 50% Renal Clearance: 0.4 L/kg/h Renal Excretion: 95% TBC: 0.8 L/kg/h $t_{1/2}$: 1.9 h			

Generic Drug Name	ACB [1]	ARS [2]	ADME[3]	Effect of		
				Sex on ADME	Age on ADME	Genetics on ADME
Carbamazepine	2		F: 70-79% Distribution: 76% bound to serum proteins, the CSF/serum ratio 0.22 V_d: 0.8 to 2 L/kg Metabolism: Liver, 98%, extensive via CYP3A4, inducer of CYP3A4 and CYP1A2 Renal Excretion: 72% Fecal Excretion: 28% TBC: 80 mL/min $t_{1/2}$: 12-17 h		Patients 70 years and older had a decreased clearance by approximately 70%	
Cetirizine	1	2	F: rapid and complete Distribution: 93% bound to serum proteins V_d: 0.5-0.8 L/kg Metabolism: Liver, minimal Renal Excretion: 60% Fecal Excretion: 10% TBC: 53 mL/min $t_{1/2}$: 7.4-9 h		The $t_{1/2}$ is prolonged by 50% in older adults and in patients with chronic liver disease as compared to normal healthy adults	

Generic Drug Name	ACB [1]	ARS [2]	ADME[3]	Effect of		
				Sex on ADME	Age on ADME	Genetics on ADME
Chlorpheniramine	3	3	F: good V_d: 3.2 L/kg Metabolism: Liver, extensive Renal Excretion: 50 Fecal Excretion: <1% TBC: 234-470 mL/h/kg $t_{1/2}$: 20 h			
Chlorpromazine	3	3	F: 32% Distribution: 90-99% bound to serum proteins, CSF concentration 5 times the plasma concentration V_d: 8-160 L/kg Metabolism: Liver, large extent Renal Excretion: 23% $t_{1/2}$: 6 h			
Cimetidine	1	2				

Generic Drug Name	ACB [1]	ARS [2]	ADME[3]	Effect of		
				Sex on ADME	Age on ADME	Genetics on ADME
Clomipramine	3		F: 20% to 78% Distribution: 97% bound to serum proteins, mostly albumin, CSF:plasma ratio is 2.6 V_d: 7-20 L/kg Metabolism: Liver, extensive Renal Excretion: 51-60% Fecal Excretion: 24-32% TBC: 12.7-56.5 L/h $t_{1/2}$: 19-37 h	The ratio of absolute serum concentration in comparison to the dose-adjusted serum concentration is 1.1-1.5-fold higher in women than in men which suggests a dose reduction of 10-30% for females	There is a 1.5-fold higher ratio of absolute serum concentration to dose adjusted serum concentration in the oldest age group in comparison to controls < 40 years of age	
Clozapine	3		F: 50-60% Distribution: 97% bound to serum proteins V_d: 6 L/kg Metabolism: Liver, extensive via CYP2D6, CYP1A2 and CYP3A4 Renal Excretion: 50% Fecal Excretion: 30% $t_{1/2}$: 8-12 h	TBC differs between men and women: Men - 36.7 L/h; Women - 27 L/h	TBC differs by age at 39 years of age or older clearance is decreased by 0.219 L/h	

Generic Drug Name	ACB [1]	ARS [2]	ADME[3]	Effect of		
				Sex on ADME	Age on ADME	Genetics on ADME
Codeine	1		Distribution: 7-25% bound to serum proteins V_d: 3-6 L/kg Metabolism: Liver, extensive by CYP2D6, CYP3A4 and UDP-glucuronosyltransferases Renal Excretion: 90% $t_{½}$: 3 h			A specific CYP2D6 genotype are ultra-rapid metabolizers (UM) of codeine who convert codeine into morphine, more rapidly and completely which may lead to higher than expected serum morphine levels, increasing the risk of overdose symptoms even at labeled doses
Colchicine	1		F: approximately 45% Distribution: 39% bound to albumin V_d: 5-8 L/kg Metabolism: Liver, partial via CYP3A and p-glycoprotein substrate Renal Clearance: 0.727 L/h/kg Renal Excretion: 40-65% Fecal Excretion: extensive TBC: 30.3 L/h $t_{1/2}$: 26.6-31.2 h	In a single dose study, the plasma $t_{1/2}$ in elderly males was 30 h and 34 h in elderly females	Following a single oral dose of colchicine 0.6 mg, the mean apparent $t_{1/2}$ was 24.92 ± 5.34 h for subjects age 18-30 years (n=21) and 30.06 ± 10.78 h for subjects of mean age 62.83 years (n=18)	

Generic Drug Name	ACB [1]	ARS [2]	ADME[3]	Effect of		
				Sex on ADME	Age on ADME	Genetics on ADME
Cyclobenzaprine	2	2	F: 33-55% Distribution: 93% bound to serum proteins Metabolism: Liver, extensive via P450 CYP3A4, CYP1A2, CYP2D6 Renal Excretion: 51% TBC: 0.7 L/min $t_{1/2}$: 18 h		In those >65 years of age receiving cyclobenzaprine hydrochloride extended release 30 mg capsules, the plasma $t_{1/2}$ was prolonged (50 h) compared to younger subjects (32 h)	
Cyproheptadine	2	3	Metabolism: Liver 57% Renal Excretion: 40% Fecal Excretion: 2-20% $t_{1/2}$: 16 h			

Generic Drug Name	ACB [1]	ARS [2]	ADME[3]	Effect of		
				Sex on ADME	Age on ADME	Genetics on ADME
Darifenacin	3		F: 15-25% Distribution: 98% bound to serum proteins, mostly alpha-1-acid glycoprotein V_d: 163 L Metabolism: Liver, extensive via CYP3A, CYP2D6 Renal Excretion: 60% Fecal Excretion: 40% TBC: 32-40 L/h $t_{1/2}$: 13-19 h	Total body clearance is 31.1% lower in females than males		Approximately 7% of Caucasians and 2% of African Americans are PM of CYP2D6 metabolized drugs which shunts its metabolism to CYP3A4, C_{Max}/AUC for oral darifenacin 15 mg once daily at steady state was 1.9 for PM and 1.7 for extensive metabolizers (EM)
Desipramine	3	2	$V_{d:}$ 33-42 L/kg Metabolism: Liver, extensive Renal Excretion: 70% $t_{1/2}$: 14.3-24.7 h	Faster oral clearance in older men than older women	$t_{1/2}$ is prolonged in older adults ($t_{1/2}$ 30 h)	"Slow" metabolizers have a $t_{1/2}$ 77 h
Desloratadine	1		Distribution: 82-87% bound to serum proteins Metabolism: Liver, extensive via CYP2C8 Renal Excretion: 40.6% Fecal Excretion: 46.5% TBC: 150 L/h $t_{1/2}$: 19-40 h			

Generic Drug Name	ACB [1]	ARS [2]	ADME[3]	Effect of		
				Sex on ADME	Age on ADME	Genetics on ADME
Diazepam	1		F: ~ 98% Distribution: 95-99.3% bound to serum proteins, CSF concentration is 1.6% of the total plasma concentration V_d: 0.8-1 L/kg Metabolism: Liver, extensive Renal Excretion:75% $t_{1/2}$: up to 48 h	Protein binding is significantly greater in males than in females (1.87 L/kg in young females versus 1.34 L/kg in young males). Greater clearance in women than men based on CYP3A4 clearance. Shorter $t_{1/2}$ in men compared to women (32 versus 46.2 h)	Protein binding is significantly greater in older females than younger females (2.46 L/kg in older females versus 1.38 L/kg in younger females), the V_d is larger for older males than younger males (1.65 L/kg for older males versus 1.19 L/kg for younger males), $t_{1/2}$ increases by about 1 h for each year beginning with a $t_{1/2}$ of 20 h at 20 years, the mean $t_{1/2}$ increased with age to 79 h (range, 37-169 h)	
Dicyclomine	3	3	F: rapidly absorbed V_d: 3.65 L/kg Metabolism: Liver, extensive via CYP3A Renal Excretion: 79.5% Fecal Excretion: 8.4% $t_{1/2}$: 1.8 h			

Generic Drug Name	ACB [1]	ARS [2]	ADME[3]	Effect of		
				Sex on ADME	Age on ADME	Genetics on ADME
Digoxin	1		F: 60-80% Distribution: 25% bound to serum proteins, does cross the blood brain barrier V_d: 475-500 L Metabolism: Liver 13%, substrate of p-glycoprotein Renal Excretion: 50-70% Fecal Excretion: 3-5% $t_{1/2}$: 36-48 h	Slower digoxin clearance in females	In the elderly, the V_d may be reduced, which could increase serum concentrations, elimination may occur more slowly in older adults, due to age-related decline in renal function	
Dimenhydrinate	3		F: well absorbed Metabolism: Liver, extensive			
Diphenhydramine	3	3	F: 65-100% Distribution: 76-85% bound to serum proteins V_d: 480-292 L/70 kg Metabolism: Liver 50% TBC: 11.7-49.2 mL/min/kg $t_{1/2}$: 4-8 h			

Generic Drug Name	ACB [1]	ARS [2]	ADME[3]	Effect of		
				Sex on ADME	Age on ADME	Genetics on ADME
Doxepin	3		Distribution: 80% bound to serum proteins V_d: 11,930 L Metabolism: Liver, extensive via CYP2D6, CYP2C19 Renal Excretion: <3% $t_{1/2}$: 15.3 h	Females had significantly higher dose-corrected serum concentration doxepine/N-doxepine (29 %)	Patients older than 60 years had significantly higher dose corrected serum concentration of doxepin and N-doxepin (48 %), than patients up to 60 years	
Doxylamine	3		F: good $t_{1/2}$: 10.1-13.11 h		$t_{1/2}$ in older men (mean age, 66 years) is 15.5 +/- 2.1 hours, in older women (mean age, 73 years), the $t_{1/2}$ was longer than in young women, but the difference was not statistically significant (12.2 h versus 10.1 h)	
Fentanyl	1		Distribution: 80-86% bound to serum proteins V_d: 4-6 L/kg Renal Excretion: <7%, Fecal Excretion: 1-9% TBC: 42-53 L/h $t_{1/2}$: 3-27 h (depending on dosage form)			

Generic Drug Name	ACB [1]	ARS [2]	ADME[3]	Effect of		
				Sex on ADME	Age on ADME	Genetics on ADME
Fesoterodine	3		F: 52% Distribution: 50% bound to serum proteins V_d: 169 L Metabolism: Liver, extensive via CYP2D6, CYP3A Renal Excretion: 70%, Fecal Excretion: 7%		In older adults, renal clearance of fesoterodine is reduced	
Fluvoxamine	1		F: 53% Distribution: 80% bound to serum proteins, mostly albumin V_d: 25 L/kg Metabolism: Liver, extensive, Inhibitor of CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4 Renal Excretion: 94% Fecal Excretion: 7% $t_{1/2}$: 15.6 -16.3 h	Higher serum concentration in women than men at 100 mg orally	In older patients the clearance of fluvoxamine was reduced by 50%	

Generic Drug Name	ACB [1]	ARS [2]	ADME[3]	Effect of		
				Sex on ADME	Age on ADME	Genetics on ADME
Furosemide	1		F: 47-70% Distribution: 91-99% bound to serum proteins, mostly albumin V_d: 0.2 L/kg Metabolism: Liver 10% Renal Clearance: 2 mL/min/kg Renal Excretion: 60-90% Fecal Excretion: 7-9% TBC: 76 mL/min $t_{1/2}$: 30-120 min		$t_{1/2}$ is prolonged in older adults	
Haloperidol	1	1	F: 60-70% Distribution: >90% bound to serum proteins V_d: 9.5-21.7 L/kg Metabolism: Liver, extensive via CYP3A Renal Excretion: 33-40% Fecal Excretion: 15%			

Generic Drug Name	ACB [1]	ARS [2]	ADME[3]	Effect of		
				Sex on ADME	Age on ADME	Genetics on ADME
Hydralazine	1		F: 38-50% Distribution: 88-90% bound to serum proteins V_d: 0.3 to 8.2 L/kg Metabolism: Liver, extensive Renal Excretion: 3-14% Fecal Excretion: 3-12% $t_{1/2}$: 3-5 h			
Hydrocortisone	1		F: 96% Distribution: 90% bound to serum proteins, mostly corticosteroid-binding globuli V_d: 34 L Metabolism: Liver, extensive via CYP3A Renal Excretion: extensive TBC: 18 L/h $t_{1/2}$: 1-2 h			
Hydroxyzine	3	3	V_d: 16 L/kg Metabolism: Liver $t_{1/2}$: 3-20 h		A mean $t_{1/2}$ of 29.3 h reported after 0.7 mg/kg hydroxyzine syrup to 9 healthy, fasting adults mean age 69.5 years	

Generic Drug Name	ACB [1]	ARS [2]	ADME[3]	Effect of Sex on ADME	Age on ADME	Genetics on ADME
Hyoscyamine	3	3	F: complete Renal Excretion: majority unchanged $t_{1/2}$: 7.47 h			
Imipramine	3	3	F: 94-96% Distribution: 89% bound to serum proteins V_d: 10-20 L/kg Metabolism: Liver, extensive via CYP2C19 $t_{1/2}$: 6-18 h		In older adults $t_{1/2}$ ranges from 25-30 h	
Isosorbide	1		F: approximately 100% Distribution: <5%% bound to serum proteins V_d: 0.6-0.7 L/kg Metabolism: Liver 98% Renal Clearance: 371 mL/h Renal Excretion: 93% Fecal Excretion: 1% TBC: 115-140 mL/min $t_{1/2}$: 5 h			
Loperamide	1	2	F: 0.3% Renal Excretion: 1% Fecal Excretion: 25-40% $t_{1/2}$: 7-15 h			

Generic Drug Name	ACB [1]	ARS [2]	ADME[3]	Effect of		
				Sex on ADME	Age on ADME	Genetics on ADME
Loratadine	1	2	Distribution: 97% bound to serum proteins Metabolism: Liver, extensive via CYP3A, CYP2D6 $t_{1/2}$: 12-15 h		Older adults (n=12) reported to have a $t_{1/2}$ of 17.5 h (range of 11 to 38 h)	
Loxapine	2		F: complete Distribution: 96.6% bound to serum proteins Metabolism: Liver, extensive via CYP1A2, CYP3A4, CYP 2D6, p-glycoprotein inhibitor $t_{1/2}$: 17.6 h			
Meperidine	2		Distribution: 65-80% bound to serum proteins, mostly albumin and alpha-1-acid glycoprotein V_d: 3.1-5 L/kg Metabolism: Liver, extensive $t_{1/2}$: 3.2-3.7 h		In older adults, meperidine is less protein bound; however, the clearance rate is unchanged, therefore the V_d may be greater with more available free drug, and in older adults the $t_{1/2}$ is extended	

Generic Drug Name	ACB [1]	ARS [2]	ADME[3]	Effect of		
				Sex on ADME	Age on ADME	Genetics on ADME
Methocarbamol	3	1	F: completely Metabolism: Liver, extensive Renal Excretion: 10-15% Fecal Excretion: small amount $t_{1/2}$: 0.9-2 h			
Metho-trimeprazine	2		V_d: 29.8 L/kg Metabolism: Liver Fecal Excretion: small amount $t_{1/2}$: 15 h			
Metoprolol	1		F: 50% Distribution: 10% bound to serum albumin, CSF concentration close to the plasma concentration V_d: 3.2-5.6 L/kg Metabolism: Liver, extensive via CYP2D6 Renal Excretion: 95% $t_{1/2}$: 3-4 h			In CYP2D6 PM the mean $t_{1/2}$ of metoprolol is 7 to 9 h

Generic Drug Name	ACB [1]	ARS [2]	ADME[3]	Effect of		
				Sex on ADME	Age on ADME	Genetics on ADME
Morphine	1		F: 20-40% Distribution: 20-36% bound to serum proteins V_d: 1-6 L/kg Metabolism: Liver Renal Excretion: 90% Fecal Excretion: 7-10% TBC: 20-30 mL/min/kg $t_{1/2}$: 1.5-4.5 h			
Nifedipine	1		F: complete Distribution: 92-98% bound to serum proteins Metabolism: Liver, extensive via CYP3A4 Renal Excretion: 80% Fecal Excretion: 20% TBC: 4.3 mL/min/kg $t_{1/2}$: 2 h	Greater clearance in women, due to CYP3A4 and is 20-30% higher in young women than young men, women reach higher plasma levels at same dose	Clearance is significantly reduced in older subjects (unrelated to renal function) compared to younger subjects, following IV administration clearance in older subjects was 348 mL/min compared with 519 mL/min in young subjects	
Nortriptyline	3	2	F: 60% Distribution: 86-95% bound to serum proteins V_d: 15-27 L/kg Metabolism: Liver, extensive via CYP2D6 Renal Excretion: 2% $t_{1/2}$: 15-39 h	Plasma levels mostly affected by CYP2D6 genotype and sex with females experiencing higher plasma levels	The $t_{1/2}$ may be greater than 90 h in older adults	Nortriptyline plasma levels are mostly affected by CYP2D6 genotype and sex with females experiencing higher plasma levels

Generic Drug Name	ACB [1]	ARS [2]	ADME[3]	Effect of		
				Sex on ADME	Age on ADME	Genetics on ADME
Olanzapine	3	2	F: well absorbed Distribution: 93% bound to serum proteins, mostly albumin and alpha-1-acid glycoprotein V_d: 1,000 L Metabolism: Liver, extensive via CYP1A2, CYP2D6 Renal Excretion: 57% Fecal Excretion: 30% TBC: 26.1 L/h $t_{1/2}$: 21-54 h	Men from a population including individuals with Alzheimer's disease or schizophrenia cleared olanzapine 38% faster than women	The mean $t_{1/2}$ was 1.5 times greater in healthy patients aged ≥ 65 years compared with younger patients age < 65 years, according to a study of 24 healthy subjects	
Orphenadrine	3		F: 95% Renal Excretion: 60% $t_{1/2}$: 13.2-20.1 h			
Oxcarbazepine	2		Distribution: 40% bound to serum proteins Vd: 49 L Metabolism: Liver, extensive Renal Excretion: >95% Fecal Excretion: <4% $t_{1/2}$: 2 h			

Generic Drug Name	ACB [1]	ARS [2]	ADME[3]	Effect of		
				Sex on ADME	Age on ADME	Genetics on ADME
Oxybutynin	3	3	F: 6% Distribution: >99% bound to serum proteins, mostly alpha-1-acid glycoprotein Metabolism: Liver, extensive via CYP3A4 Renal Excretion: <0.1% $t_{1/2}$: 2-3 h	Oxybutynin was not shown to have any differences in AUC and C_{Max} for men or women	Oxybutynin follows the trend of increasing peak plasma levels and bioavailability with increasing age and frailty	
Paroxetine	3	1	F: complete Distribution: 93-95% bound to serum proteins Metabolism: Liver, extensive via CYP2D6, also an inhibitor of CYP2D6 Renal Excretion: 64% Fecal Excretion: 36% TBC: 76 mL/min $t_{1/2}$: 15-21 h	Sex is correlated to paroxetine plasma concentration, estimates of V_2 in male subjects were 461.30 ± 259.75 and in female subjects were 346.41 ± 255.81	A naturalized study of paroxetine showed a 2-fold higher ratio of absolute serum concentration to dose adjusted serum concentrations in the oldest age group in comparison to controls < 40 years of age	
Perphenazine	3	3	F: 20% V_d: 10-34 L/kg Metabolism: Liver, extensive via CYP2D6 Renal Excretion: 80% TBC: 100 L/h $t_{1/2}$: 8.4-12.3 h			

Generic Drug Name	ACB [1]	ARS [2]	ADME[3]	Effect of		
				Sex on ADME	Age on ADME	Genetics on ADME
Prednisone	1		F: 92% Distribution: 70% bound to serum proteins, mostly albumin and corticosteroid-binding globuli V_d: 0.4-1 L/kg Metabolism: Liver, extensive $t_{1/2}$: 2-3 h			
Quetiapine	3	1	F: 100% Distribution: 83% bound to serum proteins Vd: 10 L/kg Metabolism: Liver, extensive via CYP3A4 Renal Excretion: 73% Fecal Excretion: 20% $t_{1/2}$: 6-7 h	Sex was not shown to effect pharmacokinetics of quetiapine	In a pharmacokinetic study, quetiapine clearance was reduced by 40% in patients ≥65 years (n=9) compared with young patients (n=12)	

Generic Drug Name	ACB [1]	ARS [2]	ADME[3]	Effect of		
				Sex on ADME	Age on ADME	Genetics on ADME
Quinidine	1		F: 70-80% Distribution: 80-88% bound to serum proteins, mostly albumin and alpha-1-acid glycoprotein V_d: 2-3 L/kg Metabolism: Liver, extensive via CYP3A4 Renal Clearance: 1 mL/min/kg Renal Excretion: 5-20% Fecal Excretion: 1-3% TBC: 3-5 mL/min/kg $t_{1/2}$: 6-8 h	Women clear quinidine at a faster rate than men and women have ECG changes in response to drug activity much quicker than men which is not explained by quinidine clearance		
Ranitidine	1	1	F: 50% Distribution: 15% bound to serum proteins V_d: 1.04-4.09 L/kg Metabolism: Liver, minor Renal Clearance: 24.6-31.8 L/h Renal Excretion: 3-70% Fecal Excretion: 3.1 mL/min/kg TBC: 1.29-1.44 L/h/kg $t_{1/2}$: 1.9-3 h		The $t_{1/2}$ is 3-4 hours in older adults after oral administration likely due to a decrease in renal function	

Generic Drug Name	ACB [1]	ARS [2]	ADME[3]	Effect of		
				Sex on ADME	Age on ADME	Genetics on ADME
Risperidone	1	1	F: 70% Distribution: 90% bound to serum proteins V_d: 1-2 L/kg Metabolism: Liver, extensive via CYP 2D6 Renal Clearance: 0.96 L/h Renal Excretion: 70% Fecal Excretion: 14% TBC: 3.2-13.7 L/h $t_{1/2}$: 3-20 h	Sex related differences in risperidone metabolism are unlikely to be significant	When the plasma concentration was adjusted for subject body weight or maintenance dose there were still significant differences between groups with the oldest group having the highest adjusted concentration	Polymorphisms of CYP2D6 are more responsible for variation in risperidone metabolism than sex
Scopolamine	3		Metabolism: extensive Renal Excretion: <10% $t_{1/2}$: 9.5 h			

Generic Drug Name	ACB [1]	ARS [2]	ADME[3]	Effect of		
				Sex on ADME	Age on ADME	Genetics on ADME
Solifenacin	3		F: approximately 90% Distribution: 98% bound to plasma proteins, primarily alpha-1-acid glycoprotein V_d: 599-671 L Metabolism: Liver, extensively via CYP3A4 Renal Clearance: 0.67-0.76 L/h Renal Excretion: 3-6% Fecal Excretion: 22.5% TBC: 9.4 L/h $t_{1/2}$: 40-68 h		Solifenacin has a longer $t_{1/2}$ due to slower elimination and to longer time to reach C_{Max} in older adults, this can be explained by the reduced absorption of solifenacin in older adults. Exposure to solifenacin is increased about 1.2-fold in older subjects	
Theophylline	1		F: well absorbed Distribution: 40% bound to serum proteins V_d: 450 mL/kg Metabolism: Liver, extensive via CYP1A2 Renal Excretion: 10-13% Fecal Excretion: 7% TBC: 76 mL/min $t_{1/2}$: 8.7 h		Protein binding reduced in older adults, clearance reduced in older adults 0.59 +/- 0.07 mL/kg/min, and increased mean $t_{1/2}$ of 9.8 h (1.6-18 h) in healthy older non-smokers and was not significantly different from clearance values in otherwise healthy non-smoking younger asthmatics	

Generic Drug Name	ACB [1]	ARS [2]	ADME[3]	Effect of		
				Sex on ADME	Age on ADME	Genetics on ADME
Thioridazine	3	3	V_d: 17.8 L/kg Metabolism: Liver, extensive Renal Excretion: small amounts $t_{1/2}$: 21-24 h			
Tolterodine	3	2	F: 77% V_d: 113 L Metabolism: Liver, extensive via CYP2D6 Renal Excretion: 77% Fecal Excretion: 17% $t_{1/2}$: 1.9-3.7 h			Metabolism is slowed in individuals who are CYP2D6 PM as metabolism is shunted to CYP3A4, $t_{1/2}$ is prolonged to 6.5 h with single doses and 9.6 h with multiple doses
Trazodone	1	1	F: 65% Distribution: 89-95% bound to serum proteins V_d: 0.47-0.84 L/kg Metabolism: Liver, extensive Renal Clearance: 3-5.3 L/h Renal Excretion: 70-75% Fecal Excretion: 21% TBC: 5.3 L/h $t_{1/2}$: 7 h			

Generic Drug Name	ACB [1]	ARS [2]	ADME[3]	Effect of		
				Sex on ADME	Age on ADME	Genetics on ADME
Triamterene	1		F: 30-70% Distribution: 55-67% bound to serum proteins Metabolism: Liver 80% Renal Excretion: 21% $t_{1/2}$: 1.5-2.5 h		$t_{1/2}$ was 4.3 h in young adults, and was prolonged to 6.5 h in an older patient	
Trifluoperazine	3	3	F: readily absorbed Distribution: 90-99% bound to serum proteins Metabolism: Liver $t_{1/2}$: 24 h			
Trospium	3		F: 9.6% Distribution: 50-85% bound to serum proteins V_d: 395 L Metabolism: Liver Renal Clearance: 29.07 L/h Renal Excretion: 5.8% Fecal Excretion: 85.2% $t_{1/2}$: 20 h			

Generic Drug Name	ACB [1]	ARS [2]	ADME[3]	Effect of		
				Sex on ADME	Age on ADME	Genetics on ADME
Venlafaxine	1		Distribution: 27-30% bound to serum proteins V_d: 7.5 L/kg Metabolism: Liver, extensive via CYP2D6 Renal Clearance: 0.074-0.079 L/h/kg Renal Excretion: 87% Fecal Excretion: 2% TBC: 1.3 L/h/kg $t_{1/2}$: 5 h	Venlafaxine serum concentrations differed in men and women with higher concentrations achieved by women (215 nmol/L and 151 nmol/L), the ratio of absolute serum concentration in comparison to the dose-adjusted serum concentration is 1-1.5-fold higher in women than in men	The concentration to dose ratio of venlafaxine was 1.5-fold higher in adults over 65 in comparison to controls <40 years old	The serum concentration of N-desmethyl-venlafaxine was 5.5-fold higher in a subset of CYP2D6 PMs ($p < 0.01$) and 22-fold higher in second subset of CYP2D6 PMs ($p < 0.001$) than in extensive metabolizers

Generic Drug Name	ACB [1]	ARS [2]	ADME[3]	Effect of		
				Sex on ADME	Age on ADME	Genetics on ADME
Warfarin	1		F: completely absorbed Distribution: 99% bound to serum proteins V_d: 0.14 L/kg Metabolism: Liver, extensive via CYP2C9, CYP2C19, CYP2C8, CYP2C18, CYP1A2, CYP3A4 Renal Excretion: 92% TBC: dependent on CYP2C19 genotype $t_{1/2}$: 1 week			

(Truven Health Analytics, 2015)

APPENDIX 2: COPYRIGHT PERMISSION

Sex and gender differences in polypharmacy in persons with dementia: A scoping review

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A collaborative intervention for deprescribing: The role of stakeholder and patient engagement

Author: Shanna Trenaman,Marjorie Willison,Bryn Robinson,Melissa Andrew

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