Medication Review in Cognitive Impairment and Dementia: Comparison of Instruments

by

Rishabh Sharma

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Author's Declaration

I hereby declare that I am the sole author of this thesis. This is a true copy of the thesis, including any required final revisions, as accepted by my examiners.

I understand that my thesis may be made electronically available to the public.

Abstract

Background: - Cognitive impairment (CI) and dementia are significant concerns in older adults in Canada. Drug-related problems (DRPs) are common and can cause up to 30% of hospitalizations in older individuals, including adverse drug reactions, drug interactions, potentially inappropriate medication (PIM) use, and medication adherence. Prescribing in older patients with multiple morbidities, especially with dementia, is a complex process that demands regular review of medications to provide quality care to dementia patients.

Objective: - The primary objective was to compare the mean number of DRPs using the Medication Review in Cognitive Impairment and Dementia (MedRevCiD) Checklist to the Medication Appropriateness Index (MAI) criteria in older adults with CI and/or dementia. The secondary objective was to identify which explicit tool, Beers Criteria 2023, or the Screening Tool of Older People Potentially Inappropriate Prescriptions (STOPP) Criteria 2023, identified more PIM use among older adults with CI or dementia.

Methods: - A cross-sectional study was carried out with older adults receiving care for CI or dementia. Forty-four patients from the Multi-specialty Interprofessional Team-based (MINT) memory clinic were recruited to participate in the study. The researcher employed two distinct tools, namely the MAI and the MedRevCiD Checklist, to conduct a medication review. PIMs were identified utilizing the Beers Criteria 2023 and the STOPP Criteria 2023. The Wilcoxon signed-rank test was used to assess whether there is a significant difference in the mean number of DRPs identified by the MedRevCiD versus MAI. Bivariate logistic regression analysis was employed to identify potential factors associated with DRP and PIM use.

Results: - A total of 134 DRPs were identified in 44 patients per the MedRevCiD checklist. The average number of DRPs identified was 3.05, with a standard deviation (SD) of 4.0 DRPs per person. Notably, over half of the DRPs (53%, n= 71) identified fell into domain 6 of the MedRevCiD checklist (optimizing medication use). In comparison, 81 DRPs were identified in 44 patients per MAI criteria (mean: 1.84 per person, SD 2.9) DRPs per person. The majority of the DRPs identified using MAI criteria (44.4%, n= 36) were from clinically significant drug-disease/condition interactions. There was a significant difference in the mean number of DRPs between the two instruments (Z= -4.8, p-value <0.001). In this study, at least one PIM was used by 47.7% (n= 21) and 27.2% (n= 12) of participants based on Beers and STOPP criteria, respectively. Binary logistic regression revealed a statistically significant association between the number of comorbidities (P= 0.002), number of medications per day (P= 0.032) with DRP use as per MAI criteria. For each additional comorbidity, there was 1.86 times higher odds of experiencing DRPs and 1.20 times higher odds of having DRPs according to MAI criteria. Individuals with nine or more comorbidities had 8.4 times higher odds of being prescribed PIMs (p = 0.027, 95% confidence interval (CI): 1.27 – 55.39); given the wide range of the confidence interval it is essential to note that there was considerable uncertainty about the strength of the association.

Discussion: - The findings of this study provided insights into the higher prevalence of DRPs among older adults with CI or dementia. The MedRevCiD Checklist emerged as a valuable tool, demonstrating a heightened ability to uncover DRPs in this population. This underscores the importance of utilizing tools tailored to the unique needs of individuals with dementia when assessing DRPs. Furthermore, identifying PIMs using Beers and STOPP criteria highlights the

significance of addressing PIMs in this demographic. This study adds valuable insights to the progressing comprehension of medication complexities in older adults facing CI and/or dementia.

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I extend my deepest gratitude to my family, whose unwavering support has been the cornerstone of my academic journey. Throughout the demanding periods of thesis writing, their constant encouragement and understanding have been my pillar of strength.

Dedication

To my parents: my father, Raj Kumar and my mother, Mamta.

For the unwavering support, sacrifices, and boundless love that have been the cornerstone of my journey.

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List of Abbreviations

CI	Cognitive Impairment
DRP	Drug-related problem
ADR	Adverse drug reaction
PCNE	Pharmaceutical Care Network Europe
PIM	Potentially Inappropriate Medication
MAI	Medication Appropriateness Index
AGS	American Geriatric Society
EGS	European Geriatric Society
STOPP	Screening Tool of Older Persons potentially inappropriate Prescriptions
MedRevCiD	Medication Review in Cognitive Impairment and Dementia
MINT	Multi-specialty Interprofessional Team-based
CIn	Confidence Interval
ATC	Anatomical Therapeutic Chemical
CrCl	Creatinine Clearance
DDI	Drug-drug Interactions
IQR	Inter quartile range
SD	Standard deviation
OR	Odds ratio
AchEI	Acetylcholinesterase inhibitor
UK	United Kingdom

BPSD	Behavioral and Psychological Symptoms of Dementia
eGFR	estimated Glomerular Filtration Rate

Chapter 1: Introduction

1.1 Introduction to dementia

Dementia is a progressive syndrome usually characterized by a decline in cognitive function-thinking, remembering, reasoning, and behavioral abilities to such a point that it may interfere with daily activities.[1] The risk of dementia increases with age. Globally, in the last few decades, many countries have experienced significant demographic shifts, including substantial gains in life expectancy, resulting in an aging population. In turn, the aging of the global population is contributing to a growing prevalence of neurodegenerative diseases, particularly dementia.[2] For example, a quarter of the persons 65 years and older have cognitive impairment (CI) or dementia; the prevalence increases to 40% in those aged 80 years and over.[3] With the growth in the proportion of those aged 65 years and older, the prevalence of dementia will rise as well. The prevalence of dementia is expected to double every five years.[3] In Canada, an estimated 402,000 older adults suffer from dementia, including Alzheimer's disease, and 76,000 new cases are identified yearly.[4] Researchers predict that almost one million Canadians will have dementia by 2030. Furthermore, they predict that by 2050, more than 1.7 million Canadians will have dementia.[5]

1.1.1 Burden of dementia

The rising prevalence of dementia has significant implications for the social, psychological, physical, and economic impact on patients, their caregivers, families, and society.[4] Social isolation can compound the challenges, as patients withdraw from social activities, and caregivers have limited time for personal interactions.[6] Dementia can cause significant emotional distress for both patients and their families. Patients often experience confusion, frustration, and anxiety, while

family members may feel overwhelmed and sad as they witness the decline in their loved one's cognitive abilities.[6] In terms of physical impact, patients may experience mobility issues, muscle weakness, and a decline in overall physical health. Activities of daily living, such as dressing and feeding, become increasingly challenging.[6] On a societal level, the physical impact of dementia is reflected in the demand for healthcare and long-term care services.[7] There is a need for specialized facilities and trained healthcare professionals to address the physical needs of dementia patients.[7] In addition to being the seventh leading cause of mortality, it stands as a major contributor to impairment and dependency among older individuals globally.[6,8] Individuals with any form of dementia typically experience a higher mortality rate compared to those without dementia. Dementia is associated with various health complications and challenges, which contribute to an increased risk of mortality for affected individuals.[8] The economic impact of dementia is a significant and concerning issue, both globally and for individual countries and healthcare systems. Dementia imposes substantial economic costs related to healthcare, long-term care, and lost productivity. The annual cost of dementia to the total healthcare system, including the out of pocket cost of caring for people with dementia, was $10.4 billion in 2016 and is expected to increase by 2031, as per the reports of the National Population Health Study of Neurological Conditions.[5] Additionally, it is anticipated that by 2031, the estimated 19.2 million informal, unpaid caregiver hours —which were tentatively valued at $1.2 billion in 2011—will double.[5] Moreover, a research initiative led by the National Institute of Health (NIH) computed the overall healthcare costs for four distinct groups during the final five years of life.[9] One group had dementia. Heart disease, cancer, or other causes claimed the lives of the different three categories. Insurance, hospitalization, medicine, nursing home, hired workers, and in-home medical care were all

included in the total expenses. The findings of the study indicated that healthcare costs for individuals with dementia were notably higher in the final years of their lives compared to those who succumbed to other diseases, including cancer and heart disease.[9]

1.1.2 Life expectancy for individuals with dementia

Life expectancy for individuals with dementia varies widely depending on the type of dementia, the stage at which it is diagnosed, the age of the person when diagnosed, and various other factors such as overall health and access to care.[10] Alzheimer's disease is the most common type of dementia. On average, individuals diagnosed with Alzheimer's may live for 8 to 10 years after diagnosis, although some may live for much longer, especially if the diagnosis is made in the early stages. However, in advanced stages, life expectancy tends to be shorter, often due to complications like infections.[11] The average life expectancy for individuals diagnosed with vascular dementia is around five years. The life expectancy of vascular dementia patients is lower than that of Alzheimer’s dementia patients due to its association with cardiovascular risk factors and the potential for recurrent cerebrovascular events.[11] Life expectancy for individuals with Lewy body dementia (DLB) is typically shorter than for Alzheimer's disease, with an average of about 5 to 7 years from the time of diagnosis. The physical symptoms of DLB raise a person's risk of infections and falls.[11] The life expectancy for patients with frontotemporal dementia (FTD) is expected to be around 6 to 8 years. Dementia tends to advance more quickly in people with FTD with motor neuron disease, a movement disorder.[11] The 2023 Alzheimer’s disease fact and figures special report titled “The patient journey in an era of new treatments” released by the Alzheimer’s Association unveils the impact of Alzheimer's dementia on individuals, caregivers, the government, and the nation's healthcare system. Between 2000 and 2019, the number of fatalities

from Alzheimer's disease more than doubled to 145%, whereas the number of deaths from heart disease, the leading cause of death, declined by 7.3%.[12.]

1.1.3 Comorbidities in individuals with dementia

Older adults with dementia often have multiple comorbid conditions such as hypertension, diabetes mellitus, coronary artery disease, stroke, and heart failure.[13] Furthermore, a study conducted in the UK disclosed that, on average, individuals with dementia experienced 4.6 chronic illnesses in addition to their dementia. Moreover, other geriatric conditions, such as delirium, falls, and incontinence, were found to be more prevalent in this population.[14] Older adults with dementia tend to have an average of four comorbidities, compared to older adults without dementia, who typically have an average of two comorbidities.[15,16] The presence of comorbidities in dementia places individuals at a higher risk of hospitalization, longer hospital stays, and greater healthcare expenditures for their coexisting health conditions compared to people without dementia.[17] These comorbid conditions often require specific medications to manage and treat them effectively. The healthcare needs of older adults with both dementia and comorbidities necessitate taking several medications to address each unique health concern.

1.1.4 Medication use in individuals with dementia

Medication use in older adults with CI and dementia is challenging because of age-related physiological and cognitive changes such as increased body fat, a decline in renal and liver function, and a decline in cognitive function that put older adults with a disease at a higher risk of medication toxicity.[18] For instance, as individuals age, they often experience an increase in body fat and a decrease in lean body mass. Medications are distributed and metabolized differently in

individuals with altered body composition, potentially affecting drug efficacy and safety.[19] Moreover, the kidneys play a crucial role in filtering and excreting medications from the body. Renal function naturally declines with age, which can lead to slower drug clearance and an increased risk of drug accumulation and toxicity.[20]

Given their cognitive issues, it should come as no surprise that managing medications is difficult for those with dementia, leading to drug-related problems (DRPs), hospital admissions linked to medication, and dependency on others to help with medication management duties. Even though medication non-adherence affects people of all ages, diseases, and demographics and can be either intentional or unintentional, CI and dementia have been found to have a particularly negative effect on medication adherence.[21] Additionally, following a prescribed regimen can be difficult for older adults with dementia due to complex medication regimens, memory loss, and other cognitive impairments.[22] The use of medications in persons with dementia is fraught with problems. For example, older adults with CI and/or dementia experience worsening of their cognition due to the anticholinergic activity of certain medications.[23] Similarly, they may be more prone to the effects of medication non-adherence due to forgetfulness.[24] These types of encounters are frequently identified as DRPs.

Older adults with multiple comorbidities may be prescribed numerous medications, leading to polypharmacy (which refers to the use of 5 to 9 medications per day). More than half of older adults with dementia are prescribed five or more medications per day.[13] According to cross-sectional analysis, an average of eight drugs were used by patients with dementia (PWD) (n= 918), compared to three by persons without dementia (PWOD) (n= 26,543). Comparing PWD and PWOD, PWD had a considerably greater likelihood of receiving a prescription for five to ten

drugs.[25] Compared to younger persons, older adults with CI or dementia are more susceptible to the adverse effects of medication.[26]

Additionally, polypharmacy use and age-related physiological changes can pose a significant risk for DRP use in this population.[27,28] Polypharmacy use in older adults with CI or dementia can increase the risk of adverse drug reaction (ADR), falls resulting in head injury, drug-related hospital admission, mortality, and worsening of dementia.[25] Furthermore, polypharmacy use in this population, especially anticholinergic and sedative agents, may exacerbate memory loss and increase functional impairment.[27] Polypharmacy use increases the risk of DRPs, leading to poor medication compliance, poor quality of life, drug-related hospital admissions, and increased healthcare costs for the patient.[29] It is very important to address this issue in this population to prevent various DRPs, improve medication adherence, and get optimal patient outcomes.

1.2 Drug-related problems in older adults

A DRP is defined by Pharmaceutical Care Network Europe (PCNE) as any drug therapy-related incident or situation therapy that actually or potentially interferes with desired health outcomes.[30] Hepler and Strand define DRP as any incident or situation pertaining to a patient's drug therapy that actually or potentially interferes with achieving an optimal outcome.[31] There are several established classification systems used to categorize DRPs.[32] Classification systems for DRPs can vary in their focus and purpose. Different classifications may prioritize different aspects of medication therapy, and their utility depends on the specific context in which they are applied. Some classification systems focus on assessing the impact of medications from the patient's perspective, including outcomes, quality of life, and patient satisfaction (patient-centred).[32] Process-centered classification concentrates on the various stages of the medication use process,

such as prescribing, dispensing, and administration. Moreover, certain classifications are designed for research purposes, while others are specifically crafted for pharmacy practice or the evaluation of drug use.[32,33]

Among all the classification systems, The PCNE Classification system is a widely recognized classification system for classifying DRPs in various patient populations, including older adults with dementia, due to its patient-centred approach, which is especially important when dealing with older adults with dementia.[30] It focuses on the outcomes of therapy and the patient's perspective, ensuring that the classification reflects this population's unique needs and challenges. Furthermore, this system allows for the classification of DRPs related to inappropriate drug therapy, potential interactions, safety concerns, adherence issues, and more.[30]

1.2.1 Type of DRPs

DRPs classified according to PCNE classification for DRPs Version 9[30]

1. Problems (also potential)

a). Treatment effectiveness: - There is a (potential) problem with the (lack of) effect of the pharmacotherapy

b). Treatment safety: - Patient suffers or could suffer from an adverse drug event (ADE)

2. Causes (including possible causes for potential problems)

a). Drug selection: - Related to the selection of the drug

b). Drug form: - Related to the selection of the drug form

c). Dose selection: - Related to the selection of the dosage schedule

d). Treatment duration: - Related to the duration of treatment

e). Dispensing: - Related to the logistics of the prescribing and dispensing process

f). Drug use process: - Related to the way the patient gets the drug administered by a health professional or carer, despite proper instructions (on the label)

g). Patient-related: - Related to the patient and his behavior (intentional or non-intentional). Patient transfer related to the cause of the DRP can be related to the transfer of patients between primary, secondary, and tertiary care, or transfer within one care institution.

1.2.1.1 Potentially inappropriate medication (PIM) as a specific type of DRP

PIM are considered as medications whose risk outweighs their benefits, especially when equally effective and safer treatment alternatives are available.[28] The use of PIM in older adults was found to be associated with increased adverse events, DRPs, prolonged hospitalization, risk of falls, and increased healthcare costs for the patient due to hospital admission or increased length of stay.[29,34,35] Figure 1-1 illustrates the interconnectedness among comorbidity, polypharmacy, PIM, and DRPs. Several epidemiological studies have explored the extent of PIM usage in older adults. Literature indicates that older adults with CI or dementia had a higher prevalence of PIM- ranging from 10 to 64%, from different settings and different countries.[27,36,37] In order to determine the prevalence of PIMs in older persons with CI or dementia living in the community, Patel et al. carried out a systematic review and reported the prevalence ranged between 15% to 46.8%, with anticholinergics and benzodiazepines as the most frequently listed PIMs.[28] Roux et al. conducted population-based research using the Quebec Integrated Chronic Disease Surveillance System to evaluate the 1-year persistence of PIM consumption and find associated factors in community-dwelling older people in Quebec, Canada. Continual PIM therapy without a break for more than 60 days between prescription renewals represented one year of PIM usage. A quarter of individuals

(19,051/75,844) had used at least one PIM for one year. Persistence was substantially connected with increasing age, male gender, taking many medications, and having chronic illnesses.[38]

1.2.2 Consequences of DRPs

DRPs in older adults can have various consequences, including adverse drug reactions, hospital admissions, medication non-adherence, worsening health conditions, decreased quality of life, increased healthcare costs, psychological and emotional impact, and functional impairment.[39] Adverse drug events, drug-drug interactions, and PIM usage are examples of DRP, which are widespread and account for up to 30% of hospitalizations among older adults.[40] Older adults with CI or dementia are even more at risk, with DRPs thought to be partially or entirely responsible for 41% of hospital admissions in these groups.[41] Moreover, the risk of falls and fractures is elevated among older adults with dementia or CI due to medications with sedative or anticholinergic effects, resulting in injuries that compromise mobility and well-being.[42] DRPs, such as the use of PIM, can exacerbate cognitive impairment, leading to further decline in cognitive function.[43] This can worsen the individual's ability to perform daily activities and participate in social interactions. ADR, drug interactions, or the side effects of medications can contribute to physical and functional decline in older adults with dementia. This may lead to difficulties with mobility, self-care, and an increased risk of falls.

1.2.2.1 Prevalence of drug-related problems in persons with CI and/or dementia

A significant proportion of the older adults with CI and dementia were exposed to DRPs. In one study, 66% (140/212) of the population were noted to have at least one DRP using the Cipolle and Strand classification.[44] The most common DRPs were adverse drug reactions (n = 103), followed

by ineffective drug/inappropriate drug (n = 54), and unnecessary drug therapy (n = 54). In another study, 93% of study participants (414/446) had DRP. The most often reported DRPs by pharmacists were administration and compliance problems (60%), drug interactions (17%), and problems with inappropriate drug choice (15%).[45] Given the complexity and high risks of DRPs in older adults with dementia, a systematic and regularly performed medication review is needed to identify and address DRPs.

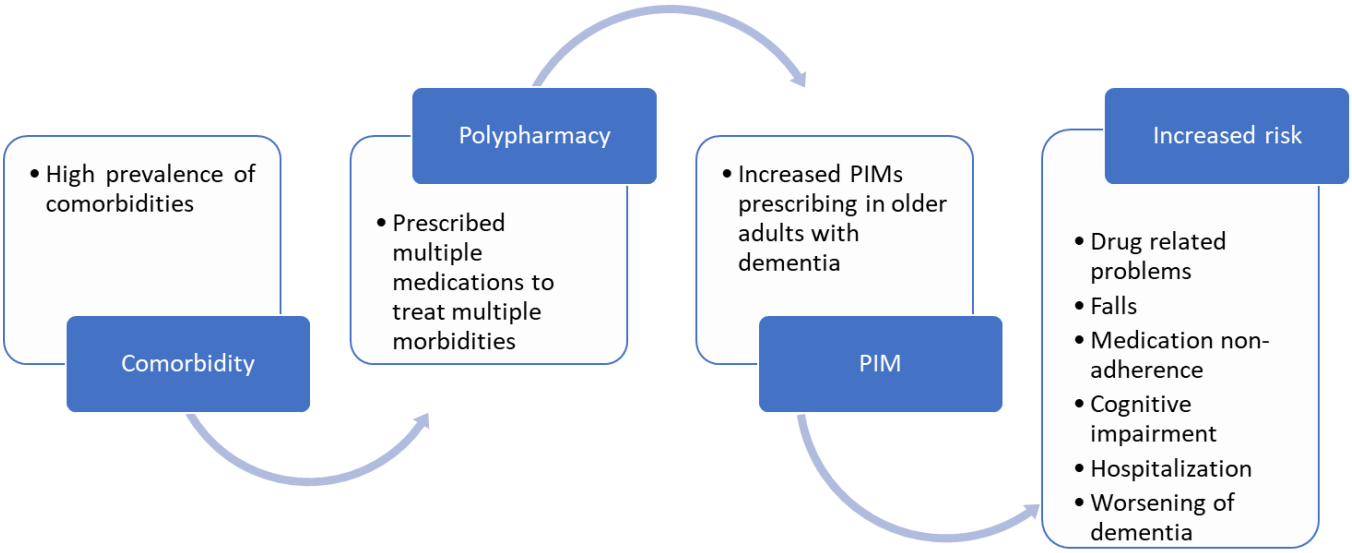

Figure 1-1: Interconnectedness between comorbidity, polypharmacy, potentially inappropriate medication, and drug-related problems

1.3 Medication review

According to PCNE, a medication review is a structured assessment of a patient's medications to optimize medication use and improve health outcomes. This includes identifying DRPs and

recommending interventions.[46] Medication reviews include assessment of medications prescribed regularly, extracting information from the medical records, and interviewing the patient to identify DRPs.[46]

1.3.1 Rationale for medication review

Optimizing medication prescribing in elderly individuals with dementia is a crucial step because of all the drug-related issues, the complexity of the pharmaceutical regimen, and changes in the goals of treatment as the illness advances.[47] By addressing the proper course of therapy and avoiding polypharmacy and the resulting drug-drug or/and drug-disease interactions, several important goals can be accomplished such as reduction of DRPs, improved adherence, increased quality of life, reduced healthcare cost.[48] Moreover, prescribing in older patients with multiple morbidities, especially with dementia, is a complex process due to several interconnected factors such as comorbidity challenges, polypharmacy, and risk of DRPs that demand regular review of medications to provide quality care to dementia patients.[49]

1.3.2 Implication of medication review

A medication review conducted by a pharmacist or multidisciplinary team in older adults with dementia or CI helps optimize their drug regimen, identify, and resolve DRPs, and reduce hospital admissions due to DRPs.[50,51] Moreover, regular reviews allow healthcare professionals to assess if prescribed medications effectively manage symptoms or if adjustments are needed. Medication reviews can identify any challenges in medication adherence that individuals with dementia may face.[52,53] A randomized controlled trial (RCT) conducted by Gustafsson et al. in 2017 reported that a medication review conducted by a clinical pharmacist can significantly reduce PIM usage in the

intervention group, between admission and after medication review, from 20.3 percent to 14.2 percent ($p = 0.002$), particularly the use of anticholinergic drugs, which decreased significantly from 7.1 percent to 3.3 percent.[54-56]

1.3.3 Tools for assessment of medication use in persons with dementia

The problems associated with medication use in older adults have driven the development of several tools that enable healthcare professionals to evaluate and optimize medication regimens for older adults. These tools have been developed via consensus techniques, expert opinions, and professional judgment. Some instruments enable clinicians to use their clinical judgment (implicit criteria), while others provide explicit directions clinicians can use to examine medication use.[57] Implicit criteria rely on the healthcare professional's clinical expertise, experience, and judgment of a patient's unique circumstances, including their medical history, clinical presentation, and general health. Implicit criteria allow for a more personalized and patient-centred approach to medication management.[57] However, implicit criteria depend on the healthcare professional subjective judgment, which may introduce bias or result in different interpretations of medication appropriateness. One of the most recognized implicit criteria used during medication reviews is the Medication Appropriateness Index (MAI) criteria.[58] Implicit criteria in the Medication Appropriateness Index involve the healthcare provider's subjective assessment of various aspects of medication therapy, including dosing, drug selection, and regimen complexity, considering the specific needs and characteristics of the patient.

In contrast, explicit criteria provide clearly defined statements or guidelines for medication use. For example, the most commonly used explicit criteria are the American Geriatric Society Beers criteria and the European Geriatric Society updated Screening Tool of Older Persons Potentially

Inappropriate Prescriptions.[59] For instance, the Beers Criteria may indicate that certain medications like benzodiazepines, which are commonly used to treat anxiety or insomnia, should generally be avoided in older adults due to their potential to cause side effects such as dizziness, falls, and cognitive impairment.[60] The Beers Criteria offers clear and evidence-based guidance to healthcare providers when making medication decisions for older patients, promoting safer and more appropriate medication use. The major advantage of explicit criteria is that because they are standardized, they can be easily applied consistently by different healthcare professionals. This makes it easier to compare results across studies and settings.[61]

Despite the availability of these accepted criteria, there is a gap in practical, feasible tools specifically designed to address medication use in older adults with cognitive impairment or dementia. These conditions present unique challenges, and existing criteria may not adequately address this population's specific needs and concerns. Moreover, there is no standardized tool to assist pharmacists in thoroughly assessing all medication-related concerns in persons with CI or dementia. This led to the development of the Medication Review in Cognitive Impairment and Dementia (MedRevCiD) checklist that aims to fill this gap and provide healthcare professionals with a practical and standardized tool for assessing medication-related concerns in this vulnerable population.

The MedRevCiD Checklist was created to assist pharmacists in identifying issues needing in-depth assessment in individuals with dementia. Figures 1-2 visually represent the steps in constructing the MedRevCiD checklist. The MedRevCiD checklist is a combination of explicit and implicit criteria.

1.3.4 Medication Review in Cognitive Impairment and Dementia (MedRevCiD) checklist

The core topics associated with DRPs in persons with CI or dementia are categorized into six domains consisting of clinical questions to be assessed.

- Medication Management and Adherence
- Drug Induced Cognitive Impairment or Worsening
- Conditions Associated with Cognitive Impairment and Dementia
- Treatment Options for Dementia
- Behavioral and Psychological Symptoms of Dementia
- Optimizing Medication Use

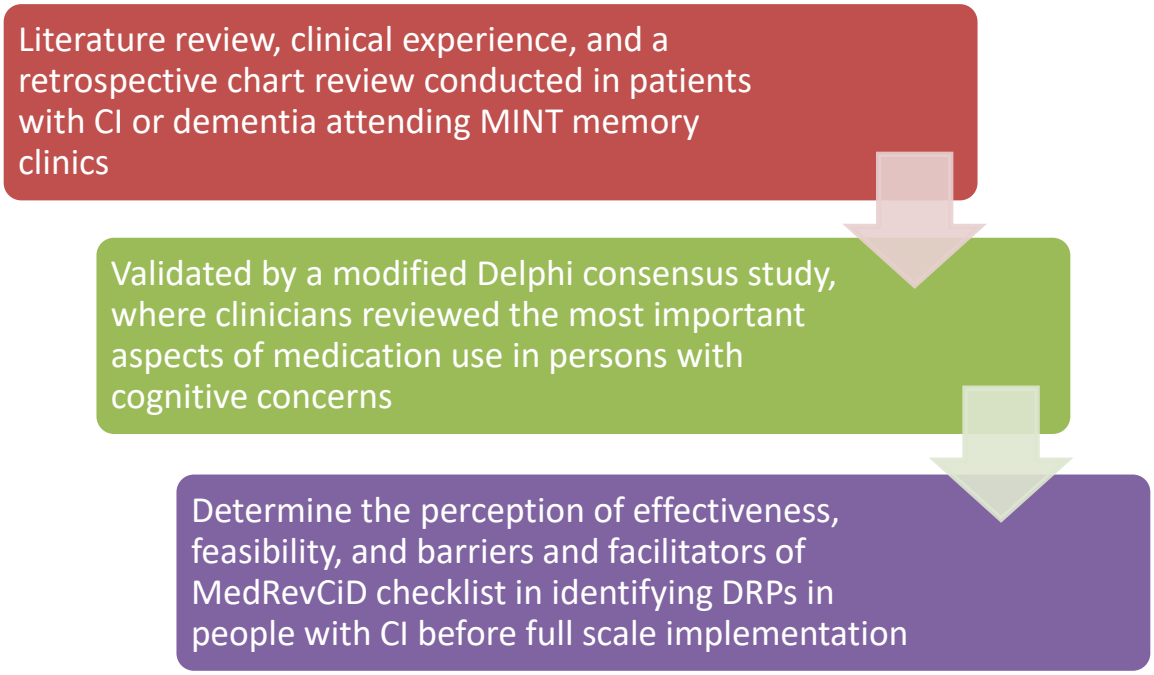

Figure 1-2: The MedRevCiD checklist construction. Adapted from Patel et al[62]

1.3.5 Explicit criteria vs Implicit criteria vs Medication Review in Cognitive Impairment and Dementia (MedRevCiD) checklist

It is important to note the differences between tools that use implicit criteria from those that use explicit criteria. Table 1-1 highlights the similarities and differences in these criteria.

Table 1-1: Explicit criteria vs Medication Appropriateness Index (MAI) vs Medication Review in Cognitive Impairment and Dementia (MedRevCiD) checklist

Domain	Beers criteria 2023 (Explicit)	STOPP criteria 2023 (Explicit)	MAI (Implicit)	MedRevCiD checklist (Explicit + Implicit)
Evidence-based or expert consensus driven	✓	✓	✓	✓
Provides a list of medications that should be avoided in older adults with CI or dementia	✓ Subsection in the independent of diagnosis category	✓ Subsection of list of medications	X Healthcare professionals needs to identify DRPs using their subjective assessment	✓
Conditions associated with CI and dementia	X	X	X	✓ Subjective assessment[f]
Deprescribing	X	X	X	✓ Subjective assessment[g]
DRPs as per PCNE				
1. Drug selection				
Inappropriate drug according to guidelines	✓	✓	✓ Subjective assessment	✓ Subjective assessment

No indication for drug	X	X	✓ Subjective assessment	✓ Subjective assessment
DDI	X DDI section not specific for CI and Dementia	X DDI section not specific for CI and Dementia	✓ Subjective assessment	✓ Subjective assessment[a]
Inappropriate duplication of therapeutic group	X	X	✓ Subjective assessment	✓ Subjective assessment
No or incomplete drug treatment	X	X	✓ Subjective assessment	✓ Subjective assessment
Too many different drugs/active ingredients prescribed for indication	X	X	X	X
2. Drug form				
Inappropriate drug form/ formulation	X	X	X	X
3. Dose selection				
Drug dose too low	X	X	✓ Subjective assessment	✓ Subjective assessment[b]
Drug dose too high	X	X	✓ Subjective assessment	✓ Subjective assessment
Dosage regimen not frequent	X	X	✓ Subjective assessment	✓ Subjective assessment

Too frequent	X	X	✓ Subjective assessment	✓ Subjective assessment
Dose timing instructions wrong, unclear	X	X	✓ Subjective assessment	✓ Subjective assessment
4. Treatment duration Too short or too long	X	X	✓ Subjective assessment	✓ Subjective assessment[c]
5. Dispensing Related to the logistics of the prescribing and dispensing process	X	X	X	X
6. Drug use process The way the patient gets the drug administered by a healthcare professional	X	X	X	X
7. Patient related	X	X		
Nonadherence (Intentionally)	X	X	X	✓ Subjective assessment[d]
Drug overuse or unnecessary use by the patient	X	X	✓ Subjective assessment	✓ Subjective assessment
Patient takes food that interacts	X	X	X	X
Patient stores drug inappropriately	X	X	X	✓

				Subjective assessment[d]
Inappropriate timing or dosing intervals	X	X	X	✓ Subjective assessment[d]
Patient unintentionally administers/uses the drug in a wrong way	X	X	X	✓ Subjective assessment[d]
Patient physically unable to use drug/form as directed	X	X	X	✓ Subjective assessment
Patient unable to understand instructions properly	X	X	X	✓ Subjective assessment
8. Medication reconciliation problem	X	X	X	X
9. Least expensive	X	X	✓ Subjective assessment	X

[a] Is the patient taking anticholinergic medications (e.g., tolterodine, amitriptyline, diphenhydramine), bradycardia causing agents (e.g., beta blockers), with QT prolongations risk (e.g., citalopram, amitriptyline, risperidone) medications with cholinesterase inhibitor therapy
[b] Is each medication being taken at the appropriate dose and duration for its reason for use?
[c] If the patient is taking antidepressants, is the dose and duration appropriate for its reason for use?
[d] Domain 1 of the MedRevCiD checklist helps in determining whether patient can manage their medications and if they are adherent to their medications
[e] Is the drug the least expensive alternative compared to others of equal utility?
[f] List of commonly encountered medical conditions which may impact or worsen CI or dementia
[g] Consider referring to the Bruyere deprescribing guidelines of deprescribing algorithms for PPIs, antihyperglycemics, antipsychotics, benzodiazepines, Z-drugs, and cholinesterase inhibitors and memantine

1.4 Thesis goal

The overarching goal of this research is to enhance the identification and management of DRPs among older adults with CI or dementia. By rigorously validating the MedRevCiD checklist and comparing its effectiveness against the gold standard MAI, this study aims to identify and categorize DRPs within this vulnerable population. To achieve this goal, this research addresses the following key objectives.

1. To identify gaps in the current knowledge regarding the impact of medication reviews on clinical outcomes, and to identify the different types of DRPs reported in older adults with dementia.
2. To compare the mean number of DRPs identified using the MedRevCiD checklist and Medication Appropriateness Index (MAI) criteria in older adults with CI and/or dementia.
3. To identify which explicit tool, Beers Criteria or STOPP, identify more PIM use among older adults with CI or dementia.

1.5 Thesis Outline

This thesis is comprised of following chapters:

Chapter 1: A brief introduction of cognitive impairment and dementia, drug-related problems, polypharmacy, potentially inappropriate medications, tools for assessment of medication use in older adults, and Medication Review for Cognitive Impairment and Dementia (MedRevCiD) checklist.

Chapter 2: A scoping review to identify gaps in current knowledge about the impact of medication reviews on clinical outcomes in older adults with dementia

Chapter 3: Study Rationale, objectives, and hypothesis

Chapter 4: An overview of research methods used in this project

Chapter 5: A summary of findings from the research project

Chapter 6: Discussion and Conclusion

Chapter 2: Medication reviews and clinical outcomes in persons with dementia: A scoping review

This chapter is published as follows:

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2.1 Overview

Abstract: Persons diagnosed with dementia are often faced with challenges related to polypharmacy and inappropriate medication use and could benefit from regular medication reviews. However, the benefit of such reviews has not been examined in this population. Therefore, the current scoping review was designed to identify the gaps in the current knowledge regarding the impact of medication reviews on the clinical outcomes in older adults with dementia. Relevant studies were identified by searching three databases (Ovid MEDLINE, Ovid EMBASE, and Scopus) from inception to January 2022 with a combination of keywords and medical subject headings. After the removal of duplicates and ineligible articles, 22 publications of the initial 8346 were included in this review. A total of 57 outcomes were identified, including those pertaining to the evaluation of medication use (n = 17), drug-related interventions (n = 11), drug-related problems (n = 10), dementia-related behavioral symptoms (n = 8), cost-effectiveness (n = 2), drug-related hospital admissions (n = 1), as well as outcomes classified as other (n = 7). Gaps identified through this scoping review included the paucity of studies measuring the impact of medication reviews on the medication management capacity and medication adherence, quality of life, and mortality.

Keywords: Older adults; dementia; medication review; drug-related problems

2.2 Introduction

Dementia is an umbrella terms that encapsulated a number of neurodegenerative, irreversibly progressive disorders that are marked by cognitive decline and a steady reduction in everyday function, and it is typically accompanied by behavioral issues.[1]

Cognitive impairment (CI) or dementia affects the ability to learn, memory, reasoning, focus, understanding, language, and judgment. Given that the risk of being diagnosed with dementia increases with age, the global prevalence of dementia is expected to increase from 50 to 150 million by 2050, with the aging of the world population.[3-5] Dementia is presently the seventh leading cause of death, and it is one of the primary causes of impairment and dependency in older people worldwide.[6] People with dementia and their caregivers, family, and society at large all experience social, psychological, physical, and financial repercussions. In Canada, the annual healthcare cost of dementia, including the out-of-pocket cost of caring for people with dementia, was CAD 10.4 billion in 2016.[5,63] Older adults who have dementia commonly experience coexisting medical conditions, including hypertension, diabetes mellitus, coronary artery disease, stroke, and heart failure. These comorbidities are highly prevalent among this population.[64] Older adults who have CI or dementia are particularly at risk for drug-related problems (DRPs), with 41% of hospital admissions in older adults with dementia thought to be partially or entirely related to DRPs, which is higher than older adults without dementia.[13] Older adults with dementia have more comorbid conditions and are often prescribed multiple medications, which further increases the risk of DRPs.[25] Studies have reported that more than half of older adults with dementia are prescribed five or more medications per day.[13] The use of multiple medications, or polypharmacy, in older adults with dementia was found to be associated with the use of potentially inappropriate medications (PIMs), which are medications that increase the risk of adverse events. The literature reports the higher prevalence of PIMs among older adults with dementia, ranging between 10.2 and 63.4%.[27,36,65,66] Additionally, managing medications in people with dementia may lead to drug-related hospital

admissions, medication mistakes, and dependency on others to help with medication management responsibilities.[67] Adherence to a prescribed regimen can be very difficult for older adults with dementia due to complex medication regimens, memory loss, and other cognitive deficits.[22] Polypharmacy, complex medication regimens, and the use of PIMs in older adults with dementia are associated with an increased risk of adverse events and drug interactions, medication nonadherence, an increased risk of hospitalization or prolonged hospitalization, and economic burden on patients and the healthcare system.[54,68] Moreover, prescribing decisions made for older adults with dementia lack unbiased scientific evidence, as this population has been excluded from 85% of the clinical trials.[69]

Optimizing medications in elderly individuals with dementia is a crucial step in addressing the complexity of prescribing medication and changing the treatment goals as the illness advances.[18,70] Regular reviews of medications could potentially address this concern. Pharmaceutical Care Network Europe (PCNE) states that a medication review is a structured assessment of a patient's medications to optimize medicine usage and enhance health outcomes.[71] Medication reviews include several components, such as an assessment of the medications prescribed regularly and a review of medical information such as laboratory workups, diagnostic imaging from the medical records, and an interview with the patient to identify DRPs and implement interventions to address them.[72] Several clinical trials and observational studies have been conducted to evaluate the effectiveness of medication reviews in persons with dementia. However, there is a high degree of variability in the methodologies and outcomes examined. Therefore, the aim of our scoping review is to identify gaps related to the impact of medication reviews conducted in older adults with dementia on DRPs and clinical outcomes.

2.3 Methods

The foundation for the conduct of this scoping review was the 5-stage framework developed by Arksey and O'Malley. We also used the PRISMA Extension for Scoping Reviews (PRISMA—ScR) to report the results.[73,74] We followed the five steps recommended by Arksey and O'Malley to conduct the scoping review, first, by identifying the research question; second and third, by identifying and selecting the relevant studies for inclusion in the review; fourth, by charting the data; and fifth, by collating, summarizing, and reporting the results.

Step 1: Identifying the Research Question

As stated before, this scoping review was conducted to identify gaps in the current knowledge regarding the impact of medication reviews on clinical outcomes, and to identify the different types of DRPs reported in older adults with dementia. Pharmacists could conduct medication reviews of people with dementia on their own or with a multidisciplinary team of people.

Step 2: Identifying the Relevant Studies

A single reviewer (R.S.) prepared a comprehensive search strategy with the help of a research librarian. Ovid EMBASE, Ovid MEDLINE, and Scopus were searched from inception to January 2022. The search terms used in each database included a combination of medical subject headings and keywords (limited to title, abstract, and keywords) related to medication reviews, older adults, and dementia and linked by the Boolean operators (AND, OR), as shown in Appendix A-1 Advanced search options, such as truncation use on keywords where appropriate, subject heading explosion, and adjacency features, were

used based on the database functionality. Results were exported from each database into Microsoft® Excel® (Office 365 ProPlus Version 1906), where duplicates were removed.

Step 3: Study selection

The first 520 articles were screened by two reviewers (R.S. and H.P.) to establish the inter-rater reliability in screening between the two researchers. Given the strength of the inter-rater reliability (Kappa coefficient of 0.92), the two reviewers independently screened 50% of the remaining article titles and abstracts. The bibliographies of the pertinent studies were also screened for additional relevant studies. The studies were included if (1) participants were older adults (age ≥ 55 years) diagnosed with dementia and/or cognitive impairment; (2) they were referenced as medication reviews. Studies were excluded if (1) patient participants were not older adults (aged <55 years); (2) patient participants were older adults but not diagnosed with dementia; (3) they included non-human populations; (4) they were published in a non-English language; and (5) they were editorials, commentaries, opinions, letters to the editor, systematic reviews or meta-analyses, or case reports.

Step 4: Data charting

Data extraction from the included studies was carried out using a Microsoft® Excel® spreadsheet, specifically the Office 365 ProPlus Version 1906. The following data were abstracted: the study design (qualitative/quantitative studies/randomized controlled trials (RCTs), non-RCTs, retrospective studies) and study details (study population demographics, year of publication, country, publication year, intervention details, sample size, DRPs identified, recommendations accepted to resolve DRPs, inclusion/exclusion criteria, study outcomes, and results). Data abstractions were

completed by two reviewers (R.S. and N.M.) independently, after which they were compared to ensure accuracy, consistency, and completeness.

Step 5: Collating, summarizing, and reporting the results

The following data were collected and summarized: demographic data; characteristics of the studies, including the study design, year of publication, and country of origin; and the effectiveness of the medication review. Additionally, the review encompassed an evaluation of the medication effectiveness, incorporating both quantitative data and narrative descriptions. This comprehensive approach allowed for a thorough assessment of the research findings. Results were categorized and summarized based on the clinical outcomes reported in terms of identifying DRPs, types of DRPs, changes in the number of prescribed medications, recommendations to resolve DRPs, and reductions in drug usage, mortality, and hospital admissions among older adults with dementia.[32,44,55,56]

The types of care settings,[75] pharmacist care interventions,[76] DRPs, and drug-related interventions (DRIs) are defined in Appendix A-2.

2.4 Results

The initial search yielded 8346 citations; 3050 duplicates were removed. Of the remaining 5296 articles, 5091 did not meet the inclusion criteria by abstract and title. The full texts of the remaining 205 articles identified 21 articles and one conference abstract (see Figure 2-1).

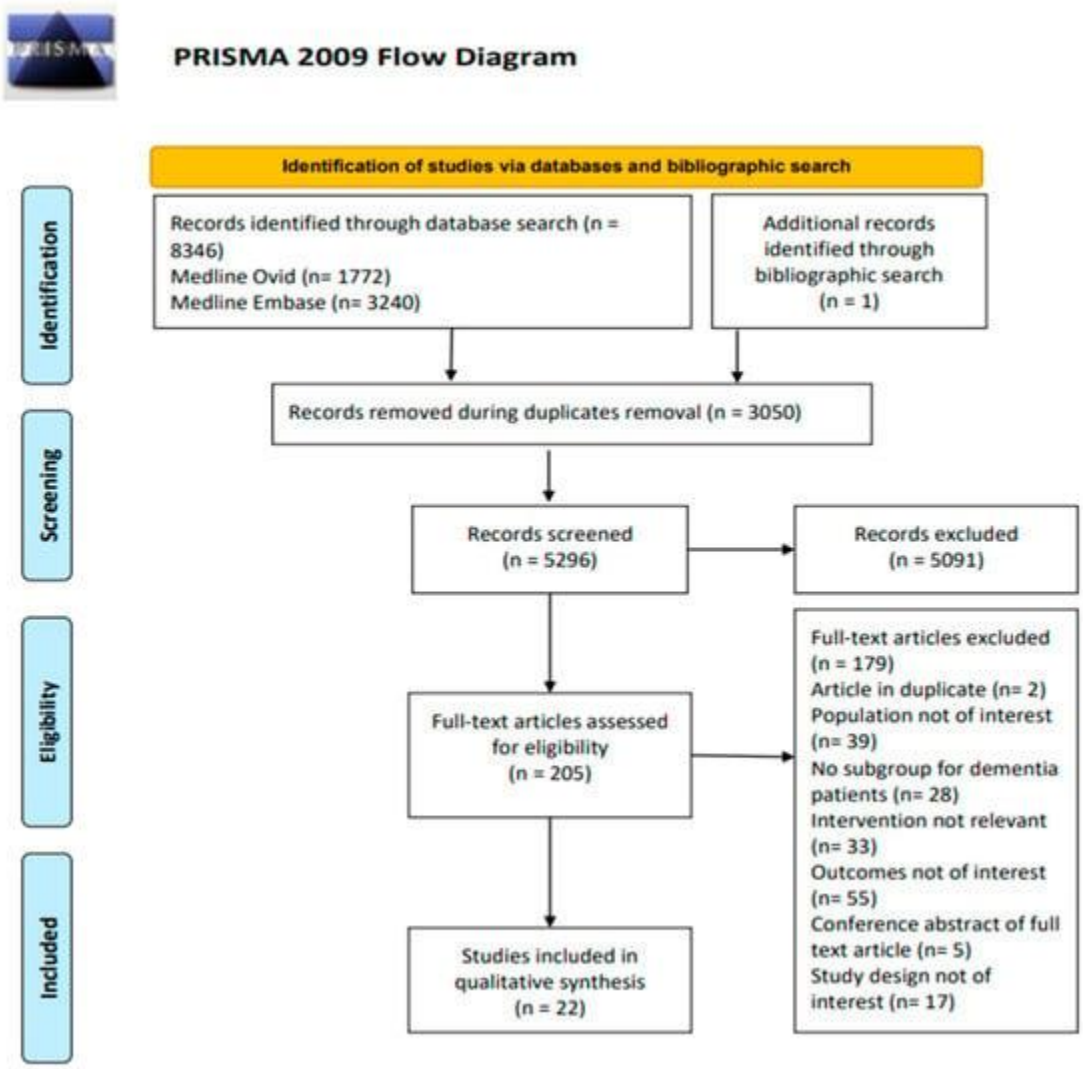

Figure 2-1:- PRISMA flow diagram

Of the studies included Ballard et al., 2016,[77,78] and Smeets et al., 2021,[79-81] published data on the same population. Gustafsson et al., 2017,[44,54-56] published four studies within four years commencing from 2017. A randomized controlled trial was published in 2017 and included 460 patients (intervention group = 230; control group = 230) from acute internal

medicine wards and orthopedic wards.[54] Gustafsson et al. conducted three more secondary analyses using data from the RCT.[44,55,56]

2.4.1 Study characteristics

The study designs included observational pre–post studies (n = 4),[67,81-83] retrospective studies (n = 7),[70,84-89] prospective studies (n = 5),[45,90-93] an audit (n = 1),[94] feasibility studies (n = 2),[95,96] and randomized controlled trials (n = 3).[44,77,79] Detailed descriptions of the included studies are summarized in Appendix A-3.

A total of 133,024 patients were included in 22 studies. The minimum–maximum mean ages of the participants ranged from 78.33 to 87.9 years old (not reported in three studies). Out of 22 studies, 17 studies included both women and men. About 65.7% (n = 86,645) of the population in the studies were females, which is 1.9 times more than the male population in the studies (not reported in five studies).

Of the included 22 studies, 1 study each was conducted in Canada,[82] the Netherlands,[79] Slovenia,[81] France,[87] Taiwan,[45] Australia,[96] northern Sweden,[54] Germany,[89] Denmark,[92] and Hong Kong,[93] 5 studies were conducted in the USA,[70,84-86,90] 3 studies were conducted in the UK,[77,94,95] and 4 studies were conducted in Spain.[67,83,88,91] All the studies were published within the previous ten years.

Nine studies were conducted in long-term care facilities,[77,79,82,83,88,90-92,95] six studies in community settings,[81,84-86,89,96] five studies in hospital settings,[67,68,83,87,93,94] and one study in all three settings and one study in both a long-term care facility and community setting.[45,70]

2.4.2 Information about interventions

Appendix A-4 provides a summary of the interventions and their reported outcomes for each study included in the review. In terms of cognitive pharmacy services and specifically for clinical assessment (see Appendix A-2), medication reviews were conducted by the pharmacists independently in 15 studies,[54,71,82-88,90,92-96] and in collaboration with multidisciplinary teams in 6 studies.[45,67,79,89,91] One study reported a medication review conducted by a therapist.[77] The multidisciplinary teams in the six studies included a combination of a variety of healthcare professionals, such as "elderly care physicians", nurse assistants, geriatric clinical pharmacists, physical and leisure therapists, administrators, neurologists, psychiatrists, geriatricians, primary care general practitioners, dementia specialists, nurses with expertise in dementia care, dieticians, physical therapists, occupational therapists, clinical psychologists, and social workers. Pharmacists or multidisciplinary teams identified and reported DRPs in 10 studies as part of clinical assessments in comprehensive medication management.[44,85-88,90,91,93,94,96] In eight studies, pharmacists or multidisciplinary teams also recommended appropriate interventions for DRPs identified during the medication reviews.[84,85,87,88,91,92,96] There were eight instances of pharmacists actively monitoring the outcomes of interventions and completing the essential follow-up tasks concerning the assessment part of complicated medication management.[44,79,82-84,87,89,91,96]

Only one research study identified pharmacists as a source of drug information and counseling to people with dementia, family members, and carers.[93] In four reports for educational and advisory services to healthcare professionals, pharmacists served as a

source of drug information and conducted educational sessions for other healthcare professionals.[83,94,95,96]

2.4.3 Type of outcomes reported

Fifty-four outcomes relating to medication reviews have been reported in 22 studies. About one-fifth (10/54) of the studies have reported outcomes related to DRPs,[44,45,85-88,90,93,94,96] followed by drug-related interventions (n = 11),[36,44,84-88,91,92,96] evaluations of medication use (n = 16),[25,45,71,77,79-81,85-92,94] cost-effectiveness (n = 2) ,[88,95] and drug-related admissions (n = 1) (see Figure 2-2).[45]

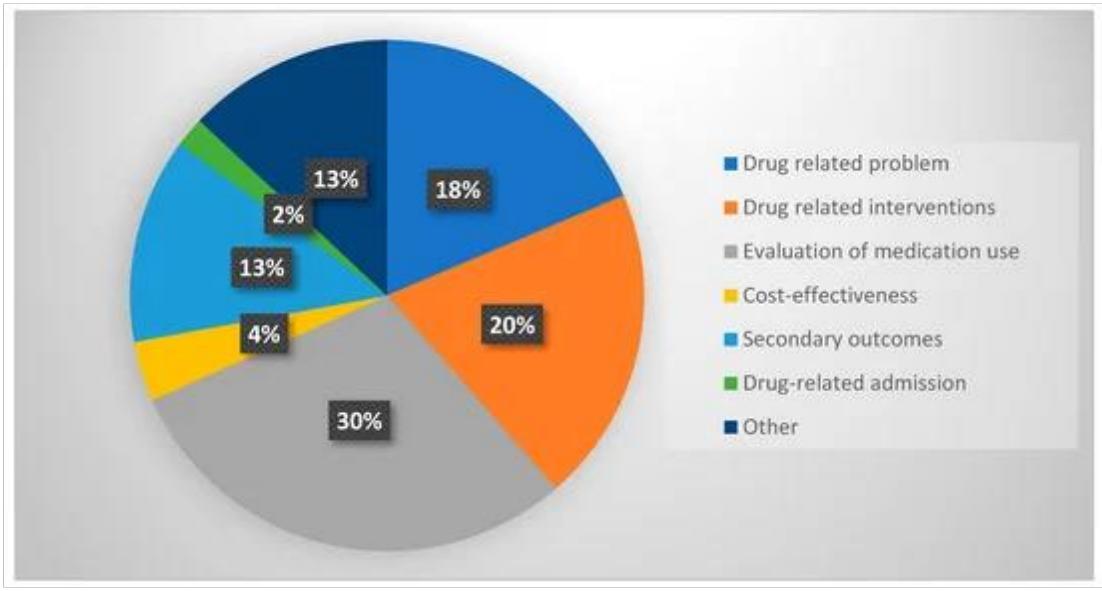

Figure 2-2: Percentage of reported outcomes by type

2.4.4 Effect of medication review

2.4.4.1 Evaluation of medication use

The impact of medication reviews on important clinical outcomes is outlined in Appendix A-5. Sixteen studies reported medication usage in older adults with dementia.[36,44,55,56,71,75-

[79,82,83,85-89,94] Hernandez et al. reported that 87.7% (57/65) of the population in the study was taking ≥ 5 drugs per day, and 38.5% (25/65) were on hyper-polypharmacy (taking ≥ 10 drugs per day).[91] Almost two-thirds of the study population were prescribed antipsychotics (78.5%), followed by analgesics in 66.2%, and antidepressants in 53.9%. Nine out of ten studies reported the average number of medications per patient as ≥ 5, ranging from 6.4 to 13.3 per patient.[36,44,82,83,86,90,91,94,96] Results reported in six studies indicated a significant decrease in the average number of drugs per patient after medication reviews conducted by pharmacists independently or with multidisciplinary teams.[36,44,55,56,75-77,82,94] The intervention for one study involved a medication review conducted by a pharmacist using the medication review guidance (MRG) tool. The study was conducted among nursing home residents in Quebec. At the end of a 104-day follow-up, Wilchesky et al. found a substantial reduction in the overall number of regular drugs by 12.1%.[82] Another study reported an overall 28% decrease in the number of psychotropic drugs prescribed, with the largest decrease reported in antipsychotic use (49.66%).[83] The intervention consisted of a review of the drugs used by the participating patients, carried out by a multidisciplinary team that involved one primary care physician and one pharmacist, as well as the nursing home doctors and nurses. At baseline, the average number of psychotropic medications administered per patient was 2.71; at one-month post-intervention, it was 1.95; and at six months, it was 2.01 ($p \leq 0.001$ at both time points). A study conducted by Dong et al. reported the implications of Medicare Part D's Comprehensive Medication Review (CMR) on Alzheimer's patients' adherence to medication.[70] The proportions of nonadherent Medicare beneficiaries in the intervention group for each prescription category decreased after they obtained a CMR, but the

proportions in the comparison group grew over time. For instance, the proportion of beneficiaries in the intervention group who did not take their diabetic medications decreased from 13.1% to 9.8% in 2017. However, the percentage of nonadherent beneficiaries in the comparison group increased by 1.2%, as shown in Appendix A-5.

2.4.4.2 Drug-related problems

Ten studies reported on DRP outcomes.[44,45,85-88,90,93,96] Four studies defined DRPs based on established systems. For example, one study each used the Westerlund system,[32] ASHP classification 1996,[97] Cipolle/Morley/Strand classification,[98] and PCNE Classification V 6.2,[99] and two studies did not use any standard classification system, as shown in Table 2-1. The numbers of DRPs identified during medication reviews ranged from 11 to 1077. Wucherer et al. reported 1077 DRPs in 92.8% (414/446) of patients. Furthermore, the authors reported that the total number of DRPs was associated with the number of drugs taken (b = 0.07; 95% Confidence Interval (CIn): 0.05–0.09; $p < 0.001$) based on a multivariate Poisson regression analysis.[89] Similar results have also been reported by another study. In one study, a multiple Cox regression model was employed to analyze the data. The results indicated that drug-related problems (DRPs) were more prevalent in certain populations. Specifically, a higher number of drugs used by individuals was associated with a greater likelihood of DRPs (odds ratio (OR): 1.255; 95% CIn: 1.137–1.385). Additionally, populations with histories of strokes, and particularly earlier strokes, exhibited a significantly higher risk of DRPs (OR: 5.042; 95% CIn: 2.032–12.509). Similarly, individuals with heart failure (OR: 2.66; 95% CIn: 1.64–4.30) and diabetes mellitus (OR: 2.32; 95% CIn: 1.41–3.81) were also more likely to experience DRPs.[44,54-56]

Six studies reported outcomes on medication appropriateness.[44,85,87,90,94,96] Pharmacists' interventions have been shown to decrease the number of PIMs used in patients after medication reviews. Pearson et al. reported a change in the mean number of PIMs in patients living with dementia from 1.5 PIMs per patient at baseline to 0.9 PIMs per patient at the 180-day follow-up after medication review.[84] In another study, the use of PIMs decreased significantly in the intervention group between admission and after medication review, from 20.3% to 14.2% ($p = 0.002$), particularly in the use of anticholinergic drugs (from 7.1% to 3.3%; $p = 0.005$) and NSAIDs, (from 3.3% to 0.9%; $p = 0.025$).[44,54-56] Hernandez et al. reported a significant difference ($p < 0.001$) between the mean (SD) Medication Appropriateness Index (MAI) scores at admission and post-intervention (4 (4.6) vs. 0.5 (2.6)).[91]

Table 2-1:- Type of drug-related problems reported

Study	**Types of Drug-Related Problems Reported**
Pearson et al., 2021[84]	2019 Beers Criteria Total of 59 PIMs identified in the 40 patients (average 1.5 PIMs/patient)
Levine et al., 2021[85]	• Unnecessary drug therapy = 1 DRP • Overuse [a] = 6 DRPs • Underuse [b] = 28 DRPs
Aziz et al., 2018[94]	2015 STOPP Criteria • 164 drugs prescribed
Melville et al., 2020[86]	2012 Beers Criteria • 62 (59%) patients received at least one PIM
Novais et al., 2021[87]	Westerlund System[32] • Total of 543 DRPs • Non-conformity to guidelines/contra-indication = 156 (28.7%) DRPs

	• Drug without indication = 118 DRPs • Improper administration = 82 DRPs • Supratherapeutic dosage = 51 DRPs • Untreated indication = 40 DRPs • Subtherapeutic dosage = 35 DRPs • Drug monitoring = 26 DRPs • Drug interaction = 17 DRPs • Adverse drug reaction = 17 DRPs • Failure to receive drug = 1 DRP
Hernandez et al., 2020[91]	• ASHP classification 1996[97] • Total 175 DRPs (2.97 per patient) in 90.8% of patients • Actual and potential adverse drug events = 33 DRPs • Medication prescribed inappropriately for a particular condition = 29 DRPs • Therapeutic duplication = 18 DRPs • Inappropriate dose = 17 DRPs • Medication with no indication = 15 DRPs • Condition for which no drug is prescribed = 14 DRPs • Length = 14 DRPs • Schedule = 13 DRPs • Failure to receive the full benefit of prescribed therapy = 8 DRPs • Actual and potential drug–drug interactions that are clinically significant = 6 DRPs • Drug diseases that are clinically significant = 4 DRPs • Lack of understanding of the medication = 2 DRPs • Inappropriate-dose renal impairment = 1 DRPs • Dosage form = 1 DRP
Cross et al., 2020[96]	Beer's 2015 Criteria or 2015 STOPP Criteria • 25 (54.3%) patients using ≥ 1 PIM cog
Gustafsson et al., 2017[44,54-56]	2015 STOPP/START Criteria • 326 DRPs were identified in 153 (72.2%) patients • Cipolle/Morley/Strand classification [53] • Total of 310 DRPs reported in 140 (66%) patients • Unnecessary drug therapy = 54 DRPs • Needs additional therapy = 37 DRPs

	• Ineffective/inappropriate drug = 54 DRPs • Adverse drug reaction = 14 DRPs • Too-high dosage = 44 DRPs • Drug use process errors = 26 DRPs • Adherence = 4 DRPs • Monitoring = 13 DRPs • Drug interaction = 23 DRPs
Wucherer et al., 2017[89]	Inappropriate drugs according to the PRISCUS list reported in 105 (22.9%) patients. PCNE Classification V 6.2 [54] • Total of 1077 DRPs in 414 (92.8%) patients • Ineffective/inappropriate drug = 158 DRPs • Adverse drug reaction = 27 DRPs • Administration and compliance = 645 DRPs • Drug interaction = 180 DRPs • Dosage = 67 DRPs
Wong et al., 2016[93]	• Total of 11 DRPs reported
Pearson et al., 2021[84]	2019 Beers Criteria Total of 59 PIMs identified in the 40 patients (average 1.5 PIMs/patient)

[a] Overuse of medications refers to instances in which drugs are prescribed or taken without a clear medical necessity or indication. In the context of advanced dementia, an example of overuse would be the administration of memory-enhancing agents, which may not provide significant benefits for individuals at this stage. Similarly, the use of supplements like ginkgo or vitamin E, which lack substantial evidence for cognitive enhancement, can also be considered examples of overuse.
[b]. Underuse of medications occurs when individuals who could benefit from a particular treatment or intervention do not receive it. In the case of dementia, underuse was identified in situations in which individuals met specific criteria but were not receiving pharmacotherapy. This included individuals with Montreal Cognitive Assessment (MoCA) scores of 25 or lower who were designated as having dementia based on the study's criteria. However, individuals with advanced dementia (MoCA scores below 10) were excluded from consideration for medication, as the potential benefits in this group were deemed to be limited.
PIMcog: potentially inappropriate medication for a person with cognitive impairment.

2.4.4.3 Drug-related interventions

Eight studies reported the total number of proposed recommendations to the prescriber by the pharmacist or multidisciplinary team after the medication review.[84,85,87,88,90-92,96] In their retrospective chart review, Melville et al. present data on the identification of the number and categories of medication-related recommendations made by a geriatric clinical

pharmacist in their Caring for Older adults and Caregivers at Home (COACH) Program. The geriatric clinical pharmacist proposed a total of 248 recommendations to the prescribers after the medication review.[86] The three most frequent recommendations were stopping a drug, reducing the dose, and changing to a potentially safer alternative.[86] Providers accepted 110 (44%) of the drug-related recommendations given by the pharmacist within six months of the medication review. In the Cross et al. study, pharmacy professionals made 121 deprescribing recommendations, followed by 52 on adherence and medication management, and another 88 on care-related activities, such as monitoring/investigative testing.[96] At six months, 136 of the 209 suggestions (52.1%) had either been fully or partially carried out.

2.5 Discussion

This scoping review, which examined the impact of medication reviews and interventions in older adults with dementia, found that reviews reduce polypharmacy as well as inappropriate medication use. The need for pharmacists is underlined, especially considering the issue of high-risk medicine and polypharmacy frequently seen in people with dementia.[13,25,27,36,68,54] Studies included in this scoping review suggested that the inclusion of a pharmacist care intervention had favorable results, indicating that pharmacist engagement may improve the medication management concerns in this population. The results of this scoping review are consistent with the results of McGrattan et al.'s systematic review, which highlights the positive impact on medication-related outcomes.[100] With just three papers included, this systematic review emphasizes the lack of research on medication management for persons with dementia (PWDs). Similar results are also reflected in a recently published RCT by Liu et al. on community-dwelling persons living

with dementia (PLWDs) that assessed the effect of the Care Ecosystem (CE) collaborative dementia care program on the PIM use among this population. The CE resulted in significantly fewer PIMs used by PLWDs.[101]

The present scoping review has determined a few clinical, practical, and scientific gaps in studies examining outcomes such as medication adherence, cost-effectiveness, and the reporting of dementia-specific core outcomes:

1. The results obtained from RCTs are the most reliable evidence to assess an intervention's effectiveness because the randomization process can minimize the risk of bias influencing the results.[102] No RCT was conducted in the community setting for patients with dementia.

2. Only one study each was identified in this scoping review for Canada, Australia, the Netherlands, Slovenia, France, Taiwan, northern Sweden, Germany, Denmark, and Hong Kong. The studies conducted in these countries only included patients from one care setting. There is a need for more evidence for these countries in which patients are included from all types of care settings.

3. Nine studies reported data from the LTC setting, and only one, by Hernandez et al., reported DRPs in persons with dementia from the LTC setting.[91] There is a scarcity of studies reporting DRPs in persons with dementia from the LTC setting.

4. A lack of studies examining medication management and medication adherence as outcomes of medication reviews: A scoping review conducted by Hudani et al. in 2016 reported the nonadherence prevalence in older adults with CI or dementia, which ranged from 2 to 59%, which is not surprising considering the polypharmacy use, cognitive impairment, and complex medication regimens in this population.[103] Furthermore, the

situation is much more difficult for individuals with CI or dementia due to various cognitive deficiencies, leading to increased nonadherence rates.[103] In this scoping review, we identified only one study that reported on medication nonadherence as an outcome of medication reviews in persons with CI and dementia.[70] Clinical practice in memory clinics includes evaluating the medication management capacity in this group. Still, it is not apparent why most of the studies did not report the effects of medication reviews on the medication management and adherence in this population. Any medication review conducted in this population should examine the medication adherence.

5. A lack of research examining the cost-effectiveness of conducting a medication review: No study in this scoping review examined the impact of medication reviews on the overall cost, such as reductions in the medication cost, hospitalization cost, medical expenses, etc. Maidment et al. have reported data on costs, such as trainer and care home staff costs.[95] The authors conducted a mixed-method feasibility study that included a comprehensive clinical medication review conducted by a specialized dementia care pharmacist. Their findings revealed that the mean cost associated with the staff time for the medication review alone was GBP 104.41 per participant. In contrast, when accounting for both the medication review and the intervention (which included training), the mean cost rose to GBP 372.80 per participant. These cost assessments provide valuable insights into the financial aspects of implementing medication review interventions in dementia care. Only one other study has reported data on the clinical, economical, and organizational dimensions of DRI in the cognitive behavioral unit. Novais et al. conducted a study from retrospective data on medication reviews in a cognitive behavioral unit (CBU).[87] These units are designed for people with responsive behavioral abnormalities linked to

Alzheimer's disease and related dementias (ADRD). Pharmacists discovered pertinent DRPs during medication reviews and made recommendations to the patients' physicians. A total of 543 DRPs and DRIs were recorded for patients hospitalized in the CBU. According to pharmacists, 55.2% of pharmaceutical interventions decrease the costs of care, and 16.6% increase the costs.[87] No study was found in this scoping review that reported on the cost aspect in detail or whether the medication review conducted by a pharmacist decreases the overall cost, such as reduction in the medication cost, hospitalization cost, medical expenses, etc.

6. A lack of patient and caregiver satisfaction as an outcome of medication reviews: The success of any intervention greatly relies on the patient receiving the care, the caregivers, and other healthcare professionals. The studies included in this scoping review reported no data on the satisfaction levels of patients, caregivers, or healthcare teams related to the medication review. The level of satisfaction will help the researcher to evaluate the patient, caregiver, and healthcare satisfaction and the potential acceptability of medication reviews by older adults with dementia.

7. A lack of studies reporting on quality of life: There is a scarcity of studies examining the impact of medication reviews on the quality of life in people with dementia. In this scoping review, an RCT was conducted by Ballard et al. to measure whether a review of antipsychotic medications, either alone or in conjunction with evidence-based, non-pharmacological methods, has a substantial positive impact on health-related quality of life.[77] Two DEMQOL-Proxy domains (negative emotion and appearance) significantly worsened in individuals receiving antipsychotic reviews. The DEMQOL is a 28-item self-reported tool used to assess the health-related quality of life (HRQL) of people with

dementia. The caregiver fills out a 31-item examination called the DEMQOL-Proxy, which examines the patient's cognition, adverse emotions, positive emotions, daily activities, and appearance. More studies need to be conducted to see whether the medication review increases the quality of life among older adults with dementia or not.

8. A lack of application of a dementia-specific core outcome set: The studies included in this scoping review showed variations in the measuring techniques and reported results. For instance, some studies have reported drug-related interventions without identifying DRPs, and not all studies followed up with the patients to measure the effects of the medication review. An international core outcome set for clinical trials of medication reviews in polypharmacy and multimorbid older people has been published.[104] The creation of core outcome sets for clinical trials has produced a variety of advantages, reduced the possibility of reporting bias, increased the chance of clinically meaningful results, and decreased the trial-to-trial variation in results.[105] Establishing a core outcome set for medication management interventions in primary care for individuals with dementia simplifies the research process by providing a standardized set of outcomes to evaluate the intervention's effectiveness in this population. This approach enhances consistency and comparability across studies, making it easier for researchers to gauge the impacts of these interventions on individuals with dementia.

2.5.1 Strengths and Limitations

The robust and comprehensive search approach employed to find the range of research published globally is the main strength of this scoping review.

It is important to be aware of the limits of this scoping review. As we only considered English-language papers, language bias may have influenced it.

2.6 Conclusions

This scoping review highlights that medication reviews conducted by pharmacists independently or in collaboration with other healthcare professionals in any setting may have a positive outcome on medication use among older adults with dementia. A reduction in medication use after medication review was a key finding in this scoping review. However, this scoping review identified that studies examining quality of life, medication management, and medication adherence as outcomes of medication reviews were lacking. However, it is very difficult to draw a robust conclusion due to the variability in the reported outcomes and several limitations. The lack of standardized criteria to identify and categorize DRPs, the lack of data on comorbidities, and the lack of dementia-specific core outcomes are a few gaps that should be addressed in future research studies.

Chapter 3: Study Rationale & Objectives

3.1 Rationale for the study

Older adults with dementia or cognitive impairment (CI) often face a higher risk of experiencing drug-related problems due to a combination of factors, including substantial comorbidities, polypharmacy (using multiple medications), and age-related physiological changes.[54,89,106] Existing literature reveals this population's high prevalence of drug-related problems (DRPs).[54] Moreover, there is a high prevalence of potentially inappropriate medication (PIMs) reported in this population using different implicit, explicit, or both criteria.[27,28] Ensuring the safe and appropriate use of medications is paramount in older adults, particularly those with cognitive impairment or dementia. DRPs can lead to adverse drug reactions, hospitalizations, reduced quality of life, and increased caregiver burden.[40]

Regular medication reviews are highly beneficial and often necessary for older adults with dementia and/or CI for several reasons. Several studies identified in the scoping review have demonstrated the benefits of medication reviews among this population. The findings from Wilchesky et al. and Dong et al. reported a significant reduction in medication use, particularly in the use of psychotropic medications.[82,83] Dong et al. reported an overall 28% decrease in the number of psychotropic drugs prescribed, with the largest decrease reported in antipsychotic use (49.66%).[83] Medication reviews help in identifying and discontinuing unnecessary medications.[107] Medication reviews help identify and address DRPs, such as dosage too high, inappropriate medications, potential drug-drug interactions, and potential drug-disease/condition interactions.[108] The studies conducted by Pearson et al. and Pfister et al. demonstrate the positive impact of pharmacist interventions, particularly medication reviews, in reducing the use of PIMs in older adults with dementia or CI.[54,84] Pearson et

al. reported a change in the mean number of PIMs in patients living with dementia from 1.5 PIMs per patient at baseline to 0.9 PIMs per patient at the 180-day follow-up after medication review.[84]

Although various tools and criteria have been developed to assist healthcare professionals in evaluating and optimizing medication regimens for older adults, there is no standardized tool that is specifically designed to guide medication reviews for older adults with dementia. Dr Patel's lab created a Medication Review in Cognitive Impairment and Dementia (MedRevCiD) checklist by using data gathered from a literature review, clinical experience, and a retrospective chart review conducted in patients who have received care at MINT memory clinics for CI and/or dementia.[62] The MedRevCiD checklist is a newly developed tool designed to facilitate medication reviews specifically for individuals with CI and/or dementia. The content of the MedRevCiD checklist was validated by a modified Delphi consensus study, where clinicians reviewed the most important aspects of medication use in persons with cognitive concerns.[62] Moreover, a feasibility study was also conducted to determine the perception of effectiveness, feasibility, and barriers and facilitators of the MedRevCiD checklist in identifying DRPs in people with CI before full-scale implementation.[62]

Comparing the performance of the MedRevCiD checklist to another tool with implicit criteria is an imperative step to validate further its effectiveness in identifying DRPs in this population. Therefore, it is necessary to compare the MedRevCiD checklist with the Medication Appropriateness Index (MAI) to ascertain their suitability for older adults with dementia or CI and to determine if MedRevCiD is better at identifying more DRPs than MAI. It is crucial to evaluate their performance to ensure the validity, efficacy, and

practical value of evaluation tools like the MedRevCiD checklist in clinical practice. This comparison will provide valuable insights into the strengths and potential areas for improvement of the MedRevCiD checklist, ultimately enhancing its utility in clinical practice. This comparison study is part of a series of studies aimed at validating the MedRevCiD checklist.

The researchers have developed various implicit and explicit measures to determine the prevalence and risk factors associated with using PIMs in older adults.[59,61] There is a scarcity of research on PIM use in older adults with cognitive impairment or dementia within Canada. This research gap underscores the need for further studies to understand better the prevalence, risk factors, and implications of PIMs in these individuals, particularly within the Canadian healthcare system. Very few studies have been conducted to explore PIM use in older adults with CI and/or dementia in Canada. Addressing this knowledge gap can contribute to improved medication management and the overall well-being of older adults with CI and/or dementia in Canada. Since the high prevalence of PIMs in older adults, there are recent updates in the most used explicit criteria (Beers Criteria 2023 and Screening Tool of Older Persons' Potentially Inappropriate Prescriptions (STOPP) criteria 2023).[28] This study will determine the prevalence of PIMs among the older population using the updated Beers 2023 and STOPP criteria 2023. Moreover, comparing the performance of assessment tools, such as the Beers Criteria and the STOPP criteria, is essential for determining which tool identifies more PIMs among older adults with CI and/or dementia.

Finally, it is essential to report specific key outcomes when researching medication reviews by pharmacists. Applicable core outcome sets proposed by Beuscart et al. and McGrattan et al. refer to studies examining medication reviews in multimorbid older adults with polypharmacy and for persons with dementia in primary care, respectively.[104,105] Medication over- and under-use, PIM, clinically significant DDI, medication side effects, adverse drug events, medication appropriateness, falls, and behavioural and psychological symptoms of dementia are core outcomes that can be examined when comparing the two instruments.

Therefore, this will be the first study to apply different criteria to identify and report DRPs among older adults with CI or dementia receiving care in these clinics. This study will also categorize the identified DRPs according to the Pharmaceutical Care Network Europe (PCNE) to ensure that DRPs identified through different tools, such as MedRevCiD and MAI, can be uniformly classified, strengthening the credibility of the research outcomes.

3.2 Research Hypothesis

We hypothesize that the MedRevCiD checklist will identify more DRP per patient than MAI in older adults with CI or dementia receiving care at primary care. We are expecting a difference of 1 mean DRP per patient between the MedRevCiD checklist and MAI, respectively.

3.3 Objectives

The primary objective of this research is to

- To compare the mean number of DRPs identified using the MedRevCiD checklist and MAI (gold standard) in older adults with CI or dementia

The secondary objectives of this research are:

- To identify which explicit tool, Beers Criteria or the STOPP, identify more PIMs use among older adults with CI or dementia

Chapter 4: Research Methodology

4.1 Study design and study setting

This research project was designed as a cross-sectional study and carried out at a Multi-specialty Interprofessional Team-based (MINT) memory clinic in Kitchener-Waterloo.

4.2 Study Location

MINT memory clinics are specialized healthcare facilities or departments that offer thorough examination, diagnosis, and treatment of memory and cognitive impairments.[109,110] MINT memory clinics are run by an interdisciplinary team of healthcare professionals who specialize in assessing, treating, and caring for patients suffering from memory-related conditions, such as Alzheimer's disease and other forms of dementia.[110,111]

4.3 Study participants

4.3.1 Sampling Strategy

For this study, a purposive sample approach was employed. This technique is a non-probability method used in research to select a specific group of individuals or elements from a larger population intentionally based on predetermined criteria or specific characteristics.[112,113] Purposive sampling is a deliberate participant selection method employed in cross-sectional studies. It enables researchers to efficiently target specific groups or individuals based on their relevance to the study's objectives, especially when limited resources or the population is small and diverse.[114]

4.3.2 Eligibility criteria

Participants included in this study were: 1) Older adult patients (age ≥ 65 years) (both genders); 2) diagnosed with dementia and cognitive impairment (CI); 3) receiving care at

MINT memory clinic; 4) taking one or more medications (prescription and over-the-counter medicine); 5) willing to provide consent. Consent from the caregiver was taken if the patient could not give consent.

The research excluded participants if they were: 1) Unwilling to give informed consent; 2) taking only Natural health products (NHP); 3) diagnosed with cognitive decline as a part of normal ageing.

4.3.3 Sample size

The sample size was determined in consultation with the statistician and determined by using R studio.[115] The sample size calculation was based on the primary research hypothesis. We assumed a mean difference of 1 point in the average number of identified drug-related problems (DRPs) per person using the Medication Review in Cognitive Impairment and Dementia (MedRevCiD) checklist and the Medication Appropriateness Index (MAI). Our assumption was based on the results of two previous studies. The first study, conducted in interdisciplinary primary care memory clinics, revealed an average of 1.9 DRPs per person.[116] In the second study by Hernandez et al. who employed the MAI criteria on patients with dementia, admitted controlling BPSD in a long-term care psychogeriatrics unit in an intermediate care hospital in Barcelona, Spain.[91] An average of 2.97 DRP per patient was reported, although the standard deviation was not provided.[91] We use a standard deviation of 1.8, which is almost similar to the Vincent study.[116] These two studies serve as a reference point to estimate the expected difference in DRP identification between the two tools. We determined the sample size with 80% statistical

power and 95% confidence. The total estimated minimum sample size required for the study was 28 patients.

pwr.t.test (d=1/1.8, sig.level=.05, power = .80, type='one.sample', alternative = 'two.sided')

4.4 Study procedures

4.4.1 Screening and recruitment

Participants with CI or dementia were recruited from a MINT Memory clinic between Jan and August 2023. Participant eligibility was assessed based on the inclusion and exclusion criteria. The consent to participate in the study was obtained if the participants met the eligibility criteria. If the patient could not give informed consent and caregivers were helping patients with their day-to-day activities, then the caregiver was approached to provide the consent to participate. An experienced pharmacist in the MINT memory clinic, and an investigator in the study (Tejal Patel), invited the patient to participate. This interaction involved providing the patient with information about the study and explaining its purpose, procedures, potential benefits, and associated risks. During this invitation, the pharmacist addressed the patient's questions or concerns about the study. The patient was provided with the opportunity to review written materials, ask questions, and take the necessary time to make an informed decision about whether they wanted to participate. If the patient agreed to participate, formal informed consent was obtained after ensuring the patient fully understood the study details. If the patient declined to participate, their decision was respected, and they were not enrolled in the study.

4.4.2 Data collection

For each patient included in the study, all the information related to patients was obtained from the electronic medical records. A standardized data collection form approved by the Office of Research Ethics was used to collect the following data from the participants (see Appendix B)

1. Gender, age, marital status
2. Social history: Smoking, Alcohol
3. Current medical problems, allergies, a recent history of falls
4. Prescribed medications (including dose, route of administration, regimen, directions, indication, start date)
5. Lab investigation specific to drugs causing DRPs.

The medications were classified based on the Anatomical Therapeutic Chemical (ATC) classification system. The ATC system is a globally recognized and accepted classification system for pharmaceuticals. The ATC system contains several levels of categorization and a hierarchical structure. It starts with anatomical groups (such as the organ or system a medicine operates on). Then, it gets more specific as it gets more to therapeutic subgroups and specific medicinal components. This hierarchical approach allows for the organization of drugs based on their properties and intended use.[117] The medication data encompassed prescribed and over the counter (OTC) drugs the patient administered daily.

Laboratory investigations specific to drugs causing DRPs were extracted from the patient medical records. As an illustration, if needed, the creatinine clearance (CrCl) for the study participants was determined from the patient serum creatinine level using the Cockcroft-Gault equation.[118]

4.4.3 Medication review

In this study, a patient chart review was conducted by a researcher (RS) for the participants included in the study. The researcher applied MAI criteria, MedRevCiD checklist, Beers criteria, and STOPP criteria for each study participant without looking at the pharmacists' and physicians' notes. After using these criteria, the researcher further reviewed the chart notes the pharmacist and the physician left during the visit. The process involved thoroughly assessing the patients' medications to identify potential DRPs. The researcher employed two distinct tools: the MAI and the MedRevCiD Checklist. The initial step in this review process was identifying and categorizing DRPs using the MAI criteria.

After completing the assessment using the MAI criteria and identifying the relevant DRPs, the researcher applied the MedRevCiD Checklist. The checklist helped uncover any additional DRPs that may not have been identified during the initial assessment with the MAI criteria. This two-step procedure made it possible to examine DRPs in greater detail, which helped to create a more comprehensive picture of the difficulties the research participants had when taking their medications. The review/application of the MedRevCiD checklist and MAI criteria was limited to one visit in this research study.

4.4.3.1 DRPs as per Medication Appropriateness Index (MAI)

The researcher (RS) determined the presence of DRPs in the patient using the MAI checklist. MAI is a well-established tool used in healthcare for the identification of DRPs in individual patients. It was developed to assess the appropriateness of medication use in older adults.[58] The MAI consists of 10 criteria worded as questions. By applying these criteria, the researcher could identify DRPs falling within various categories and systematically assess the appropriateness of medication use in the study participants.

1). Is there an indication for the drug?

2). Is the medication effective for the condition?

3). Is the dosage correct?

4). Are the directions correct?

5). Are the directions practical?

6). Are there clinically significant drug-drug interactions?

7). Are there clinically significant drug-disease/condition interactions?

8). Is there unnecessary duplication with other drugs?

9). Is the duration of therapy acceptable?

10). Is this drug the least expensive alternative compared to others of equal utility?

4.4.3.2 DRPs as per MedRevCiD Checklist

The researcher also employed the MedRevCiD checklist to identify DRPs among the study participants. Additionally, the researcher detected and reported DRPs that were not identified through the utilization of the MAI criteria. These identified DRPs were subsequently categorized into six domains, each encompassing clinical questions that required evaluation and assessment. This comprehensive approach allowed for a thorough analysis of medication-related issues in the research subjects.

- Medication Management and Adherence
- Drug Induced Cognitive Impairment or Worsening
- Conditions Associated with Cognitive Impairment and Dementia
- Treatment Options for Dementia

- Behavioral and Psychological Symptoms of Dementia
- Optimizing Medication Use

Each domain contains several clinical questions that help identify issues or DRPs in individuals with dementia or CI. Examples of these questions are: Is the patient taking any medications, or any combination of prescription over the counter or natural health products that can cause or worsen CI? (Domain 2); Some medical conditions can impact and/or worsen CI and/or dementia such as cardiomyopathy, depression, chronic obstructive pulmonary disease (COPD), falls, heart failure, sleep disorders, stroke, vitamin B12 deficiency etc. Does the patient have any of the following conditions and in your opinion, are they being optimally managed? (Domain3)

4.4.3.3 Potentially Inappropriate medication use

PIMs were identified using the Beers criteria 2023 and screening tool of older people's potentially inappropriate prescriptions (STOPP) criteria 2023. PIMs were categorized into the following categories

1. Independent of diagnosis
2. Dependent of diagnosis
3. Used with caution
4. Potentially clinically important drug-drug interactions
5. PIMs based on kidney function of the patient

4.4.3.4 DRPs categorized as per Pharmaceutical Care Network Europe (PCNE) criteria

The medications were documented and categorized based on the ATC classification system. Potential DRPs were detected and categorized according to their types and root causes, employing the PCNE classification system, particularly version 9.1, which was most recently revised in 2019.[30] The PCNE DRP classification system is a widely accepted and validated framework for classifying DRPs in different healthcare contexts. It includes five primary domains: Problems (P), Causes (C), Planned Interventions (I), Intervention Acceptance (A), and the Status of the DRP (O).

4.4.3.5 Pharmacist recommendations

The researcher examined the documentation in the medical record detailing the medication review conducted by the pharmacist during the patient's visit to memory clinics. Once the DRPs were identified, the researcher determined if there were any recommendations proposed by the pharmacist at the patient level, prescriber level, and drug level as mentioned in PCNE classification version 9.[30]

1. At prescriber level:
    a) Prescriber informed only
    b) Prescriber asked for information
    c) Recommendation proposed to prescriber
    d) Recommendation discussed with prescriber
2. At patient level:
    a) Patient (drug) counselling
    b) Written information provided (only)

c) Patient referred to prescriber

d) Spoken to family member/caregiver

3. At drug level:

a) Drug changed to …

b) Dosage changed to …

c) Formulation changed to …

d) Instructions for use changed to …

e) Drug paused or stopped

f) Drug started

4.4.3.6 Drug-drug interactions (DDI)

A drug-drug interaction (DDI) was characterized by one substance affecting the activity of another drug when both are taken concurrently, irrespective of whether adverse events are likely to happen.[119] For this study, all prescribed drugs were assessed using the Lexicomp database version 2021.03.01 to identify potential interactions between medications taken by patients.[120] Lexicomp is a comprehensive clinical drug information database and resource widely used in healthcare settings. It provides a range of information about medications, including prescription and over-the-counter drugs, herbal supplements, and more. These potential drug interactions were categorized based on their severity and the impact they could have on drug efficacy. In terms of the severity rating, DDIs were grouped into four categories: major, moderate, and minor interactions. A Major Drug-Drug Interaction (DDI) refers to a significant interaction between two or more drugs that can result in substantial clinical consequences. The risks associated with the simultaneous use

of these agents typically outweigh the benefits, and, as a general guideline, concurrent use of these medications should be avoided.[120] Moderate DDIs were interactions that have a clinically noticeable impact but may not be as severe as major interactions. The benefits of concurrent therapy may still outweigh the risks in many cases. A patient-specific assessment is imperative to evaluate whether the advantages of concurrent therapy outweigh the potential risks. Specific actions must be undertaken to optimize the benefits and/or mitigate the risks associated with the simultaneous use of the agents.[120] Minor DDIs are interactions that typically have little or no clinical impact. The benefits of concurrent therapy usually outweigh the minimal or negligible risks. To identify potential adverse effects, it is crucial to implement an appropriate monitoring plan. In certain cases, dosage adjustments for one or both agents may be necessary to optimize patient outcomes.[120] The focus here was solely on assessing the risk of potential unfavorable outcomes associated with drug interactions.

4.4.4 Follow-ups

Follow-up was completed at 1-month post-implementation of the medication review process to report the status of the DRP (problem solved, a problem not solved, problem partially solved).

4.5 Study outcomes

The following outcomes are reported in this study:

- ❖ DRPs identified using the MedRevCiD checklist compared to MAI
    - Total and average number of DRPs

- The proportion of patients identified with at least one DRP using the MedRevCiD checklist and MAI

❖ PIMs identified using the Beers criteria and STOPP criteria

- Total and average number of PIMs per patient
- Type of PIMs
- The proportion of patients identified with at least one PIM using both tools

❖ Categorized all DRPs identified using MedRevCiD and MAI using the PCNE criteria V9

- Type of DRPs
- The proportion of patients identified with major, moderate, and minor DDI using Lexicomp database

4.6 Statistical Analysis

The statistical analysis was carried out utilizing the IBM Statistical Package for Social Science Statistics for Windows, Version 24.0 (SPSS Inc., Chicago, Ill., USA), and STATA version Stata/SE 15.0 for Windows (Cor, 2017).[121,122] For describing population characteristics and medication use, percentages were used to represent categorical variables, while mean ± standard deviation (SD) or median ± interquartile range (IQR) were used to describe continuous variables, depending on the data's normalcy distribution. The student- t test or Mann Whitney U was used for continuous variable to compare the baseline demographics and clinical characteristics between two groups (Patients with DRPs versus Patients without DRPs). Between- group differences among the categorical variables were analyzed using the Fisher's exact test due to sample size less than 50.

Bivariate logistic regression analysis was employed to identify potential factors associated with using DRPs and PIMs, including patient demographics such as age and gender, as well as clinical characteristics like the number of comorbidities and the number of prescribed medications. The results are presented as odds ratios (ORs) and 95% confidence interval (CIn). A P-value less than 0.05 was considered to indicate statistical significance.

The Wilcoxon signed rank test was used to assess whether there is a significant difference in the number of DRPs identified by the MedRevCiD versus MAI. The Wilcoxon test was employed because the data was not normally distributed. This is a non-parametric statistical test that is usually used to detect whether there is a significant difference between two similar groups or conditions.

The McNemar test was used to compare the distribution of the patients with DRPs identified by the MedRevCiD checklist versus the MAI criteria. The McNemar test is a statistical test used to analyze paired categorical data, especially when determining whether there is a significant change in the distribution of a binary outcome (e.g., yes/no, presence/absence) under two different categories.

4.7 Ethics clearance

The Office of Research Ethics at the University of Waterloo granted this research project ethical clearance under the reference number ORE#44673 (detailed information can be found in Appendix C). Approval to conduct the study was also obtained from the Centre for Family Medicine, Family Health Team. Throughout the recruitment phase, all participants or their caregivers willingly provided signed informed consent to participate

in the study. Detailed information on the approved information letter, verbal script, consent form, and thank you letter for participants or caregivers can be found in Appendix D.

Chapter 5: Results

5.1 Patient demographics and clinical characteristics

5.1.1 Baseline demographics

Over nine months, 44 patients were enrolled in the study. Among the participants, 20 individuals, which accounts for 45.5% were female, while 24 individuals (54.5%) were male. The average age of the study patients was 80.2 years (Standard Deviation (SD) 6.2). One-fourth (n = 11) of the patients were aged ≥ 85 years, followed by 60% (n= 26), aged between 75 and 84 years. Table 5-1 presents a comprehensive overview of the baseline demographic information of the study participants.

Table 5-1: Study participants demographics

Characteristics	**Total (N= 44) n (%)**
Age of the patient, mean ± SD	80.2 ± 6.2
65- 69 years	2 (4.5)
70- 74 years	5 (11.5)
75- 79 years	13 (29.5)
80- 84 years	13 (29.5)
≥ 85 years	11 (25)
Sex	
Male	24 (54.5)
Female	20 (45.5)

Marital Status	
Married	38 (86.4)
Separated	1 (2.2)
Widowed	5 (11.4)
Alcohol	
Never	20 (45.5)
Occasional drinker	11 (25)
Active regular drinker	13 (29.5)
Smoking	
Never	24 (54.5)
Ex-smoker	17 (38.7)
Active smoker	3 (6.8)

*Occasional drinker: Occasional drinkers may have a drink during social gatherings, celebrations, or other special events, but they do not regularly consume alcohol as part of their daily or weekly routine.

Active regular drinker: Regularly consume alcohol or most of the days of the week as part of their daily routine

5.1.2 Study participants clinical characteristics

Among 44 patients, 36.4 % (n= 16) patients had mild cognitive impairment (MCI), followed by one-fifth of patients (n= 9) who had mixed dementia, and 11.4% (n= 5) patients had vascular cognitive impairment, as described in Table 5-2.

Most study participants (61.4%, n= 28) had six or more comorbidities, (mean number of comorbidities was 6.7 ± 3.4). Around one-fifth of the patients (n= 9) had ≥ 9, followed by

41% (n= 18) had 6 to 8 comorbidities. Interestingly, there was only one patient who did not have any comorbidities, as described in Table 5-2. The most common comorbidities were hypertension (63.6%, n= 28), followed by hyperlipidemia (including hypercholesterolemia) (31.8%, n= 14), chronic kidney disease (27.2%, n= 12), and obstructive sleep apnea (25% n= 11). Furthermore, half of the patients (52.3%, n= 23) had a history of falls, as described in Table 5-2. Table 5-3 gives information about the most common comorbidities among study participants.

Table 5-2: Study participants clinical characteristics

Clinical characteristics	**Total (N= 44) n (%)**
Cognitive Impairment/dementia	
Mild CI	16 (36.4)
Mixed dementia	9 (20.5)
Vascular CI	5 (11.4)
Subjective cognitive decline	4 (9.1)
Dementia	4 (9.1)
Evolving neurocognitive disorder	3 (6.8)
Probable or possible Alzheimer's disease	3 (6.7)
Comorbidities	
Number of comorbidities per person, mean ± SD	6.7 ± 3.4
0	1 (2.3)
1- 5	16 (36.3)
6- 8	18 (41)

≥ 9	9 (20.4)
Recent history of falls	
Absent	21 (47.7)
Present	23 (52.3)

SD, Standard deviation

Table 5-3: Distribution of most commonly occurring comorbidities among study participants

Disease	**(N=44) n (%)**
Hypertension	28 (63.6)
Hyperlipidemia (including Hypercholesterolemia)	14 (31.8)
Chronic kidney disease	12 (27.2)
Obstructive sleep apnea	11 (25)
Benign prostate hyperplasia	10 (22.7)
Type 2 diabetes mellitus	9 (20.4)
Osteoporosis	8 (18.1)
Osteoarthritis	8 (18.1)
Gastroesophageal reflux disease	8 (18.1)
Asthma	8 (18.1)
Hyperlipidemia	8 (18.1)
Anxiety	7 (15.9)
Hypothyroidism	7 (15.9)
Transient ischemic attack	6 (13.6)

Cerebrovascular accident	6 (13.6)
Myocardial infarction	5 (11.3)
Vitamin B12 deficiency	4 (9)
Coronary artery disease	4 (9)
Glaucoma	4 (9)
Peripheral neuropathy	4 (9)
Atrial fibrillation	4 (9)
Migraine	4 (9)
Depression	4 (9)
Congestive heart failure	4 (9)
Diverticulosis	3 (6.8)
Fibromyalgia	3 (6.8)
Erectile dysfunction	3 (6.8)
Colonic polyps	3 (6.8)
Thyroid nodule	3 (6.8)
Others	71
Total number of diagnoses	273 in 44 participants

*Others:- Diagnosis reported in ≤ 2 patients

Anemia=2; Lower urinary tract symptoms=1; Sinus bradycardia=2; Rheumatoid arthritis=1; Angioedema=1; Seborrheic dermatitis=2; Cardiomyopathy=2; Third degree heart block=2; Insomnia=2; Chronic obstructive pulmonary disease=1; Dyslipidemia=1; Agitation=2; Hepatic encephalopathy=1; Hepatitis=2; Right Bundle Branch Block=2; Vitamin D deficiency=1; Urinary tract infections=1; Parkinson=1; Ischemic heart diseas=2; Type 1 diabete1; Lumbar degenerative disc disease=1; Postural dizziness=1; Renal cysts=2; Cutaneous T cell lymphoma=1; Penile lichen sclerosis=1; Hyponatremia=1; Microscopic colitis=1; Seborrheic keratosis=1; Short lip of Barrett's esophagus=1; Carpal tunnel syndrome=1; Sjogren’s syndrome=2; Invasive malignant melanoma=1; Celiac disease=1; Overactive bladder=1; Ischemic white matter disease=1; Alcohol use disorder=1; Fatty alcoholic liver=1; Right posterior frontal meningioma=1; Umbilical hernia=1; Gout=1; Psoriasis=2; Allergic rhino conjunctivitis=1; Lyme arthritis=1; Invasive mammary carcinoma=1; Polymyalgia rheumatica=1; Benign multinodular goiter=1; Irritable bowel syndrome=1; Sick sinus syndrome=1; Restless leg syndrome=1; Varicose

veins=1; Gastrointestinal bleeding=1; Basal cell carcinoma=2; Mitral valve sclerosis=1; Valvular heart disease=1; Parry-Romberg disease=1; Seizure=1; Vision impaired- non artery ischemic ophthalmic neuropathy=1

5.2 Medication use among the study participants

The medication prescribed among the study participants was categorized by Anatomical Therapeutic Chemical (ATC) codes, as presented in Table 5-4. A total of 375 medications were prescribed among the 44 study participants. The median number of medications per day was 7.5 (interquartile six medications per day). The number of prescribed medications per person daily ranged from 1 to 21. Almost half of the study participants (47.7%, n= 21) were prescribed 5-9 medications per day (polypharmacy), and 38.6% (n= 17) were prescribed ≥10 medications per day (hyper polypharmacy). The three most frequently prescribed medication categories were from the nervous system (81.8%, n= 36), followed by the cardiovascular system (81.8%, n= 36), and blood and blood-forming organs (77.3%, n= 34). Table 5-4 provides information about the medication utilization among the study participants based on the ATC classification.

Table 5-4:- Medication use among the study participants according to ATC classification

Characteristics	**Total (N= 44)** **n (%)**
Number of medications per person, median (IQR)	7.5 (6)
Medications per day	
1- 4	6 (13.6)
5- 9	21 (47.7)
≥10	17 (38.6)

ATC classification	
G Genito urinary system and sex hormones	16 (36.4)
A Alimentary tract and metabolism	32 (72.7)
B Blood and blood forming organs	34 (77.3)
C Cardiovascular system	36 (81.8)
S Sensory organs	4 (9.1)
N Nervous system	36 (81.8)
L Antineoplastic and immunomodulating agents	4 (9.1)
H Systemic hormonal preparations	7 (15.9)
R Respiratory system	9 (20.5)
M Musculo-skeletal system	8 (18.2)
D Dermatological	7 (15.9)

5.3 Identified drug-related problems (DRPs)

5.3.1 Comparison of number of DRPs between the MedRevCiD checklist and MAI criteria

In this section, we present the results of the Wilcoxon signed-rank test, which assessed whether there is a significant difference between the number of DRPs identified using the MedRevCiD checklist and MAI criteria. Table 5-5 shows the mean number of DRPs and minimum-maximum DRPs identified using the MedRevCiD checklist and MAI criteria. In 28 patients, the number of DRPs identified using MAI criteria was less than the number of DRPs identified using the MedRevCiD checklist, as shown in Table 5-6. A Wilcoxon signed rank test revealed a significant difference in the number of DRPs identified using

MAI criteria versus the MedRevCiD checklist, Z= -4.8, p-value= <0.001. In simpler terms, a significant negative Z value -4.806 in the context of the Wilcoxon signed-rank test suggests that the second variable (DRPs as per MedRevCiD) tends to be higher than the first variable (DRPs as per MAI criteria).

Table 5-5: Wilcoxon Signed Ranks test

	N	**Mean ± SD**	**Range**
Number of DRPS as per MedRevCiD	44	3.05 ± 4.0	0- 20
Number of DRPS as per MAI	44	1.84 ± 2.9	0- 14

Table 5-6: Test statistics of Wilcoxon signed rank test

		N	**Mean Rank**	**Sum of Ranks**	**Z**	**P-value (2-tailed)**
Number of DRPs as per MAI- Number of DRPs as per MedRevCiD	Negative ranks	28[a]	14.50	406.00	-4.8[b]	<0.001
	Positive ranks	0[b]	0.00	0.00		
	Ties	16[c]				
	Total	44				

a. Number of DRPs as per MAI< Number of DRPs as per MedRevCiD

b. Number of DRPs as per MAI> Number of DRPs as per MedRevCiD

c. Number of DRPs as per MAI= Number of DRPs as per MedRevCiD

P-value <0.05 considered statistically significant

5.3.2 DRPs identified as per Medication Review in Cognitive Impairment and Dementia (MedRevCiD) checklist and Medication Appropriateness Index (MAI) criteria

A total of 134 DRPs were identified in 44 patients using the MedRevCiD checklist, giving a median of 2 (minimum-maximum range 0- 20) DRPs per patient. Whereas 81 DRPs were identified in 44 patients per MAI criteria, with a median of 2 (min-max range 0- 14) DRPs per patient. Figure 5-1 and Table 5-7 provide the distribution of patients with DRPs per MedRevCiD and MAI criteria. At least one DRP was identified in 81.8% (n= 36) and 56.8% (n= 25) of the study population using the MedRevCiD checklist and MAI criteria, respectively. Almost one-tenth of the study participants had eight or more DRPs per the MedRevCiD checklist. The number of patients identified with eight or more DRPs using MAI criteria was less than those in another group (6.8%, n= 3). One important thing to note is that the difference in the total number of DRPs identified using the MedRevCiD checklist versus the MAI criteria was 53 (see Table 5-7).

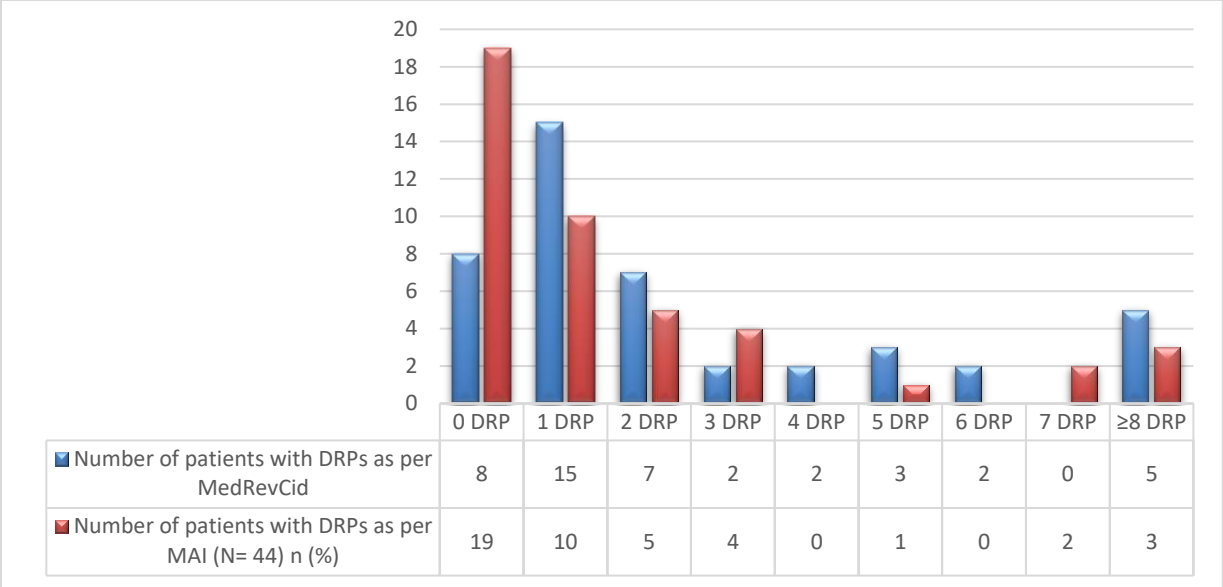

Figure 5-1:- Distribution of number of patients with DRPs as per MedRevCiD and MAI criteria

Table 5-7:- DRPs as per MedRevCiD and MAI criteria

Characteristics	**DRPs as per MedRevCiD (N= 44) n (%)**	**DRPs as per MAI (N= 44) n (%)**
0 DRP	8 (18.2)	19 (43.2)
1 DRP	15 (34.1)	10 (22.7)
2 DRP	7 (16)	5 (11.4)
3 DRP	2 (4.5)	4 (9.1)
4 DRP	2 (4.5)	0 (0)
5 DRP	3 (6.8)	1 (2.3)
6 DRP	2 (4.5)	0 (0)
7 DRP	0 (0)	2 (4.5)

≥8 DRP	5 (11.4)	3 (6.8)
Total number of DRPs, (min- max)	134 (0- 20)	81 (0- 14)
Average number of DRPs per patient, mean ± SD	3.05 ± 4.0	1.84 ± 2.9
Median (IQR)	2 (4)	2 (3)

SD, Standard deviation; IQR, Inter Quartile Range

5.3.3 Characterization of DRPs using MedRevCiD checklist

As mentioned earlier, 134 DRPs were identified among 44 patients using the MedRevCiD checklist. The average number of DRPs identified was 3.05 ± 4.0 DRPs per person. Notably, more than half of the DRPs (53%, n= 71) identified fell into domain 6 of the MedRevCiD checklist (optimizing medication use), followed by 17.1% (n= 23) of the identified DRPs from domain 2 (drug-induced cognitive impairment or worsening), 12.6% (n= 17) identified DRPs were from domain 1 (medication management and adherence), 9.7% (n= 13) DRPs were from domain 3 (conditions associated with CI and dementia), and 3.8% (n=5) of the identified DRPs were from domain 4 (treatment options for dementia) and domain 5 (behavioral and psychological symptoms of dementia) each, respectively (see Figure 5-2).

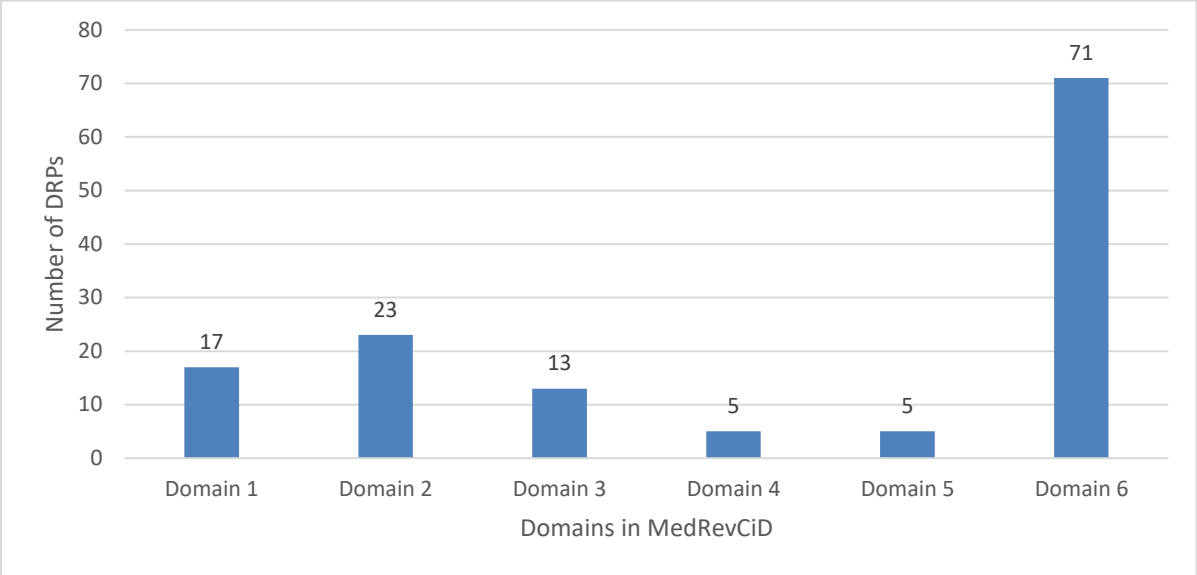

Figure 5-2:- Number of DRPs in each domain of MedRevCiD

5.3.3.1 DRPs identified from the Domains of MedRevCiD checklist

Domain 1: Medication Management and Adherence

A total of 17 DRPs were identified under this domain. The distribution of DRPs in each domain of MedRevCiD is summarized in Table 5-8. Out of 17 DRPs identified, 6 DRPs were related to intentional non-adherence to drugs. As an illustration, one patient in the study was diagnosed with benign prostate hyperplasia, and the patient was prescribed tamsulosin 0.4 milligrams (mg) once daily. During the medication review, it was found that the patient was non-adherent to tamsulosin, but it appears to have been an intentional decision. Another example of DRPs from this domain is one of the patients in the study who was prescribed vitamin B12 1000 micrograms (mcg) once daily and atorvastatin 20 mg once daily in the evening. There were intentional and unintentional non-adherence related DRPs identified in the same patient. The patient was not taking vitamin B12 doses intentionally. On the other hand, it was difficult for the patient to remember to take

atorvastatin at night. So, the patient was missing a few doses unintentionally. Additionally, one of the patients identified with poor medication adherence, which was related to functional impairment. Only 2 DRPs found were related to inappropriate medication management. There were some issues with the wrong medication packaging in the dosette box in one of the patients.

Domain 2: Drug induced cognitive impairment or worsening

In this domain, the use of medications that may cause or worsen CI were identified in the study participants during the medication review and were reported as DRPs in this study (see domain 2 of Table 5-8). A total of 23 DRPs were identified from domain 2. A total of 16 drugs have been identified in this domain that were identified as DRPs. The most common drugs marked as DRPs from this domain were gabapentin (3 DRPs) and oxycodone (3 DRPs), followed by zopiclone (2 DRPs), hydromorphone (2 DRPs), and methocarbamol (2 DRPs).

Domain 3: Conditions associated with CI and dementia

This domain focuses on medical conditions which may impact or worsen cognition. During the medication review, the researcher looked at commonly encountered conditions in this population which can potentially impact or worsen CI. The following examples of questions are included in this domain: *Does the patient have any of the conditions which can potentially impact or worsen CI? Are they optimally managed?* Almost 10% (n= 13) of DRPs were reported from this domain. The most common condition that impacts CI and/or dementia is vitamin B12 deficiency. For example, one patient had MCI, and another was diagnosed with mixed dementia. The vitamin B12 level reported in both patients was

<300 picomoles per liter (pmol/L). Ideally, patients should be taking Vitamin B12 supplementation, but one of the patients was not taking any supplementation, and another was taking the supplementation as needed. Another medication condition identified as DRP from this domain was atrial fibrillation. The patient had atrial fibrillation and was treated with warfarin, an anticoagulant medication. So, ideally, the targeted International Normalized Ratio (INR) should be between 2- 3. The INR reported in the patient was 3.2, which was out of the target range. So, atrial fibrillation is reported as a DRP in this domain.

Domain 4: Treatment option for Dementia

This domain focuses on anti-dementia drugs, especially if the patient takes a cholinesterase inhibitor (AchEI) or memantine. During the medication review, a total of 5 DRPs were identified from this domain. Two DRPs were identified, in which the patient was taking AchEI with medications that can result in bradycardia, such as bisoprolol (beta-blocker) and amiodarone (antiarrhythmic agents). One of the DRPs identified was related to the side effects patients experienced from using donepezil (AchEI).

Domain 5: Behavioral and psychological symptoms of dementia

Domain 5 of the MedRevCiD checklist determines if antidepressant and/or antipsychotic therapy should be initiated or if current antidepressant and/or antipsychotic therapy is indicated, effective, and safe. A total of 5 DRPs were identified from domain 5 of the MedRevCiD checklist. Out of 5 DRPs, 2 DRPs were related to mirtazapine (tetracyclic antidepressant) use, as it was not effective for insomnia in one patient, and more disrupted sleep was reported due to its use. A decrease in hemoglobin level due to duloxetine use was reported in one patient (refer to domain 5 of table 5-8).

Domain 6: Optimizing medication use

This domain focuses on assessing and addressing ways to improve a patient's medication regimen's effectiveness, safety, and appropriateness. More than half of the DRPs identified using MedRevCiD belong to this domain. Domain 6 consists of 8 questions assessing and optimizing medication use to ensure that patients receive the most effective and safe treatment. The questions covered in domain 6 of MedRevCiD are like MAI criteria questions. For example, are there any clinically significant drug-drug interactions? Drug-disease/conditions interactions? Is each medication being taken at the appropriate dose and duration for its reason for use? Domain 6 also refers to explicit criteria such as Beers or STOPP criteria to assess the appropriateness of medications. So, if they were identified as DRPs and didn't fall under any other five domains, all the medications were covered under this domain. All the other five domains of MedRevCiD were very specific to CI or dementia populations, but domain 6 is more general regarding drugs and disease. As an illustration, acetaminophen, methocarbamol, and cannabidiol likely provide minimal benefit for pain control for peripheral neuropathy and affect cognition. So, these medications were not effective for the reason of its use. Seven DRPs were related to medications that were not being taken at the appropriate dose and duration for their reason for use. There were 15 clinically important drug-drug interactions reported. One patient has been prescribed a combination of ≥3 of these CNS-active drugs (Gabapentin + Sertraline (Selective Serotonin Reuptake Inhibitor (SSRI)) + Oxycodone (Opioids). From the clinically significant drug-disease interactions category, major DRPs were identified for drugs prescribed to patients with a history of falls or fractures (see domain 5; subsection 6.5 from Table 5-8). There are a few other important DRPs identified, such as the use of

lorazepam, which is contraindicated in patients with sleep apnea, and aspirin use in asthma patients. 6.7 subsection of domain 6 covers all the potentially inappropriate medications (PIMs) identified using Beers and/or STOPP criteria. PIMs mentioned in subsection 6.7 of domain six were not identified as DRPs in the other five domains of MedRevCiD. For example, the use of atypical antipsychotics was identified as DRP in older adults, irrespective of diagnosis. Another example of DRP is using sertraline, and escitalopram in patients with a history of falls as per Beers and STOPP criteria.

Table 5-8:- DRP identified as per MedRevCiD

Domain	**Drugs with DRP (N= 134) n (%)**
1. Medication management and adherence	
Non-adherence to drug (intentional decision)	6 (4.4)
Inappropriate medication management	2 (1.4)
Poor medication adherence due to functional impairment	1 (0.7)
Difficult to remember to take drugs at evening or night	1 (0.7)
Medication being taken at the wrong dose (Patient administering drug once a day, but label indicates to take twice daily)	1 (0.7)
Missed few doses of medication (Unintentionally)	4 (3)
Unable to determine adherence to insulin as patient is self-dosing but unable to indicates how he decides and adjusts his insulin dosing	1 (0.7)

Choking/gagging with big medications (Janumet, Acetaminophen)	1 (0.7)
Total DRPs in domain 1	17 (12.6)
2. Drug induced CI or worsening	
Pregabalin (Gabapentinoids) due to increased risk of cognitive effects	1 (0.7)
Oxycodone (Opioid analgesic) due to impaired cognitive effects & falls	3 (2.2)
Lorazepam (Benzodiazepine)	1 (0.7)
Zopiclone (Hypnotic Z-drug)	2 (1.4)
Tapentadol (Opioid)	1 (0.7)
Codeine (Opioid)	1 (0.7)
Cyclobenzaprine (Skeletal muscle relaxant)	1 (0.7)
Bilastine (Antihistamine)	1 (0.7)
Doxepin (Tricyclic Antidepressant)	1 (0.7)
Solifenacin (Antimuscarinics agents)	1 (0.7)
Darifenacin (Antimuscarinics agents)	1 (0.7)
Hydromorphone (Opioid analgesic)	2 (1.4)
Methocarbamol (Skeletal muscle relaxant)	2 (1.4)
Cannabidiol (Cannabinoid)	1 (0.7)
Gabapentin (GABA analog)	3 (2.2)
Medical marijuana	1 (0.7)

Total DRPs in domain 2	23 (17.1)
Domain 3. Conditions associated with Cognitive impairment and dementia	
Vitamin B12 deficiency (target level 300 pmol/L)	2 (1.4)
Sleep apnea may affect cognition	1 (0.7)
Atrial fibrillation (Patient is on warfarin, but the patient's INR out of target range (2-3)	1 (0.7)
Allopurinol + Warfarin (Severe DDI as per Anticoagulant clinic) Benefit outweigh risk	1 (0.7)
Warfarin + Dabigatran (Severe DDI as per Anticoagulant clinic) Benefit outweigh risk	1 (0.7)
Warfarin + Rosuvastatin (Moderate risk as per Anticoagulant clinic) Benefit outweigh risk	1 (0.7)
Warfarin + Acetaminophen (Moderate risk as per Anticoagulant clinic) Benefit outweigh risk	1 (0.7)
Warfarin + Levothyroxine (Moderate risk as per Anticoagulant clinic) Benefit outweigh risk	1 (0.7)
Hepatic encephalopathy given alcohol use	1 (0.7)
Untreated Lacunar Infarct	1 (0.7)
Hypertension (target is <140/90 mmhg in non-frail older adults with dementia or CI)	1 (0.7)
Blood pressure on the low end as patient is taking Candesartan (Angiotensin II receptor blocker)	1 (0.7)

Total DRPs in domain 3	13 (9.7)
Domain 4: - Treatment options for dementia	
Darifenacin (Antimuscarinics agents) + Donepezil (Acetyl cholinesterase inhibitor)→ Anticholinergic Agents may diminish the therapeutic effect of Acetylcholinesterase Inhibitors→ Darifenacin can be safely tapered	1 (0.7)
Galantamine – no benefit of cognition as scores are declining	1 (0.7)
Donepezil (Acetylcholinesterase inhibitor) + Bisoprolol (Drugs that induce persistent bradycardia (beta-blocker)→ risk of cardiac conduction failure, syncope, and injury	1 (0.7)
Patient's experiencing side effects (Weight loss) of cholinesterase inhibitor (Donepezil)	1 (0.7)
Amiodarone (Antiarrhythmic agents, bradycardia-causing agents) + Donepezil (Acetylcholinesterase inhibitor, bradycardia-causing agents)→ enhance bradycardic effect Enhance QTc-prolonging effect (Benefits outweigh risk) (Indeterminate Risk - Caution)	1 (0.7)
Total DRPs in domain 4	5 (3.8)
5. Behavioral and psychological symptoms of dementia	
Mirtazapine not effective for insomnia	1 (0.7)
More disrupted sleep due to Mirtazapine use	1 (0.7)

If the patient's BPSD (delusions, agitation, Insomnia) is not responding to lower risk medications for BPSD (e.g., SSRIs or anticonvulsants) is an antipsychotic medication required for the behavior you wish to treat? → Lower risk medications were never tried for the patient's BPSD; patients directly started with Risperidone (atypical antipsychotic) for BPSD.	1 (0.7)
Duloxetine-decrease in hemoglobin level	1 (0.7)
Citalopram not optimally effective for Anxiety (BPSD)	1 (0.7)
Total DRPs in domain 5	5 (3.8)
6. Optimizing medication use	
6.1 Does every medication being taken have an appropriate reason for use?	
Reason for use of Aspirin not clear as patient determined not to have transient ischemic attack when presenting with visual symptoms	1 (0.7)
Ezetimibe (No hypercholesterolemia noted)	1 (0.7)
Reason for use of aspirin is not established	1 (0.7)
Need for Amiodarone is not clear	1 (0.7)
6.2 Is each medication effective for its reason for use	
Premarin vaginal cream for urinary incontinence (Incontinence for years, worsening in the past few months)	1 (0.7)

Acetaminophen and methocarbamol likely providing minimal benefit for pain control for peripheral neuropathy and affect cognition	1 (0.7)
Cannabidiol likely providing minimal benefit for pain control for peripheral neuropathy and affect cognition	1 (0.7)
Elevated blood pressure on visit, patient currently prescribed Candesartan (Angiotensin II receptor blocker)	1 (0.7)
Mirabegron- likely limited benefit for urinary incontinence	1 (0.7)
6.2 Is each medication being taken at the appropriate dose and duration for its reason for use?	
Ramipril	1 (0.7)
Metoprolol	1 (0.7)
Acetaminophen dosage too high	1 (0.7)
Pantoprazole use >4weeks unless for high-risk patients	1 (0.7)
Fenofibrate dosage should be less than ≤67 mg if the patient's CrCl >30 to 80 mL/minute	1 (0.7)
Pseudoephedrine and Ibuprofen use regularly, instead of PRN	1 (0.7)
Low acetaminophen dose (administer four time per day in nursing home is costly)	1 (0.7)
6.3 Is there any clinically significant drug-drug interactions	
Oxycodone + Pregabalin (Anticonvulsants, CNS depressant)	1 (0.7)
Lorazepam (Benzodiazepine) + Oxycodone (Opioid analgesic)	1 (0.7)

Lorazepam + Tapentadol (Opioid analgesic)	1 (0.7)
Cyclobenzaprine + Oxycodone (Opioid analgesic)	1 (0.7)
Cyclobenzaprine + Tapentadol	1 (0.7)
Doxepin + Oxycodone (Opioid analgesic)	1 (0.7)
Doxepin + Tapentadol	1 (0.7)
Oxycodone (Opioid analgesic) + Tapentadol	1 (0.7)
Zopiclone + Oxycodone (Opioid analgesic)	1 (0.7)
Zopiclone + Tapentadol	1 (0.7)
Doxepin (TCA) + Lorazepam (Benzodiazepines) + Tapentadol/Oxycodone (Opioids) + Cyclobenzaprine (Skeletal muscle relaxant)→ Any combination of ≥3 of these CNS-active drugs	1 (0.7)
Cyclobenzaprine (AC) + Doxepin >6mg/day (AC)	1 (0.7)
Brimonidine and timolol (Beta blockers, non-selective) + Symbicort (Budesonide and Formoterol)→ Beta blocker may dimmish the broncho dilatory effect of Symbicort	1 (0.7)
Gabapentin + Oxycodone (Opioid)	1 (0.7)
Gabapentin + Sertraline (SSRI) + Oxycodone (Opioids)→ Any combination of ≥3 of these CNS-active drugs	1 (0.7)
6.5. Clinically significant Drug-disease	
Timolol in Sinus Bradycardia	1 (0.7)
Dementia or CI	

• Doxepin >6mg/day (Antidepressant with strong Anticholinergic properties)	1 (0.7)
• Cyclobenzaprine (Muscle relaxant, Anticholinergic)	1 (0.7)
• Lorazepam (Benzodiazepine)	1 (0.7)
History of falls or fractures	
• Doxepin >6mg/day (Antidepressant with strong Anticholinergic properties)	1 (0.7)
• Cyclobenzaprine (Anticholinergic)	1 (0.7)
• Lorazepam (Benzodiazepine)	1 (0.7)
• Oxycodone (Opioid)	2 (1.4)
• Tapentadol (Opioid)	1 (0.7)
Constipation	
• Oxycodone (Opioid)	1 (0.7)
• Tapentadol (Opioid)	1 (0.7)
Sleep apnea	
• Lorazepam is contraindicated	1 (0.7)
Asthma	
• Aspirin is contraindicated	1 (0.7)
• Brimonidine and timolol	1 (0.7)
6.7 Inappropriate medications	

Duloxetine initiated (Monitor sodium levels closely when starting or changing dosages in older adults, but sodium level last checked one year back in patient)	1 (0.7)
Celecoxib (NSAID's, COX-2) in patient with eGFR level 40 ml/min/1.73m^2	1 (0.7)
Atypical Antipsychotics (Risperidone, Quetiapine) as per Beers criteria	2 (1.4)
Danazol (synthetic male testosterone)- Avoid unless indicated for confirmed hypogonadism with clinical symptoms as per Beers criteria	1 (0.7)
Apixaban (Factor Xa inhibitor) as per STOPP criteria	1 (0.7)
Gabapentin <60ml/min (Maximum recommended dose is 600 mg/day)- as per Beers criteria	1 (0.7)
Gabapentin (CNS Depressants) + Hydromorphone (Opioid agonists)→ Increased risk of severe sedation-related adverse events, including respiratory depression and death—as per Beers criteria	1 (0.7)
Amiodarone as per Beers and STOPP criteria	1 (0.7)
Rivaroxaban as per Beers and STOPP criteria	1 (0.7)
Gabapentin for non-neuropathic pain	1 (0.7)
History of falls	
• Sertraline (SSRI) as per Beers criteria and STOPP criteria	3 (2.2)

• Citalopram (SSRI) as per Beers criteria and STOPP criteria	3 (2.2)
• Escitalopram (SSRI) as per Beers criteria and STOPP criteria	1 (0.7)
• Duloxetine (SNRI) in patient with history of recent falls as per Beers criteria	2 (1.4)
• Zopiclone as per Beers and STOPP	1 (0.7)
• Risperidone (Atypical Antipsychotics)	1 (0.7)
• Codeine (Opioid) as per Beers and STOPP criteria	1 (0.7)
History of Insomnia	
• Zopiclone use for ≥ 2 weeks as per STOPP criteria	1 (0.7)
Duplicate therapy	
Duplicate therapy (Oxycodone, Tapentadol)	1 (0.7)
Total DRPs in domain 6	71 (53)

BPSD, Behavioral and Psychological Symptoms of Dementia; SSRI, Selective Serotonin Reuptake Inhibitors; SNRI, Serotonin-Norepinephrine Reuptake Inhibitors; CrCl, Creatinine Clearance; PRN, Pro re nata; CNS, Central nervous system; TCA, Tricyclic Antidepressant; AC, Anticholinergics; NSAID's, Non-Steroidal Anti-Inflammatory Drugs; COX, Cyclooxygenase; eGFR, estimated Glomerular Filtration Rate

5.3.4 Characterization of DRPs using MAI criteria

A total of 81 DRPs were identified among 44 patients using MAI criteria. The mean number of DRPs identified was 1.84 ± 2.9 DRPs per person. The MAI criteria consist of 10 questions to assess the appropriateness of medication. The criteria with the highest number of DRPs (44.4%, n= 36) were from the clinically significant drug-disease/condition interactions, followed by 28.3% (n= 23) in clinically significant drug-drug interaction, 11.2% (n= 9) DRP in medication effectiveness for the condition, 8.7%

(n= 7) DRPs in the correct dosage, and 5% (n= 4) DRPs in the indication for the drug. Only one DRP was identified for unnecessary duplication, and another for the duration of therapy was unacceptable. Notably, all the DRPs identified using the MAI criteria were also covered in the MedRevCiD checklist domains. No DRPs were found that were identified using the MAI criteria but not addressed in the MedRevCiD checklist. Furthermore, there were no DRPs identified related to correct directions, practical directions, or the least expensive alternative. Table 5-9 provides the distribution of DRPs identified using MAI criteria.

Table 5-9: DRP identified as per MAI

Domain	**Drugs with DRP (N= 81) n (%)**
1. Is there an indication for the drug	
Reason for use of Aspirin not clear as patient determined not to have transient ischemic attack when presenting with visual symptoms	1 (1.2)
Ezetimibe (No hypercholesterolemia noted)	1 (1.2)
Reason for use of aspirin is not established	1 (1.2)
Need for Amiodarone is not clear	1 (1.2)
Total DRPs	4 (5)
2. Is the medication affective for the condition	
Premarin vaginal cream for urinary incontinence (Incontinence for years, worsening in the past few months)	1 (1.2)

Mirtazapine not effective for insomnia	1 (1.2)
Acetaminophen and methocarbamol likely providing minimal benefit for pain control for peripheral neuropathy and affect cognition	1 (1.2)
Cannabidiol likely providing minimal benefit for pain control for peripheral neuropathy and affect cognition	1 (1.2)
Elevated blood pressure on visit, patient currently prescribed Candesartan (Angiotensin II receptor blocker)	1 (1.2)
Galantamine – no benefit of cognition as scores are declining	1 (1.2)
Mirabegron- likely limited benefit for urinary incontinence	1 (1.2)
Duloxetine-decrease in hemoglobin level	1 (1.2)
Citalopram not optimally effective for Anxiety (BPSD)	1 (1.2)
Total DRPs	9 (11.2)
3. Is the dosage correct	
Reduce dosage of antihypertensives	
Ramipril	1 (1.2)
Metoprolol	1 (1.2)
Gabapentin <60ml/min (Maximum recommended dose is 600 mg/day)	1 (1.2)
Acetaminophen dosage too high	1 (1.2)
Fenofibrate dosage should be less than ≤67 mg if the patient's CrCl >30 to 80 mL/minute	1 (1.2)
Pseudoephedrine and Ibuprofen use regularly, instead of PRN	1 (1.2)

Low acetaminophen dose (administer four time per day in nursing home is costly)	1 (1.2)
Total DRPs	7 (8.7)
4. Are the directions correct?	
5. Are the directions practical?	
6. Clinically significant drug-drug interaction	
Opioids + Pregabalin	1 (1.2)
Lorazepam + Oxycodone (Opioid analgesic)	1 (1.2)
Lorazepam + Tapentadol	1 (1.2)
Cyclobenzaprine + Oxycodone (Opioid analgesic)	1 (1.2)
Cyclobenzaprine + Tapentadol	1 (1.2)
Doxepin + Oxycodone (Opioid analgesic)	1 (1.2)
Doxepin + Tapentadol	1 (1.2)
Oxycodone (Opioid analgesic) + Tapentadol	1 (1.2)
Zopiclone + Oxycodone (Opioid analgesic)	1 (1.2)
Zopiclone + Tapentadol	1 (1.2)
Doxepin (TCA) + Lorazepam (Benzodiazepines) + Tapentadol/Oxycodone (Opioids) + Cyclobenzaprine (Skeletal muscle relaxant)→ Any combination of ≥3 of these CNS-active drugs	1 (1.2)
Brimonidine and timolol (Beta blockers, non-selective) + Symbicort (Budesonide and Formoterol)→ Beta blocker may dimmish the broncho dilatory effect of Symbicort	1 (1.2)

Darifenacin (Antimuscarinics, Anticholinergic agents) + Donepezil (Acetyl cholinesterase inhibitor)→ Anticholinergic Agents may diminish the therapeutic effect of Acetylcholinesterase Inhibitors	1 (1.2)
Gabapentin (CNS Depressants) + Hydromorphone (Opioid agonists)→ Increased risk of severe sedation-related adverse events, including respiratory depression and death	1 (1.2)
Allopurinol + Warfarin (Severe DDI as per Anticoagulant clinic) Benefit outweigh risk	1 (1.2)
Warfarin + Dabigatran (Severe DDI as per Anticoagulant clinic) Benefit outweigh risk	1 (1.2)
Warfarin + Rosuvastatin (Moderate risk as per Anticoagulant clinic) Benefit outweigh risk	1 (1.2)
Warfarin + Acetaminophen (Moderate risk as per Anticoagulant clinic) Benefit outweigh risk	1 (1.2)
Warfarin + Levothyroxine (Moderate risk as per Anticoagulant clinic) Benefit outweigh risk	1 (1.2)
Donepezil (Acetylcholinesterase inhibitor) + Bisoprolol (Drugs that induce persistent bradycardia (Beta-blocker)→ risk of cardiac conduction failure, syncope, and injury	1 (1.2)
Gabapentin + Oxycodone (Opioid)	1 (1.2)
Gabapentin + Sertraline (SSRI) + Oxycodone (Opioids)→ Any combination of ≥3 of these CNS-active drugs	1 (1.2)

Amiodarone (Antiarrhythmic agents, bradycardia-causing agents) + Donepezil (Acetylcholinesterase inhibitor, bradycardia-causing agents)→ enhance the bradycardic effect enhance QTc-prolonging effect (Indeterminate Risk – Caution) (Benefits outweigh risk)	1 (1.2)
Total DRPs	23 (28.3)
7. Clinically significant Drug-disease	
Sinus Bradycardia	
Timolol	1 (1.2)
History of bronchial asthma	
Brimonidine and timolol	1 (1.2)
Dementia or CI	
Doxepin >6mg/day (Antidepressant with strong Anticholinergic properties)	1 (1.2)
Cyclobenzaprine (Skeletal muscle relaxant, Anticholinergic)	1 (1.2)
Lorazepam (Benzodiazepine)	1 (1.2)
Darifenacin (Antimuscarinic)	1 (1.2)
Hydromorphone (Opioid analgesic)	3 (3.7)
Methocarbamol (Skeletal muscle relaxant)	2 (2.4)
Cannabidiol (Cannabinoid)	1 (1.2)
Gabapentin (GABA analog)	3 (3.7)
Zopiclone (Z-drug)	1 (1.2)

Medical marijuana	1 (1.2)
History of falls or fractures	
Doxepin >6mg/day (Antidepressant with strong Anticholinergic properties)	1 (1.2)
Cyclobenzaprine (Skeletal muscle relaxant, Anticholinergic)	1 (1.2)
Lorazepam (Benzodiazepine)	1 (1.2)
Oxycodone (Opioid)	2 (2.4)
Tapentadol (Opioid)	1 (1.2)
Duloxetine (SNRI)	2 (2.4)
Sertraline (SSRI)	3 (3.7)
Zopiclone (Z-drug)	1 (1.2)
Citalopram (SSRI)	3 (3.7)
Risperidone (Atypical Antipsychotics)	1 (1.2)
Escitalopram (SSRI)	1 (1.2)
Codeine (Opioid)	1 (1.2)
History of Insomnia	
Zopiclone use for ≥ 2 weeks	1 (1.2)
Total DRPs	36 (44.4)
8. Is there unnecessary duplication with another drug	
Duplicate therapy (Oxycodone, Tapentadol)	1 (1.2)
9. Is the duration of therapy acceptable?	
Pantoprazole use >4weeks unless for high-risk patients	1 (1.2)

10. Is this drug the least expensive alternative compared to others of equal utility?	

BPSD, Behavioral and Psychological Symptoms of Dementia; SSRI, Selective Serotonin Reuptake Inhibitors; SNRI, Serotonin-Norepinephrine Reuptake Inhibitors; CrCl, Creatinine Clearance; PRN, Pro re nata; CNS, Central nervous system; TCA, Tricyclic Antidepressant; AC, Anticholinergics; NSAID's, Non-Steroidal Anti-Inflammatory Drugs; COX, Cyclooxygenase; eGFR, estimated Glomerular Filtration Rate; DDI, Drug-drug interaction

5.3.5 McNemar test

The McNemar test has been used to determine if there are differences on a dichotomous dependent variable between two related groups. The 2X2 contingency table 5-10 and table 5-11 shows that there is a statistically significant difference (P-value <0.001) in the distribution of patients identified with DRPs using the MedRevCiD checklist and those identified using the MAI criteria.

Table 5-10: DRP as per MedRevCiD and DRP as per MAI criteria

	DRP as per MAI criteria	
DRP as per MedRevCiD	**Absent**	**Present**
Absent	8	0
Present	11	25

Table 5-11: Test statistics

	DRP as per MedRevCiD & DRP as per MAI criteria
N	44
P-value (2- tailed)	< 0.001

P-value <0.05 considered statistically significant

5.4 PIMs identified as per Beers criteria and STOPP criteria

In this study, the prevalence of using at least one PIM among the study participants was 47.7% (n= 21) and 27.2% (n= 12) based on Beers and STOPP criteria, respectively. Table 5-12 presents the distribution of patients identified with PIMs using both criteria. Using the Beers criterion, 50 PIMs were found, with an average of 0.9 PIMs for each patient. Whereas a total of 31 PIMs were identified using the STOPP criteria, with an average of 0.6 PIMs per patient.

Table 5-12: Distribution of patients with PIMs as per Beers and STOPP criteria

Characteristics	**PIMs as per Beers (N= 44)**	**PIMs as per STOPP (N= 44)**
0 PIM (n (%))	23 (52.3)	32 (72.7)
1 PIM (n (%))	13 (29.5)	6 (13.6)
2 PIM (n (%))	2 (4.5)	3 (6.8)
3 PIM (n (%))	4 (9.1)	2 (4.5)
≥ 4 PIM (n (%))	2 (4.5)	1 (2.3)
Total number of PIMs, (min- max)	50 (0- 6)	31 (0- 7)
Average number of PIMs per patient, mean ± SD	0.9 ± 1.3	0.6 ± 1.2
Median (IQR)	0 (1)	0 (1)

SD, Standard deviation; IQR, Interquartile range

5.4.1 Number of PIMs identified using Beers criteria

Almost 50% (n= 25) of the identified PIMs fall in the dependent of the diagnosis category, followed by 32% (n= 16) from the independent of the diagnosis category. Among the dependent of diagnosis category, PIMs from the history of falls or fractures category were

the most dominant. Drugs from the central nervous system class were most identified as PIMs from the independent of diagnosis category. Among the central nervous system class, atypical antipsychotics (risperidone) were identified as a PIM in 3 patients. A total of 7 PIMs were identified from the potentially clinically important drug-drug interaction (DDI) class, and only 1 PIM were identified from the drugs used with caution and according to kidney function category, respectively (see Table 5-13)

Table 5-13: PIM as per Beers criteria

Domain	**Drugs with PIMs (N= 50) n (%)**
Independent of diagnosis	
Endocrine system	
Danazol (synthetic male testosterone)- Avoid unless indicated for confirmed hypogonadism with clinical symptoms	1 (2)
Sulfonylureas (all, including short- and longer-acting) Gliclazide	1 (2)
Central nervous system	
Antidepressant	
Doxepin>6mg/day	1 (2)
Benzodiazepines	
Lorazepam	1 (2)

Concomitant use of Lorazepam with opioid analgesic (Oxycodone, Tapentadol)	1 (2)
Nonbenzodiazepine benzodiazepine receptor agonist hypnotics ("Z-drugs")	
Zopiclone	1 (2)
Atypical Antipsychotics	
Risperidone	3 (6)
Quetiapine	1 (2)
Pain medications	
Cyclobenzaprine	1 (2)
Skeletal muscle relaxants	
Methocarbamol	2 (4)
Gastrointestinal	
Pantoprazole use for >8 weeks unless for high-risk patients	1 (2)
Cardiovascular and Anti-thrombotic	
Amiodarone	1 (2)
Rivaroxaban for nonvalvular atrial fibrillation (long-term treatment)	1 (2)
Total PIM	16 (32)
Dependent of Diagnosis	
Dementia or CI	
Doxepin >6mg/day (Antidepressant with strong Anticholinergic properties)	1 (2)

Cyclobenzaprine (Anticholinergic)	1 (2)
Lorazepam (Benzodiazepine)	1 (2)
Risperidone	1 (2)
Quetiapine	1 (2)
Darifenacin (Anticholinergic)	1 (2)
Zopiclone (Z-drugs)	1 (2)
History of falls or fractures	
Doxepin >6mg/day (Antidepressant with strong Anticholinergic properties)	1 (2)
Cyclobenzaprine (Skeletal muscle relaxant, Anticholinergic)	1 (2)
Lorazepam (Benzodiazepine)	1 (2)
Oxycodone (Opioid)	2 (4)
Tapentadol (Opioid)	1 (2)
Duloxetine (SNRI)	2 (4)
Sertraline (SSRI)	3 (6)
Zopiclone (Z-drugs)	1 (2)
Citalopram (SSRI)	3 (6)
Risperidone (Atypical Antipsychotics)	1 (2)
Escitalopram (SSRI)	1 (2)
Codeine (Opioid analgesic)	1 (2)
Total PIMs	25 (50)
Use with caution	

1. Duloxetine initiated (Monitor sodium levels closely When initiating or altering doses in older persons, but sodium level last checked one year back in patient)	1 (2)
Drug-drug interaction	
1. Opioids + Pregabalin	1 (2)
2. Tapentadol and oxycodone (Opioid) + Lorazepam (Benzodiazepines)	1 (2)
3. Cyclobenzaprine (AC) + Doxepin >6mg/day (AC)	1 (2)
4. Doxepin (TCA) + Lorazepam (Benzodiazepines) + Tapentadol/Oxycodone (Opioids) + Cyclobenzaprine (Skeletal muscle relaxant→ Any ≥3 of CNS-active drugs	1 (2)
5. Gabapentin + Hydromorphone (Opioid analgesic)	1 (2)
6. Gabapentin + Oxycodone (Opioid)	1 (2)
7. Gabapentin + Sertraline (SSRI) + Oxycodone (Opioids)→ Any ≥3 of CNS-active drugs	1 (2)
Total PIMs	7 (14)
According to kidney function	
Gabapentin maximum recommended dose is 600 mg/day if the patient CrCl <60ml/min	1 (2)

SSRI, Selective Serotonin Reuptake Inhibitors; SNRI, Serotonin-Norepinephrine Reuptake Inhibitors; CrCl, Creatinine Clearance; CNS, Central nervous system; TCA, Tricyclic Antidepressant; AC, Anticholinergics

5.4.2 Number of PIMs identified using STOPP criteria

Using STOPP criteria, a total of 31 PIMs were found in 12 patients. Of 31 PIMs, 61.3% (n= 19) of the identified PIMs fall in the dependent of the diagnosis category, followed by

25.9% (n= 8) from the independent of the diagnosis category (see Table 5-14). Among the dependent of diagnosis category, PIMs from the drugs that predictably increase fall risk in the older adults category were the most dominant category, and it covers all the same drugs mentioned in the dependent of diagnosis History of falls and fractures in Beers criteria. However, the PIMs identified in the dementia or cognitive impairment subcategory from the dependent of diagnosis category in Beers criteria didn't cover in STOPP criteria. On the other hand, PIMs identified in the bradycardia, insomnia, and constipation subcategory of STOPP criteria were not identified as a PIM in Beers criteria dependent on the diagnosis category. From the independent of diagnosis category, apixaban was identified as a PIM in 2 patients using the STOPP criteria. There were only 3 PIMs identified from the drug-drug interaction and only 1 PIM from the PIMs as per the estimated Glomerular Filtration Rate (eGFR) level category of STOPP criteria.

Table 5-14: PIMs as per STOPP

Domain	**Drugs with PIMs (N= 31) n (%)**
Independent of Diagnosis	
1. Lorazepam use for ≥ 4 weeks	1 (3.2)
2. Duplicate therapy (Oxycodone, Tapentadol)	1 (3.2)
3. Apixaban (Factor Xa inhibitor)	2 (6.4)
4. Dabigatran (Direct oral anticoagulant)	1 (3.2)

5. Gabapentin for non-neuropathic pain	1 (3.2)
6. Amiodarone	1 (3.2)
7. Rivaroxaban	1 (3.2)
Total PIMs	8 (25.9)
1. Dependent of Diagnosis	
bradycardia (<50/min)	
Timolol (beta-blocker)	1 (3.2)
Drugs that predictably increase falls risk in older adults	
Lorazepam (Benzodiazepines)	1 (3.2)
Zopiclone (Hypnotic Z-drugs)	2 (6.4)
Oxycodone (Opioid)	2 (6.4)
Tapentadol (Opioid)	1 (3.2)
Codeine (Opioid)	1 (3.2)
Doxepin (TCA)	1 (3.2)
Sertraline (Antidepressant, SSRI)	2 (6.4)
Citalopram (SSRI)	3 (9.6)
Risperidone (Atypical Antipsychotics)	1 (3.2)
Escitalopram (Antidepressant, SSRI)	1 (3.2)

Insomnia	
Zopiclone use for ≥ 2 weeks	1 (3.2)
Constipation	
Oxycodone (Opioid)	1 (3.2)
Tapentadol (Opioid)	1 (3.2)
Total PIMs	19 (61.3)
Drug-drug interaction	
Spironolactone (Aldosterone antagonist) + Candesartan (Potassium conserving drugs such as ARB) without frequent serum potassium monitoring (risk of serious hyperkaliemia, > 6.0 mmol/l; serum K should be checked at least every six months)→ But last time Serum potassium checked more than one year	1 (3.2)
Oxycodone (Opioid) + Doxepin (TCA) + Tapentadol (Opioid) + Cyclobenzaprine (Skeletal muscle relaxant)→ Concomitant use of ≥ 2 antimuscarinic/anticholinergic drugs	1 (3.2)
Donepezil (Acetylcholinesterase inhibitor) + Bisoprolol (Drugs that induce persistent bradycardia (Beta-blocker)→ syncope, failure, injury, risk of cardiac conduction	1 (3.2)
Total PIMs	3 (9.6)
As per eGFR level	

Celecoxib (NSAID's, COX-2) in patient with eGFR level 40 ml/min/1.73m^2	1 (3.2)

TCA, Tricyclic Antidepressant; SSRI, Selective Serotonin Reuptake Inhibitors; SNRI, Serotonin-Norepinephrine Reuptake Inhibitors; NSAID's, Non-Steroidal Anti-Inflammatory Drugs; COX, Cyclooxygenase; eGFR, estimated Glomerular Filtration Rate

5.4.3 McNemar test

Table 5-15 is the contingency table for conducting a McNemar test to assess the agreement between the presence of PIMs according to Beers criteria and STOPP criteria. The p-value is 0.035, showing that there is a statistically significant difference in the number of patients with at least one PIMs identified using the Beers and STOPP criteria (see Table 5-16).

Table 5-15: PIMs as per Beer's criteria & PIMs as per STOPP criteria

	PIMs as per STOPP criteria	
PIMs as per Beers criteria	**Absent**	**Present**
Absent	20	3
Present	12	9

Table 5-16: Test statistics

	PIMs as per Beers criteria & PIMs as per STOPP criteria
N	44
P-value (2- tailed)	0.035

P-value <0.05 considered statistically significant

5.5 DRPs classified as per Pharmaceutical Care Network Europe (PCNE) version 9 criteria

A total of 119 DRPs were identified by the researcher in 44 of the study participants, giving a median of 1 (IQR 3) DRPs per patient. The distribution of patients with DRPs as per PCNE criteria is summarized in Table 5-19. The maximum number of DRPs identified in patients was 20 DRPs per patient. Out of 44 patients, 36 (81.8%) patients were identified with at least one DRP, 13.6% (n= 6) with at least 2 DRPs, followed by 6.8% (n= 3) of patients with 3 and 4 DRPs reported, respectively. There were 18.1% (n= 8) of patients identified with five or more DRPs (see Table 5-17).

Table 5-17:- Distribution of patients with DRPs as per PCNE criteria

Characteristics	**(N= 44) n (%)**
0 DRP	8 (18.2)
1 DRP	16 (36.4)
2 DRP	6 (13.6)
3 DRP	3 (6.8)
4 DRP	3 (6.8)
5 DRP	2 (4.5)
6 DRP	1 (2.3)
8 DRP	2 (4.5)
9 DRP	2 (4.5)
20 DRP	1 (2.3)
Total number of DRPs (min- max)	119 (0- 20)

Average number of DRPs per patient, mean ± SD	2.7 ± 3.6
Median (IQR)	1 (3)

5.5.1 Type of DRPs identified as per PCNE criteria

Out of the 119 DRPs identified, with an average of 2.7 DRPs per patient, the most common type of DRP was Treatment Safety P2, accounting for 63% of the reported DRPs (n= 75). Among the 19 DRPs identified from the treatment effectiveness P1 category, the most dominant subcategory was the effect of drug treatment not optimal P1.2, accounting for 12 of the reported DRPs. We have identified several DRPs related to non-adherence and inappropriate medication management, but there was no specific category in the type of DRPs. So, we have added the P3.2 subcategory in other DRPs, which was non-adherence to medication or inappropriate medication management. A total of 17 DRPs were reported from the non-adherence to medication or inappropriate medication management subcategory P3.2 from the other DRPs P3 category, followed by unnecessary drug-treatment P3.1 with 5 DRPs. Table 5-18 summarizes the type of DRPs identified as per PCNE criteria.

Table 5-18: Type of DRPs identified as per PCNE criteria

Primary domain	**Number**	**Frequency**
Types of drug-related problems		
P1. Treatment effectiveness P1		
• No effect of drug treatment P1.1	2	1.6
• Effect of drug treatment not optimal P1.2	12	10.1

• Untreated symptoms or indication P1.3	5	4.2
P2. Treatment safety		
• Adverse drug event (possibly) occurring P2.1	75	63
P3. Others		
• Unnecessary drug-treatment P3.1	5	4.2
• Problem with the cost-effectiveness of the treatment P3.2	0	0
• Non-adherence to medication, inappropriate medication management P3.2	17	14.3
• Unclear problem/complaint P3.2	3	2.6
Total	119	100

5.5.2 Cause of DRPs identified as per PCNE criteria

Among the 119 DRPs identified, the most common cause of problem reported was inappropriate drug according to guidelines/formulary C1.1 (43.6%, n= 52), followed by an inappropriate combination of drugs, or drugs and herbal or DDI C1.3 (21%, n= 25) from the drug selection C1 category. Table 5-19 provides the distribution of DRPs based on the cause of DRPs. Within the dose selection C3 category, a drug dose too high was reported as a common cause of DRPs. Among the patients related to C7 cause of DRPs category, C7.1 Patient intentionally uses/takes less drug than prescribed or does not take the drug at all for whatever reason was reported as a cause for seven identified DRPs (See Table 5-19). The most important thing to note is that the DRPs identified using MedRevCiD, MAI,

Beers, and STOPP criteria are categorized into different PCNE criteria version 9 categories.

Table 5-19: Causes of DRP (including possible causes for potential problems)

Primary domain	**Cause of the problem**	**Total number = 119, n (%)**
Drug selection C1	C1.1 Inappropriate drug according to guidelines/formulary	52 (43.6)
	C1.2 No indication for drug medications, or drugs and dietary supplements	5 (4.2)
	C1.3 Inappropriate combination of drugs, or drugs and herbal	25 (21)
	C1.4 Inappropriate duplication of therapeutic group or active ingredient	1 (0.8)
	C1.5 No or incomplete drug treatment despite existing indication	4 (3.3)
	C1.6 Too many different drugs/active ingredients prescribed for indication	
Drug form C2	C2.1 Inappropriate drug form/formulation (for this patient)	
Dose selection C3	C3.1 Drug dose too low	1 (0.8)
	C3.2 Drug dose of a single active ingredient too high	4 (3.3)

	C3.3 Dosage regimen does not frequent enough	
	C3.4 Dosage regimen too frequent	
	C3.5 Dose timing instructions wrong, unclear, or missing	
Treatment duration C4	C4.1 Duration of treatment too short	
	C4.2 Duration of treatment too long	2 (1.6)
Dispensing C5	C5.1 Prescribed drug not available	
	C5.2 Necessary information not provided or incorrect advice provided	
	C5.3 Wrong dose, strength or dosage advised	
	C5.4 Wrong drug or strength dispensed	1 (0.8)
Drug use process C6	C6.1 Inappropriate timing of administration or dosing intervals by a health professional	
	C6.2 Drug under-administered by a health professional	
	C6.3 Drug over-administered by a health professional	
	C6.4 Drug not administered at all by a health professional	
	C6.5 Wrong drug administered by a health professional	

	C6.6 Drug administered via wrong route by a health Professional	
Patient related C7	C7.1 Patient intentionally uses/takes less drug than prescribed or does not take the drug at all for whatever reason	7 (5.8)
	C7.2 Patient uses/takes more drug than prescribed	1 (0.8)
	C7.3 Patient abuses drug (unregulated overuse)	
	C7.4 Patient decides to use unnecessary drug	
	C7.5 Patient takes food that interacts	
	C7.6 Patient stores drug inappropriately	
	C7.7 Inappropriate timing or dosing intervals	
	C7.8 Patient unintentionally administers/uses the drug in a wrong way	
	C7.9 Patient physically unable to use drug/form as directed	3 (2.5)
	C7.10 Patient unable to understand instructions properly	1 (0.8)
Patients transfer related C8	C8.1 Medication reconciliation problem	

Other C9	C9.1 No or inappropriate outcome monitoring (incl. TDM)	2 (1.6)
	C9.2 Other cause; specify	
	Patient's misses doses of prescribed meds (Unintentionally)	3 (2.5)
	C9.3 No obvious cause	7 (5.8)

5.5.3 Pharmacist recommendation to solve the DRPs

Pharmacists play a crucial role in optimizing medication therapy for older adults with dementia and addressing DRPs. All the recommendations made by the pharmacist to resolve DRPs among study participants were recorded from the pharmacist's medication review plan notes. A total of 53 recommendations were listed by the pharmacist for the study participants in the medical records. Recommendations are developed in collaborative manner after discussion with the interdisciplinary team members, including physicians, nurses, social workers, and occupational therapist. Unsurprisingly, all the pharmacist recommendations were accepted (see Table 5-20). Pharmacist recommendation mainly occurred at drug level (60.3%, n= 32), followed by patient level (22.6%, n= 12). The major intervention at the drug level was the drug paused or stopped (30.1%, n= 16), followed by starting a new drug (9.4%, n= 5) for a new condition and/or pre-existing patient conditions. At patient level, patient drug counselling recommendations was the major subcategory (13.2%, n= 7), followed by patient referred to prescriber (7.5%, n= 4). Other recommendations or activity proposed by the pharmacists (13.2%, n= 7) included recommendations for alarm clock for medication reminder and laboratory tests.

Of 119 DRPs identified, 31.9% (n= 38) DRPs were solved after the pharmacist's recommendation, and 6.7% (n= 8) were partially solved **(**decreased dose of the drug but not discontinued) (see Table5-21). However, 46.2% (n= 55) of the DRP's status was unknown, and there was no need or possibility to solve the problem for 13.4% (n= 16) of the DRPs. A single drug might contribute to multiple DRPs, making it challenging to resolve all identified problems simultaneously. For instance, a drug could cause an adverse reaction, interact with other medications, and be dosed inappropriately, leading to multiple DRPs associated with that single drug. The status of some DRPs was labeled as "not known" because they were not identified by the pharmacist and weren't documented in the patient chart notes but were determined through the use MedRevCiD, MAI, Beers, or STOPP. The DRPs mentioned in other 3 categories of status of DRP (solved, not solved, partially solved) reflects what the pharmacist noted in the charts. The category "No need or possibility to solve the problem" regarding DRPs implies that the identified issue, as assessed by the pharmacist, either didn't require any intervention due to its lack of clinical significance or presented a situation where solving the problem wasn't feasible or necessary.

Table 5-20: Pharmacist recommendations

Domain	**Codes**	**Recommendations (N=53) n (%)**
11. At prescriber level	I1.1 Prescriber informed only	1 (1.8)
	I1.2 Prescriber asked for information	
	I1.3 Intervention proposed to prescriber	

	I1.4 Intervention discussed with prescriber	1 (1.8)
12. At patient level	I2.1 Patient (drug) counselling	7 (13.2)
	I2.2 Written information provided (only)	
	I2.3 Patient referred to prescriber	4 (7.5)
	I2.4 Spoken to family member/caregiver	1 (1.8)
13. At drug level	I3.1 Drug changed to …	3 (5.6)
	I3.2 Dosage changed to …	4 (7.5)
	I3.3 Formulation changed to …	1 (1.8)
	I3.4 Instructions for use changed to …	3 (5.6)
	I3.5 Drug paused or stopped	16 (30.1)
	I3.6 Drug started	5 (9.4)
14. Other recommendation or activity	I4.1 Other intervention (specify) Propose recommendation to stop drugs based on MRI results	2 (3.7)
	14.1 Consider discontinuing medication at next clinic visit if shown any benefit	1 (1.8)
	14.1 Recommend alarm clock for medication reminder	2 (3.7)
	14.1 Recommend and monitor lab test	2 (3.7)

	I4.2 Side effect reported to authorities	

Table 5-21: Status of DRP

Domain	**Codes**	**Total number of DRPs (N= 119) n (%)**
0. Not known	O0.1 Problem status unknown	55 (46.2)
1. Solved	O1.1 Problem totally solved	38 (31.9)
2. Partially solved	O2.1 Problem partially solved (decrease dose of drug but continuing)	8 (6.7)
3. Not solved	O3.1 Problem not solved, lack of cooperation of patient	1 (0.8)
	O3.2 Problem not solved, lack of cooperation of prescriber	
	O3.3 Problem not solved; intervention not effective	1 (0.8)
	O3.4 No need or possibility to solve problem	16 (13.4)

5.6 DDI identified using Lexicomp database

This study identified a total of 225 DDI in 44 study participants. Table 5-22 represents the distribution of patients based on DDI. Most of the study participants were exposed to minor DDIs (75%, n= 33), followed by 25% (n= 11) of the study participants identified with at

least one moderate DDI. Only one drug combination was identified in major DDI in one study participant, for example, the combination of timolol with formoterol (beta 2 agonist). Of 225 DDI identified, the majority were minor (86%, n= 193), followed by 13.4% (n= 31) of the DDI were moderate, and only major DDI were identified. Among the minor DDI, the most reported DDI were aspirin and perindopril, aspirin and sertraline, aspirin, and citalopram. In older adults with dementia, combining aspirin with sertraline or citalopram may potentially lead to interactions, but these interactions might not always result in clinically significant adverse effects. In most cases, this interaction might not cause significant bleeding issues, especially when using aspirin for its antiplatelet effects at low doses (typically used for cardiovascular protection). However, in certain individuals, particularly those with a history of bleeding disorders or concurrent use of other medications that affect bleeding, this interaction might be of greater concern and require closer monitoring. The minimum and maximum range for minor DDI reported by study participants was 1- 33 DDI per person. The range for moderate DDI was between 1- 11 DDI per person. Appendix E-1 summarizes the distribution of DDI among the study participants.

Table 5-22: Distribution of patients with DDI

Drug-drug interaction	**(N= 44) n (%)**
No DDI	10 (22.7)
Major DDI	1 (2.3)
Moderate DDI	
1 DDI	5 (11.4)

2 DDI	3 (6.8)
4 DDI	1 (2.3)
5 DDI	1 (2.3)
11 DDI	1 (2.3)
Total moderate	11 (25)
Minor DDI	
1 DDI	7 (15.9)
2 DDI	6 (13.6)
3 DDI	4 (9.1)
4 DDI	2 (4.5)
5 DDI	2 (4.5)
7 DDI	4 (9.1)
8 DDI	1 (2.3)
10 DDI	3 (6.8)
14 DDI	1 (2.3)
15 DDI	1 (2.3)
16 DDI	1 (2.3)
33 DDI	1 (2.3)
Total minor	33 (75)

5.7 Additional hoc analysis

5.7.1 Additional analysis for overall DRP and without DRP group

5.7.1.1 Characteristics of the study population with DRPs and without DRPs

The overall study participants were categorized into two groups: patients identified with at least one DRP and without DRPs. Overall, in this cross-sectional study over one medication review with a pharmacist at one clinic visit, 81.8% (n= 36) participants were identified with at least one DRP and 18.2% (n= 8) participants were identified without any DRPs. The descriptive analysis of the study population in terms of baseline and clinical characteristics between the two groups is presented in Table 5-23. There was no significant difference observed between the two groups, except the participants in the with DRP group had a higher mean number of comorbidities as compared to the without DRP group (P value 0.010).

Table 5-23: Demographic and clinical characteristics of the study population

Characteristics	**Total (N= 44) n (%)**	**With DRP (N= 36) n (%)**	**Without DRP (N= 8) n (%)**	**P value**
Age of the patient, mean ± SD	80.2 ± 6.2	79.7 ± 6.4	82.1 ± 5.3	0.345*
65- 69 years	2 (4.5)	2 (5.5)	0 (0)	
70- 74 years	5 (11.5)	5 (13.9)	0 (0)	
75- 79 years	13 (29.5)	10 (27.7)	3 (37.5)	

80- 84 years	13 (29.5)	12 (33.4)	1 (12.5)	
≥ 85 years	11 (25)	7 (19.5)	4 (50.0)	
Sex				
Male	24 (54.5)	19 (52.8)	5 (62.5)	0.710[#]
Female	20 (45.5)	17 (47.2)	3 (37.5)	
Marital Status				
Married	38 (86.4)	30 (83.4)	8 (100)	0.644[#]
Separated	1 (2.2)	1 (2.8)	0 (0)	
Widowed	5 (11.4)	5 (13.8)	0 (0)	
CI/dementia				
Vascular CI	5 (11.4)	5 (13.8)	0 (0)	0.877[#]
Subjective cognitive decline	4 (9.1)	3 (8.4)	1 (12.5)	
Evolving neurocognitive disorder	3 (6.8)	3 (8.4)	0 (0)	
Mild CI	16 (36.4)	13 (36.1)	3 (37.5)	
Mixed dementia	9 (20.5)	7 (19.4)	2 (25)	
Dementia	4 (9.1)	3 (8.4)	1 (12.5)	
Probable or possible Alzheimer's disease	3 (6.7)	2 (5.5)	1 (12.5)	

Comorbidities				
Number of comorbidities per person, mean ± SD	6.7 ± 3.4	7.0 ± 3.6	5.1 ± 1.1	0.010*
0	1 (2.3)	1 (2.8)	0 (0)	
1- 5	16 (36.3)	12 (33.4)	4 (50)	
6- 8	18 (41)	14 (38.8)	4 (50)	
≥ 9	9 (20.4)	9 (25)	0 (0)	
Alcohol				
Never	20 (45.5)	15 (41.6)	5 (62.5)	0.187#
Occasional drinker	11 (25)	11 (30.6)	0 (0)	
Active regular drinker	13 (29.5)	10 (27.8)	3 (37.5)	
Smoking				
Never	24 (54.5)	19 (52.8)	5 (62.5)	1.000#
Ex-smoker	17 (38.7)	14 (38.8)	3 (37.5)	
Active smoker	3 (6.8)	3 (8.4)	0 (0)	
Recent history of falls				
Absent	21 (47.7)	16 (44.5)	5 (62.5)	0.448#
Present	23 (52.3)	20 (55.5)	3 (37.5)	

SD; Standard deviation
*Student's- t test
Fisher-Freeman-Halton Exact test

5.7.1.2 Medication use among the study population with DRP and without DRP

The study participants were divided into two groups: With DRP and without DRP group. The median number of medications prescribed in the group of patients with DRPs was 8 (with an interquartile range of 6), which was notably higher than the median number of medications prescribed in the group of patients without DRPs, which was 6.5 (with an interquartile range of 10), as indicated in Table 5-24. Table 5-25 illustrates how the medications prescribed to the study participants with DRPs and without DRPs are distributed based on therapeutic and pharmacological levels. A total of 375 medications were prescribed to 44 study participants. Out of 375 medications prescribed, 59 medications were identified as causes of DRPs. Notably, the highest number of DRPs were found with medications within the Nervous System (ATC number) class. A total of 82 medications were prescribed from this class. Of the 82 medications prescribed from this class, 30 were identified as being associated with DRPs, surpassing all other classes. Appendix E-2 provides a distribution of a number of medications among the study participants with DRPs and without DRPs at the drug level. Additional details concerning the distribution of patients with DRPs as per PCNE criteria and those prescribed Nervous System drugs within the study population are presented in Appendix E-3.

Table 5-24: Medication use among the study participants with DRP and without DRP according to ATC classification

Characteristics	**Total (N= 44) n (%)**	**With DRP (N= 36) n (%)**	**Without DRP (N= 8) n (%)**
Number of medications per person, median (IQR)	7.5 (6)	8 (6)	6.5 (10)

Medications per day			
1- 4	6 (13.6)	4 (11.1)	2 (25)
5- 9	21 (47.7)	18 (50)	3 (37.5)
≥10	17 (38.6)	14 (38.9)	3 (37.5)
ATC classification			
G Genito urinary system and sex hormones	16 (36.4)	14 (38.8)	2 (25)
A Alimentary tract and metabolism	32 (72.7)	27 (75)	5 (62.5)
B Blood and blood forming organs	34 (77.3)	29 (80.5)	5 (62.5)
C Cardiovascular system	36 (81.8)	32 (88.8)	4 (50)
S Sensory organs	4 (9.1)	3 (8.3)	1 (12.5)
N Nervous system	36 (81.8)	31 (86.1)	5 (62.5)
L Antineoplastic and immunomodulating agents	4 (9.1)	3 (8.3)	1 (12.5)
H Systemic hormonal preparations	7 (15.9)	5 (13.9)	2 (25)
R Respiratory system	9 (20.5)	7 (19.4)	2 (25)
M Musculo-skeletal system	8 (18.2)	6 (16.6)	2 (25)
D Dermatological	7 (15.9)	6 (16.6)	1 (12.5)

Table 5-25:- Distribution of number of medications prescribed to the study participants with DRP at the therapeutic and pharmacological level

ATC classes and codes	Total prescribed (375 total prescribed to 44 patients) n (%)	DRP (N= 59) n (%)	Without DRP (N= 316) n (%)
G GENITO URINARY SYSTEM AND SEX HORMONES			
G04C Drugs used in benign prostatic hypertrophy	12 (3.2)	0 (0)	12 (3.8)
G04BE Drugs used in erectile dysfunction	1 (0.2)	0 (0)	1 (0.3)
G03C Estrogens	1 (0.2)	1 (1.6)	0 (0)
G03X Other sex hormones and modulators of the genital system	1 (0.2)	1 (1.6)	0 (0)
G04B Urological	7 (1.8)	3 (5)	4 (1.2)
G03B Androgens	1 (0.2)	0 (0)	1 (0.3)
G01A Anti-infective and antiseptics, excluding combinations of corticosteroids	1 (0.2)	0 (0)	1 (0.3)
Total	24 (6.4)	5 (8.4)	19 (6)
A ALIMENTARY TRACT AND METABOLISM			

A11C Vitamin A and D, including combinations of the two	19 (5)	0 (0)	19 (6)
A02B Drugs for peptic ulcer and gastro-esophageal reflux disease (GERD)	16 (4.2)	1 (1.6)	15 (4.8)
A10B Blood glucose lowering drugs, excluding insulins	14 (3.8)	0 (0)	14 (4.4)
A06A Drugs for constipation	3 (0.8)	0 (0)	3 (0.9)
A04A Antiemetics and antinauseants	2 (0.5)	1 (1.6)	1 (0.3)
A11D Vitamin B1, plain and in combination with vitamin B6 and B12	4 (1)	0 (0)	4 (1.2)
A10A Insulins and analogues	7 (1.9)	0 (0)	7 (2.2)
A11G Ascorbic acid (vitamin C), incl combinations	3 (0.8)	0 (0)	3 (0.9)

A12C Other mineral supplements	2 (0.5)	0 (0)	2 (0.6)
A03F Propulsives	1 (0.2)	0 (0)	1 (0.3)
A11A Multivitamins, combinations	1 (0.2)	0 (0)	1 (0.3)
A07E Intestinal anti-inflammatory agents	1 (0.2)	0 (0)	1 (0.3)
A12A Calcium	2 (0.5)	0 (0)	2 (0.6)
Total	75 (20)	2 (3.3)	73 (23.1)
B BLOOD AND BLOOD FORMING ORGANS			
B03B Vitamin B12 and folic acid	14 (3.8)	0 (0)	14 (4.4)
B01A Antithrombotic agents	29 (7.7)	5 (8.4)	24 (7.6)
B03A Iron preparations	1 (0.2)	0 (0)	1 (0.3)
B03X Other antiemetic preparations	1 (0.2)	0 (0)	1 (0.3)
B01AA Vitamin K antagonists	1 (0.2)	1 (1.7)	0 (0)
B05X I.V. Solution additives	1 (0.2)	0 (0)	1 (0.3)
B02B Vitamin K and other hemostatic	1 (0.2)	0 (0)	1 (0.3)

Total	48 (12.8)	6 (10.1)	42 (13.2)
C CARDIOVASCULAR SYSTEM			
C10A Lipid modifying agents	32 (8.5)	1 (1.6)	31 (9.8)
C09A Angiotensin-converting enzyme (ACE) inhibitor	10 (2.6)	1 (1.6)	9 (2.8)
C07A Beta blocking agents	9 (2.4)	2 (3.2)	7 (2.2)
C01A Cardiac glycosides	1 (0.2)	0 (0)	1 (0.3)
C03C High-ceiling diuretics	4 (1)	0 (0)	4 (1.2)
C03D Aldosterone antagonists and other potassium-sparing agents	2 (0.5)	1 (1.6)	1 (0.3)
C09C Angiotensin II receptor blocker (ARBs)	10 (2.6)	2 (3.2)	8 (2.5)
C08C Selective calcium channel blockers with mainly vascular effects	8 (2.1)	0 (0)	8 (2.5)
C08D Selective calcium channel blockers with direct cardiac effects	1 (0.2)	0 (0)	1 (0.3)

C03A Low-ceiling diuretics, thiazides	3 (0.8)	0 (0)	3 (0.9)
C01D Vasodilators used in cardiac diseases	5 (1.3)	0 (0)	5 (1.5)
C09D Angiotensin II receptor blocker (ARBs), combinations	1 (0.2)	0 (0)	1 (0.3)
C09B ACE inhibitors, combinations	4 (1)	0 (0)	4 (1.2)
C10B Lipid modifying agents, combinations	2 (0.5)	0 (0)	2 (0.6)
C01B Antiarrhythmics, class I AND III	1 (0.2)	1 (1.6)	0 (0)
Total	93 (24.8)	8 (13.5)	85 (26.8)
S SENSORY ORGANS			
S01E Antiglaucoma preparations and miotics	5 (1.3)	1 (1.6)	4 (1.2)
S01X Other ophthalmological	1 (0.2)	0 (0)	1 (0.3)
Total	6 (1.6)	1 (1.6)	5 (1.5)
N NERVOUS SYSTEM			
N06D Anti-dementia drugs	20 (5.3)	4 (6.7)	16 (5)

N06A Antidepressants	30 (8)	7 (11.8)	23 (7.2)
N02B Other analgesics and antipyretics	11 (2.9)	5 (8.4)	6 (1.8)
N02A Opioids	7 (1.8)	7 (11.8)	0 (0)
N05B Anxiolytics	2 (0.5)	1 (1.6)	1 (0.3)
N05C Hypnotics and sedatives	2 (0.5)	2 (3.2)	0 (0)
N01B Anesthetics, local	1 (0.2)	0 (0)	1 (0.3)
N05A Antipsychotics	4 (1)	3 (5)	1 (0.3)
N03A Antiepileptics	3 (0.8)	1 (1.6)	2 (0.6)
N04B Dopaminergic agents	1 (0.2)	0 (0)	1 (0.3)
N07C Antivertigo preparations	1 (0.2)	0 (0)	1 (0.3)
Total	82 (21.8)	30 (50.8)	52 (16.4)
L ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS			
L01C Plant alkaloids and other natural products	1 (0.2)	0 (0)	1 (0.3)
L01B Antimetabolites	1 (0.2)	0 (0)	1 (0.3)
L01X Other antineoplastic agents	1 (0.2)	0 (0)	1 (0.3)
Total	3 (0.8)	0 (0)	3 (0.9)

H SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS			
H03A Thyroid preparations	7 (1.8)	0 (0)	7 (2.2)
Total	7 (1.8)	0 (0)	7 (2.2)
R RESPIRATORY SYSTEM			
R01B Nasal decongestants for systemic use	1 (0.2)	0 (0)	1 (0.3)
R03A Adrenergic, inhalants	9 (2.4)	0 (0)	9 (2.8)
R06A Antihistamines for systemic use	1 (0.2)	1 (1.6)	0 (0)
R03B Other drugs for obstructive airway diseases, inhalants	3 (0.8)	0 (0)	3 (0.9)
R03D Other systemic drugs for obstructive airway diseases	1 (0.2)	0 (0)	1 (0.3)
Total	15 (4)	1 (1.6)	14 (4.4)
M MUSCULO-SKELETAL SYSTEM			
M03B Muscle relaxants, centrally acting agents	3 (0.8)	3 (5)	0 (0)

M01A Anti-inflammatory and antirheumatic products, non-steroids	2 (0.5)	1 (1.6)	1 (0.3)
M05B Drugs affecting bone structure and mineralization	3 (0.8)	0 (0)	3 (0.9)
M04A Antigout preparations	4 (1)	1 (1.6)	3 (0.9)
Total	12 (3.2)	5 (8.4)	7 (2.2)
D DERMATOLOGICALS			
D04A Antipruritic, incl antihistamines, anesthetics, etc.	1 (0.2)	1 (1.6)	0 (0)
D06A Antibiotics for topical use	2 (0.5)	0 (0)	2 (0.6)
D07A Corticosteroids, plain	4 (1)	0 (0)	4 (1.2)
D01A Antifungals for topical use	3 (0.8)	0 (0)	3 (0.9)
Total	10 (2.6)	1 (1.6)	9 (2.8)

5.7.1.3 Factors associated with the overall DRPs use

The results of the binary logistic regression are revealed in Table 5-26. There were no significant associations between the age, sex, number of comorbidities, number of

medications per day, nervous system drugs, and recent history of falls and DRP use overall. As an illustration for this analysis, "1 (Reference)" indicates that the group with 1-5 comorbidities is the reference category, against which the other categories are compared. The outcome odds for the group with 6-8 comorbidities are 1.43 times higher than the reference group, but this difference is not statistically significant since the p-value is 0.672 (greater than 0.05). For the group with nine or more comorbidities, the odds of the outcome are 2.76 times higher than the reference group. Still, again, this difference is not statistically significant, with a p-value of 0.396 (greater than 0.05).

Table 5-26:- Binary logistic regression

Characteristics	**Odds ratio**	**95% Confidence interval**	**P-value**
Age			
65- 80 years	1 (Reference)		
>80 years	0.53	0.11- 2.59	0.439
Sex			
Male	1 (Reference)		
Female	1.49	0.20- 7.19	0.619
Number of comorbidities			
1- 5	1 (Reference)		
6- 8	1.43	0.26- 7.67	0.672

≥ 9	2.76	0.26- 29.04	0.396
Number of medications per day			
1- 4 medications	1 (Reference)		
5- 9 medications	3	0.37- 24.29	0.303
≥ 10	2.33	0.28- 19.17	0.430
Nervous system drugs			
No	1 (Reference)		
Yes	3.72	0.66- 20.66	0.133
Recent history of falls			
Absent	1 (Reference)		
Present	2.08	0.43- 10.06	0.361

P-value <0.05 considered statistically significant

5.7.2 Additional analysis for DRPs identified using MedRevCiD checklist and MAI criteria

5.7.2.1 Characteristics of the study population with drug-related problem (DRPs) as per MedRevCiD checklist and MAI criteria

The study participants were categorized into two groups: participants with DRPs identified as per MedRevCiD and participants with DRPs identified as per MAI criteria. Overall, 81.8% (n= 36) participants were identified with at least one DRP per the MedRevCiD checklist and 56.8% (n= 25) participants were identified with at least one DRP using MAI

criteria. The descriptive analysis of the study population in terms of baseline and clinical characteristics between the two groups is presented in Table 5-27. The mean age of the patients in the MedRevCiD group was 79.1 ± 5.7, and the mean age in the MAI group was 80.5 ± 6.0 years. Interestingly, the participants in the MAI group had a higher mean number of comorbidities than the MedRevCiD group. In both groups, the participants were more likely to have mild cognitive impairment or mixed dementia. Concerning recent history of falls, most participants (64%, n= 16) in the MAI group have a positive recent history of falls compared to 52.8% (n= 19) in the MedRevCiD group.

Table 5-27: Demographic and clinical characteristics of the study population (DRP as per MedRevCiD and MAI criteria)

Characteristics	**Total (N= 44) n (%)**	**With DRP as per MedRevCiD (N= 36) n (%)**	**With DRP as per MAI criteria (N= 25) n (%)**
Age of the patient, mean ± SD	80.2 ± 6.2	79.1 ± 5.7	80.5 ± 6.0
65- 69 years	2 (4.5)	2 (5.5)	2 (8)
70- 74 years	5 (11.5)	5 (13.9)	1 (4)
75- 79 years	13 (29.5)	11 (30.5)	6 (24)
80- 84 years	13 (29.5)	12 (33.3)	10 (40)
≥ 85 years	11 (25)	6 (16.6)	6 (24)
Sex			
Male	24 (54.5)	20 (55.5)	13 (52)
Female	20 (45.5)	16 (44.5)	12 (48)

Marital Status			
Married	38 (86.4)	31 (86.1)	22 (88)
Separated	1 (2.2)	1 (2.7)	1(4)
Widowed	5 (11.4)	4 (11.2)	2 (8)
Cognitive Impairment/dementia			
Vascular CI	5 (11.4)	5 (13.8)	4 (16)
Subjective cognitive decline	4 (9.1)	3 (8.4)	1 (4)
Evolving neurocognitive disorder	3 (6.8)	3 (8.4)	3 (12)
Mild CI	16 (36.4)	14 (38.9)	9 (36)
Mixed dementia	9 (20.5)	6 (16.6)	5 (20)
Dementia	4 (9.1)	3 (8.4)	2 (8)
Probable or possible Alzheimer's disease	3 (6.7)	2 (5.5)	1 (4)
Comorbidities			
Number of comorbidities per person, mean ± SD	6.7 ± 3.4	7.0 ± 3.6	8.3 ± 3.4
0	1 (2.3)	1 (2.8)	0 (0)
1- 5	16 (36.3)	12 (33.3)	5 (20)
6- 8	18 (41)	14 (38.9)	11 (44)
≥ 9	9 (20.4)	9 (25)	9 (36)
Alcohol			

Never	20 (45.5)	15 (41.6)	11 (62.5)
Occasional drinker	11 (25)	11 (30.6)	6 (0)
Active regular drinker	13 (29.5)	10 (27.8)	8 (37.5)
Smoking			
Never	24 (54.5)	19 (52.8)	12 (48)
Ex-smoker	17 (38.7)	14 (38.8)	11 (44)
Active smoker	3 (6.8)	3 (8.4)	2 (8)
Recent history of falls			
Absent	21 (47.7)	17 (47.2)	9 (36)
Present	23 (52.3)	19 (52.8)	16 (64)

SD, Standard deviation

5.7.2.2 Medication use among the study population as per MedRevCiD and MAI criteria

In the DRPs identified as per the MAI criteria group, the median number of medications prescribed was 9 (IQR 6), which was lower than the median number of medications prescribed in the MedRevCiD group (7.5 (6)). The number of medications prescribed per individual per day varied between 1 and 21 in the MedRevCiD group. In comparison, the number of medications prescribed per person per day ranged from 4 to 21 in the MAI group. Notably, agents from the cardiovascular and nervous systems were the most frequently prescribed in both groups, as presented in Table 5-28. It was observed that agents from the nervous system were the most prescribed agents, so we distributed the patients identified with DRPs at the drug level to gain a more detailed understanding. Additional details concerning the distribution of patients with DRPs as per MedRevCiD

and MAI criteria and those prescribed Nervous System drugs within the study population are presented in Appendix E-4.

Table 5-28: Medication use among the study participants according to ATC classification (MedRevCiD and MAI)

Characteristics	**Total (N= 44) n (%)**	**With DRP as per MedRevCiD (N= 36) n (%)**	**With DRP as per MAI (N= 25) n (%)**
Number of medications per person, median (IQR)	7.5 (6)	7.5 (6)	9 (6)
Medications per day			
1- 4	6 (13.6)	5 (13.9)	1 (4)
5- 9	21 (47.7)	18 (50)	12 (48)
≥10	17 (38.6)	13 (36.1)	12 (48)
ATC classification			
G Genito urinary system and sex hormones	16 (36.4)	15 (41.6)	12 (48)
A Alimentary tract and metabolism	32 (72.7)	26 (72.2)	21 (84)
B Blood and blood forming organs	34 (77.3)	28 (77.7)	22 (88)
C Cardiovascular system	36 (81.8)	31 (86.1)	23 (92)

S Sensory organs	4 (9.1)	3 (8.3)	3 (12)
N Nervous system	36 (81.8)	30 (83.3)	24 (96)
L Antineoplastic and immunomodulating agents	4 (9.1)	3 (8.3)	3 (12)
H Systemic hormonal preparations	7 (15.9)	5 (13.9)	4 (16)
R Respiratory system	9 (20.5)	7 (19.4)	7 (28)
M Musculo-skeletal system	8 (18.2)	5 (13.9)	4 (16)
D Dermatologicals	7 (15.9)	6 (16.6)	4 (16)

5.7.2.3 Factors associated with DRPs use as per MedRevCiD and MAI

Regression models are usually beneficial to explore the relationship between a dependent and one or more independent variables. This study used binary logistic regression because the dependent variable outcome is dichotomous (absent/present). Binary logistic regression uses either 0 or 1 to code dependent variables. 1 means DRPs present, while 0 means DRPs absent. The relationship can be interpreted in terms of odds ratio. The odds ratio (OR) tells you how strongly two variables are associated. A high odds ratio indicates a strong association, while a low odds ratio suggests a weaker association. An odds ratio of 1 suggest no association. The results of the binary logistic regression are revealed in Table 5-29. The binary logistic regression provides no evidence of an association between age, sex, number of comorbidities, number of medications per day, nervous system drugs, and recent history of falls and DRP use as per the MedRevCiD checklist. However, the findings of binary logistic regression revealed a statistically significant association between number

of comorbidities (OR= 1.86; 95% CIn= 1.25- 2.76; P= 0.002), number of medications per day (OR= 1.20; 95% CIn= 1.01- 1.41; P= 0.032). The findings revealed the presence of nervous system drug use (OR= 14; 95% CIn= 1.54- 127.22; P= 0.019 and DRP use as per MAI criteria. Interestingly, a recent history of falls among patients was not significantly associated with DRP use as per MAI criteria. Still, the P-value is on the borderline of 0.078.

Table 5-29: Binary logistic regression

	MedRevCiD		**MAI**	
Characteristics	Odds ratio (95% CIn)	P- value	Odds ratio (95% CIn)	P- value
Age				
65- 80 years	1 (Reference)		1 (Reference)	
>80 years	0.26 (0.04- 1.50)	0.134	1.75 (0.52- 5.84)	0.363
Sex				
Male	1 (Reference)		1 (Reference)	
Female	0.8 (0.17- 3.70)	0.776	1.26 (0.38- 4.22)	0.697
Number of comorbidities*	1.21 (0.91- 1.62)	0.178	1.86 (1.25- 2.76)	**0.002**
Number of medications per day*	0.97 (0.83- 1.15)	0.788	1.20 (1.01- 1.41)	**0.032**

Nervous system drugs				
No	1 (Reference)		1 (Reference)	
Yes	1.66 (0.26-10.33)	0.583	14 (1.54-127.22)	**0.019**
Recent history of falls				
Absent	1 (Reference)		1 (Reference)	
Present	1.11 (0.24- 5.17)	0.887	3.04 (0.88-10.52)	0.078

***Continuous variable**
P-value <0.05 considered statistically significant

5.7.3 Additional analysis for PIMs

5.7.3.1 Characteristics of the study population with PIMs as per American Geriatric Society (AGS) Beers criteria and European Geriatric Society (EGS) Screening Tool of Older Persons potentially inappropriate Prescriptions (STOPP) criteria

The AGS Beers and EGS STOPP criteria were utilized to identify potentially inappropriate medications (PIMs) in this population. The results revealed that at least one PIM was identified in 47.7% (n=21) of the patient population when applying the Beers criteria and 27.3% (n=12) of the patients using the STOPP criteria. The eligible participants were divided into two groups: patients with PIMs identified according to the Beers criteria and patients with PIMs identified according to the STOPP criteria. Further details regarding the descriptive analysis of the study population in terms of baseline and clinical characteristics for these two groups can be found in Table 5-30.

Table 5-30: Demographic and clinical characteristics of the study population (PIMs as per Beers and STOPP criteria)

Characteristics	**Total (N= 44) n (%)**	**With PIMs as per Beers criteria (N= 21) n (%)**	**With PIMs as per STOPP criteria (N= 12) n (%)**
Age of the patient, mean ± SD	80.2 ± 6.2	80.7 ± 5.6	83.5 ± 4.8
65- 69 years	2 (4.5)	1 (4.8)	0 (0)
70- 74 years	5 (11.5)	2 (9.5)	0 (0)
75- 79 years	13 (29.5)	4 (19)	2 (16.6)
80- 84 years	13 (29.5)	10 (47.7)	5 (41.7)
≥ 85 years	11 (25)	4 (19)	5 (41.7)
Sex			
Male	24 (54.5)	11 (52.3)	4 (33.3)
Female	20 (45.5)	10 (47.7)	8 (66.7)
Marital Status			
Married	38 (86.4)	20 (95.2)	10 (83.3)
Separated	1 (2.2)	0 (0)	0 (0)
Widowed	5 (11.4)	1 (4.8)	2 (16.7)
CI/dementia			
Vascular CI	5 (11.4)	4 (19)	3 (25)
Subjective cognitive decline	4 (9.1)	1 (4.7)	0 (0)

Evolving neurocognitive disorder	3 (6.8)	2 (9.5)	2 (16.6)
Mild CI	16 (36.4)	8 (38)	3 (25)
Mixed dementia	9 (20.5)	4 (19)	1 (8.3)
Dementia	4 (9.1)	2 (9.5)	2 (16.6)
Probable or possible Alzheimer's disease	3 (6.7)	0 (0)	1 (8.3)
Comorbidities			
Number of comorbidities per person, mean ± SD	6.7 ± 3.4	7.6 ± 3.0	8 ± 4.1
0	1 (2.3)	0 (0)	0 (0)
1- 5	16 (36.3)	5 (23.8)	3 (25)
6- 8	18 (41)	9 (42.8)	5 (41.6)
≥ 9	9 (20.4)	7 (33.4)	4 (33.4)
Alcohol			
Never	20 (45.5)	9 (42.8)	6 (50)
Occasional drinker	11 (25)	5 (23.8)	3 (25)
Active regular drinker	13 (29.5)	7 (33.4)	3 (25)
Smoking			
Never	24 (54.5)	14 (66.6)	7 (58.4)
Ex-smoker	17 (38.7)	6 (28.6)	5 (41.6)
Active smoker	3 (6.8)	1 (4.8)	0 (0)

Recent history of falls			
Absent	21 (47.7)	7 (33.3)	4 (33.3)
Present	23 (52.3)	14 (66.7)	8 (66.7)

SD, Standard deviation

5.7.3.2 Medication use among the study population identified with PIMs as per AGS Beers criteria and EGS STOPP criteria

The PIMs identified according to Beers criteria exhibited a median of 2 prescribed medications (IQR: 1), which was comparable to the median for PIMs identified using STOPP criteria (2.5 (IQR: 1)). It is noteworthy that medications from the cardiovascular and nervous system categories were the most frequently prescribed in both groups, as depicted in Table 5-31. Given the prevalence of nervous system agents, we further delved into the distribution of patients identified with PIMs at the drug level to gain deeper insights. For additional details regarding the distribution of patients with PIMs according to Beers and STOPP criteria and those prescribed Nervous System drugs within the study population, please refer to Appendix E-5.

Table 5-31:- Medication use among the study participants according to ATC classification (PIM as per Beers and STOPP criteria)

Characteristics	**Total (N= 44) n (%)**	**With PIMs as per Beers (N= 21) n (%)**	**With PIMs as per STOPP (N= 12) n (%)**
Number of medications per person, median (IQR)	7.5 (6)	2 (1)	2.5 (1)
Medications per day			

1- 4	6 (13.6)	1 (4.7)	0 (0)
5- 9	21 (47.7)	10 (47.6)	6 (50)
≥10	17 (38.6)	10 (47.6)	6 (50)
ATC classification			
G Genito urinary system and sex hormones	16 (36.4)	8 (38.0)	3 (25)
A Alimentary tract and metabolism	32 (72.7)	18 (85.7)	11 (91.6)
B Blood and blood forming organs	34 (77.3)	17 (80.9)	11 (91.6)
C Cardiovascular system	36 (81.8)	19 (90.4)	12 (100)
S Sensory organs	4 (9.1)	3 (14.2)	2 (16.6)
N Nervous system	36 (81.8)	20 (95.2)	12 (100)
L Antineoplastic and immunomodulating agents	4 (9.1)	2 (9.5)	2 (16.6)
H Systemic hormonal preparations	7 (15.9)	4 (19)	3 (25)
R Respiratory system	9 (20.5)	7 (33.3)	3 (25)
M Musculo-skeletal system	8 (18.2)	5 (23.8)	3 (25)
D Dermatologicals	7 (15.9)	2 (9.5)	1 (8.3)

5.7.3.3 Factors associated with PIMs as per Beer's criteria and STOPP criteria

Table 5-32 revealed the results of the binary logistic regression test conducted to determine the association of independent variables (age, sex, number of comorbidities, number of medications per day, nervous system drugs, and recent history of falls) with PIMs identified as per Beers criteria and STOPP criteria. There was a marginally significant association between age > 80 years and the occurrence of PIMs as per STOPP criteria. For age > 80 years, the odds of having a PIM using Beers criteria are 2.52 times higher in this age group, but the difference is not statistically significant. The odds of having PIM using STOPP criteria are 4.38 times higher in this age group, and there is a marginal statistical significance (OR= 4.38, 95% CIn= 0.99- 19.35, P= 0.051). There was a significant association between ≥ 9 number of comorbidities and PIMs as per Beers criteria (OR= 8.4, 95% CIn= 1.27- 55.39, P= 0.027). However, no statistically significant association was observed with PIMs as per STOPP criteria. There were two marginally significant associations observed between the number of medications per day (continuous variable) (OR= 1.14, 95% CIn= 0.99- 1.32, P= 0.064), the recent history of falls present (OR= 3.11, 95% CIn= 0.90- 10.69, P= 0.072) with PIMs as per Beers criteria.

Table 5-32: Binary logistic regression

	Beers 2023		**STOPP 2023**	
Characteristics	**Odds ratio (95% CIn)**	**P- value**	**Odds ratio (95% CIn)**	**P- value**
Age				
65- 80 years	1 (Reference)			

>80 years	2.52 (0.74- 8.52)	0.135	4.38 (0.99- 19.35)	**0.051**
Sex				
Male	1 (Reference)			
Female	1.18 (0.36- 3.87)	0.783	3.33 (0.82- 13.48)	0.091
Number of comorbidities				
1- 5	1 (Reference)			
6- 8	2.4 (0.39- 9.67)	0.218	1.79 (0.35- 9.05)	0.479
≥ 9	8.4 (1.27- 55.39)	**0.027**	3.73 (0.60- 22.85)	0.154
Number of medications per day*	1.14 (0.99- 1.32)	0.064	1.09 (0.94- 1.26)	0.214
Recent history of falls				
Absent	1 (Reference)		1 (Reference)	
Present	3.11 (0.90- 10.69)	0.072	2.26 (0.56- 9.06)	0.247

*Continuous variable
P-value <0.05 considered statistically significant

Chapter 6: Discussion and Conclusion

6.1 Discussion

The research presented in this thesis focused on identifying and evaluating drug-related problem (DRP) use among older adults with cognitive impairment (CI) or dementia. The comparison was carried out using the Medication Review in Cognitive Impairment and Dementia **(**MedRevCiD) checklist and Medication Appropriateness Index (MAI) criteria. Additionally, the research delved into comparing potentially inappropriate medication (PIM) use in this population, using the Beers Criteria 2023 and the Screening Tool of Older Persons' Potentially Inappropriate Prescriptions (STOPP) Criteria 2023. Furthermore, this research categorized the identified DRPs using the Pharmaceutical Care Network Europe (PCNE) version 9 criteria.

6.1.1 Comparison of Drug-related problems identified using Medication Review in Cognitive Impairment and Dementia (MedRevCiD) checklist and Medication Appropriateness Index (MAI) criteria

This study is one of its kind that has analyzed and compared DRPs using the MedRevCiD checklist and MAI criteria in older adults with CI and/or dementia.

The proportion of patients identified with at least one DRP using the MedRevCiD checklist was higher at 81.8%, compared to 56.8% identified with at least one DRP using MAI criteria. It is important to note that this is the first study applying the MedRevCiD checklist in a clinical setting to identify DRPs. However, the findings of 56.8% of patients identified with at least one DRP per MAI criteria appear lower than the numbers reported in previously published literature. For instance, a study by Hernandez et al. was conducted in a long-term psychogeriatric unit in an intermediate care hospital in Spain.[91] Older adults

diagnosed with dementia and were admitted to control Behavioral and Psychological Symptoms of Dementia (BPSD) were included in the study. In the study, 90% (59/65) of the patients were affected by some criteria by MAI criteria, which is higher than the proportion reported in our study.[91] The observed difference in the proportion of patients with DRPs may be attributed to variations in patient populations, healthcare settings, location, or study methodologies across the studies. An essential factor contributing to this difference is that our study included patients from primary healthcare settings. Whereas Hernandez et al. have included patients from hospital settings.[91] Another important factor contributing to the observed difference is the variation in patient populations between our study and that of Hernandez et al. Our study has also included patients with subjective decline, and mild CI. While Hernandez et al. exclusively focused on patients diagnosed with dementia who were admitted to control BPSD.

In one of the cross-sectional analyses identified during our scoping review, researchers conducted a study involving community-dwelling primary care patients who screened positive for dementia in Germany. A pharmacist conducted medication reviews of the 446 included study participants. The authors used the PIE-Doc-System to classify the DRPs into five main groups mentioned in the system. Their findings revealed a striking prevalence of drug-related problems (DRPs) within this cohort, with 93% (414 out of 446) of the patients identified as having at least one DRP. The authors documented 1,077 distinct instances of DRPs within this population.[89] The authors classified the DRPs into the following five groups: Inappropriate drug choice, Administration and compliance, Dosage, Drug interactions, and Adverse drug events. Problems related to administration and

compliance were the most common group of DRPs, such as inappropriate time of application, inadequate storage, and no medication list or medication list. In our study, we identified no DRPs related to administration. However, we have identified 10 DRPs out of 134 DRPs identified using the MedRevCiD checklist related to noncompliance to drugs intentionally or intentionally.

The results obtained from our study are like those presented by Pfister et al., where data were extracted from a randomized controlled trial examining the impact of a pharmacist intervention within a hospital ward team. The Pfister study focused on patients aged 65 years or older diagnosed with either dementia or cognitive impairment (CI). The classification of DRPs in the study followed a modified adaptation of Cipolle et al.'s framework, as outlined in their referenced work.[54] The DRPs were categorized into seven distinct subgroups, including Adverse Drug Reactions (ADR), instances of dosage being too high or too low, identification of ineffective drug therapy, situations necessitating additional drug therapy, recognition of unnecessary drug therapy, and cases related to noncompliance with medication regimens. Among the 310 DRPs identified by the clinical pharmacists, 66% (140/212) of the participants. Ineffective drug/inappropriate drug (n = 54) and unnecessary drug therapy (n = 54) were the most common DRPs reported in the study. In our research, inappropriate drug, followed by drug interactions, was identified as the most common type of DRP.

A total of 134 DRPs were identified in 44 study participants using MedRevCiD. The maximum DRPs identified in a patient was 20 DRPs per person. The average number of DRPs identified in 36 patients was 2.89 ± 3.7 DRPs per person, which is higher than the

average DRPs reported in any other published study on older adults with CI and/or dementia.[54,123,124] The average number of DRPs identified using the MAI criteria was 1.84 ± 2.9 DRPs per person, which is higher than the DRPs reported in other studies.[54,123,124] One possible reason for the difference in DRP numbers is the choice of assessment tools and criteria used, as the studies have used different implicit or explicit criteria to identify the DRPs. Additionally, variations in healthcare settings, study methodologies, and patient demographics across different studies can impact the identification and reporting of DRPs.

The difference in the number of identified DRPs between the PCNE classification (119 DRPs) and the MedRevCiD (134 DRPs) might arise for several reasons. One important reason is that MedRevCiD has a broader or more specific set of criteria for identifying DRPs than PCNE. This wider scope might allow MedRevCiD to capture more nuanced or particular types of DRPs into different domains but fall under a kind of DRPs as per PCNE criteria. The subjective nature of PCNE criteria might introduce variability in how reviewers classify DRPs, which could impact the consistency and accuracy of the identified problems in the studies.

A total of 375 medications were prescribed to 44 study participants. The most frequently implicated drugs in causing DRPs in older adults with dementia were from the nervous system class. The most identified nervous system agents responsible for DRPs were donepezil (anti-dementia drugs), duloxetine and sertraline (antidepressants), gabapentin (other analgesics and antipyretics), oxycodone or hydromorphone (opioids), risperidone (antipsychotics), and zopiclone (hypnotics and sedatives). Because of the complex nature of managing chronic diseases, most patients were treated with multiple medications, some

of which may have the potential to cause drug-induced CI or worsening, leading to an increased risk of exposure to DRPs.[125,126]

In our study, almost 86.3% of the older adults experienced polypharmacy, and 38.6% experienced hyper-polypharmacy. As would be expected, older adults with dementia and/or CI are prone to be prescribed ≥ 5 medications per day.[18,23] Our study results for polypharmacy and hyper polypharmacy are similar to the results mentioned in Hernandez et al., a study in which 87.7% (57/65) of the study population were on polypharmacy and 38.5% (n= 25/65) were on hyper-polypharmacy.[91] The findings from nine out of ten studies in the scoping review underscored a prevalent use of multiple medications per patient, consistently reporting an average number of medications per patient equal to or exceeding five, ranging notably from 6.4 to 13.3 per patient per day.[36,44,82,83,86,90,91,94,96] In alignment with this trend, our study yielded comparable results, indicating a median number of medications per patient daily at 7.5, with an interquartile range (IQR) of 6 medications daily. This collective data emphasizes a widespread pattern of polypharmacy across various healthcare settings, highlighting the common practice of administering multiple medications to individual patients, which was consistently observed in both external studies and our study. The utilization of polypharmacy among older adults with dementia is often linked to increased comorbidities and a higher incidence of dementia-related complications.[23,24] Moreover, excessive use of polypharmacy or hyper-polypharmacy was also found to be associated with an elevated risk of developing dementia in one of the systematic reviews and meta-analyses conducted by Leelakanok et al.[25]

The most prescribed drugs reported in the previously published literature were antipsychotics, anti-dementia drugs, antidepressants, sedatives, and hypnotic agents.

[79,84,85,90,91] In our study, the most frequently prescribed medications in Anatomical Therapeutic Chemical (ATC) classification categories were cardiovascular system agents, nervous system agents and alimentary tract and metabolism agents. From the cardiovascular system agents, lipid modifying agents, angiotensin-converting enzyme (ACE) inhibitors, beta-blockers, and angiotensin II receptor blockers (ARBs) were the most prescribed drugs for the treatment of common chronic diseases such as hypertension and cardiovascular disease.[25] A total of 375 medications were prescribed to 44 study participants. The most frequently implicated drugs in causing DRPs in older adults with dementia were from the nervous system class. The most identified nervous system agents responsible for DRPs were donepezil (anti-dementia drugs), duloxetine and sertraline (antidepressants), gabapentin (other analgesics and antipyretics), oxycodone or hydromorphone (opioids), risperidone (antipsychotics), and zopiclone (hypnotics and sedatives). Because of the complex nature of managing chronic diseases, most patients were treated with multiple medications, some of which may have the potential to cause drug-induced CI or worsening, leading to an increased risk of exposure to DRPs.[26,27]

The results of the Wilcoxon signed-rank test, which was carried out to determine the significance of the differences between the two assessment methods, revealed a notable finding. The test outcome indicates that the number of DRPs identified using the MedRevCiD checklist is significantly higher than those identified through the MAI criteria. In simpler terms, our findings suggest that the MedRevCiD checklist may be more sensitive in recognizing DRPs in dementia care, as reflected by the statistically significant difference in DRP identification between the two tools. These results arise from the fact that the MedRevCiD checklist uses implicit questions and explicit instructions and provides more

guidance to the healthcare professionals using the checklist in this specific population. The MAI, on the other hand, is a more general tool. This means a higher proportion of patients with DRPs using the MedRevCiD checklist is expected. Therefore, it's essential to recognize that the comparison between MedRevCiD and MAI may not be entirely fair, given their distinct purposes and scopes. These results underline the importance of employing comprehensive and tailored assessment tools, such as the MedRevCiD checklist, to effectively identify and address DRPs in older adults, particularly those with dementia.

Based on the extensive findings and gaps identified in the scoping review related to medication reviews in older adults with dementia, it's crucial to capture comprehensive outcomes that can effectively demonstrate the impact of medication reviews with MedRevCiD as the foundation of such reviews. The suggested outcomes should be considered: 1. Medication adherence and management; 2. Identification of DRPs; 3. Clinical significance of the identified DRPs by discussing with the pharmacist; 4. Recommendations to resolve the identified DRPs; 5. Reduction in DRPs post-medication reviews; 6. Patient and caregiver satisfaction; 7. A core outcome set for medicines management interventions for people with dementia in primary care as mentioned in McGrattan et al. paper.

6.1.2 Types of DRPs

A total of 17 DRPs were identified from the first domain of MedRevCiD, which focuses on assessing the medication management capacity and resulting impact on medication adherence. Neither the MAI criteria nor the Beers and STOPP criteria cover this domain.[62]

The most commonly reported DRP in this domain was intentional non-adherence to drugs, followed by missing a few doses of medication unintentionally. Non-adherence to prescribed medication, intentional or unintentional, can significantly affect a patient's health.[127] Non-adherence can lead to the ineffective management of medical conditions, potentially resulting in the worsening of the underlying health condition, which is especially concerning in cases of chronic diseases like dementia.[22] Non-adherence can also lead to increased healthcare costs as it may result in more frequent doctor visits or hospitalizations due to uncontrolled symptoms or complications. In the case of dementia, non-adherence can exacerbate behavioral and cognitive symptoms, making caregiving and management more challenging.[128]

Domain 2 of the MedRevCiD appears to be primarily centered on drugs that have the potential to cause drug-induced CI or worsen existing cognitive issues.[62] In contrast, the MAI criteria have a broader focus, encompassing overall drug-disease interactions, which may involve various aspects of a patient's health beyond cognitive function. This difference in focus between the two criteria sets highlights the importance of considering the specific impact of medications on cognitive health when assessing drug-related problems in individuals, especially those with conditions like dementia. The most commonly identified drugs that may induce CI or worsen are gabapentin (Gamma-aminobutyric acid (GABA) analogue), hydromorphone (opioid analgesic), and methocarbamol (skeletal muscle relaxant). These medications are known to have potential cognitive side effects, and their impact should be carefully considered, especially in older adults and individuals with preexisting cognitive conditions like dementia.[129-132]

Another significant set of DRPs identified are those falling within domain 3, which is concentrated on medical conditions that can disrupt cognitive function and impact health outcomes in older adults with dementia.[62] Out of 134 DRPs, 13 DRPs were identified from this domain. However, it's worth noting that the MAI criteria do not extensively address these specific medical conditions and their potential impact on cognitive health. Domain 3 of MedRevCiD lists commonly encountered conditions that may impact or worsen CI and/or dementia, which no other explicit or implicit criteria provide. For instance, conditions like vitamin B12 deficiency in older adults with dementia, sleep apnea, or atrial fibrillation (especially when the patient's international normalized ratio (INR) remains outside the target range while being treated with warfarin) are examples of medical issues that can significantly impact cognitive function.[133-135] A clear and direct link between atrial fibrillation and cognitive decline or dementia can be attributed to the heightened risk of stroke associated with atrial fibrillation, as atrial fibrillation is known to at least double the risk of stroke.[135] The well-established impact of stroke on cognitive function provides a plausible connection. However, it is noteworthy that the elevated risk of dementia and cognitive decline associated with atrial fibrillation is not entirely mediated by the increased risk of stroke.[134] Additional mechanisms include silent cerebral infarcts, microbleeds associated with oral anticoagulation, and cerebral hypoperfusion. These factors collectively contribute to the complex relationship between AF and cognitive outcomes.[135] Recognizing and addressing these conditions is crucial in providing adequate care for individuals with dementia and cognitive impairment. Identifying conditions that can interfere with cognition and impact health outcomes in older adults with dementia is crucial

for the potential reversibility of cognitive impairment, improved quality of life, prevention of further decline, accurate diagnosis, and the application of appropriate treatment.[135]

Only five DRPs out of 134 DRPs were identified from domain 4 of MedRevCiD. All the identified DRPs in the domain were specific to anti-dementia drugs. Domain 4 of the MedRevCiD checklist emphasizes anti-dementia drugs, particularly cholinesterase inhibitors (AchEI) or memantine.[62] The focus is on ensuring that the current therapy involving these medications is indicated and effective while prioritizing safety considerations. Three important drug-drug interactions were identified from this domain 4 of the MedRevCiD checklist and category 6 of MAI criteria (clinically significant drug-drug interactions). The only DRP from domain 4 not identified using MAI criteria was a patient experiencing weight loss as a side effect of the cholinesterase inhibitor (Donepezil). MAI, being a general tool, may not specifically capture side effects associated with anti-dementia medications.

Of 134 total DRPs, five DRPs were identified from domain 5 of the MedRevCiD checklist. Of five DRPs, four of the DRPs were covered in both criteria, except one was not covered in the MAI criteria. The DRPs identified were if the patient's Behavioral and Psychological Symptoms of Dementia (BPSD) (delusions, agitation, insomnia) are not responding to lower-risk medications for BPSD (e.g., selective serotonin reuptake inhibitor (SSRIs) or anticonvulsants) is an antipsychotic medication required for the behavior you wish to treat.[62]

Notably, domain 6 of the MedRevCiD checklist appears to bear a strong resemblance to the ten questions outlined in the MAI criteria.[136] For instance, 6.1 question of domain 6

(Does every medication being taken have an appropriate reason for use?) is similar to question 1 of MAI criteria (Is there an indication for the drug?); 6.2 question of domain 6 (Is each medication effective for its reason for use?) is similar to question 2 of MAI criteria (Is the medication effective for the condition?) etc.

In our study, the highest number of DRPs using MAI criteria were identified from clinically significant drug-disease interaction, which is similar to the results of previously published literature.[91] There is a lack of published studies providing in-depth details on DRPs at each question level within the MAI criteria. For instance, 40% of the patients in the Hernandez et al. study was affected with DRPs from the clinically significant drug-disease interaction criteria.[91] However, it's noteworthy that the authors did not provide detailed information on the specific types of DRPs identified within each MAI criterion. This absence of comprehensive data hinders the ability to directly compare the results obtained in this study with another research.

6.1.3 PIMs use as per Beers criteria and STOPP criteria

The inclusion of explicit criteria to assess medication appropriateness within the MedRevCiD checklist is a notable distinction from the MAI criteria. This addition significantly impacts the identification of DRPs because it allows for a more focused evaluation of medications in the context of older adults, especially those with dementia. The STOPP and Beers criteria are specifically designed to highlight potentially inappropriate medications for older individuals, considering the unique considerations of this population. By incorporating these criteria, the MedRevCiD criteria can offer a more

detailed and tailored analysis of medication appropriateness, which can result in the identification of a broader range of DRPs compared to the MAI criteria.

Notably, DRPs were explicitly identified within the inappropriate medication categories of Domain 6 of the MedRevCiD checklist. However, if these same DRPs had been previously identified in any other checklist domain, they were not reiterated or mentioned again in the 6.7 category of Domain 6. This approach helps avoid duplication and provides a more streamlined and comprehensive assessment of DRPs by focusing on those directly related to medication appropriateness within the context of the checklist's specific categories. The mention of Apixaban as an inappropriate medication in the STOPP criteria, while not being discussed in any other domain within the MedRevCiD checklist, emphasizes the specificity and relevance of the STOPP criteria for evaluating the appropriateness of medications, particularly in older adults with dementia. This highlights the importance of considering multiple criteria and guidelines when assessing medication appropriateness, as different criteria may capture unique aspects and considerations related to medication use in this specific population.

Falls are a common and serious issue in older adults, and certain medications, like SSRIs and selective norepinephrine reuptake inhibitors (SNRIs), can potentially contribute to an increased risk of falls due to side effects such as dizziness and impaired balance.[137,138] SSRIs such as sertraline, citalopram, and escitalopram are considered inappropriate according to the Beers and STOPP criteria. This highlights the importance of considering multiple criteria and guidelines when assessing medication appropriateness, as different

criteria may capture unique aspects and considerations related to medication use in this specific population.

In the case of inappropriate medication use, 47.7% (n= 21) and 27.2% (n= 12) of the patients were identified with at least one PIM using Beers and STOPP criteria, respectively. The prevalence of PIMs identified using Beers criteria was similar to the results of previous studies.[122] However, the prevalence of PIMs reported using STOPP criteria was lower than in the previous studies. A systematic review from 2016 reported that DRPs were identified by STOPP criteria in a substantial proportion of elderly patients, ranging from 32.4% to 66.8%.[139] The prevalence of PIMs can vary based on factors like the specific population being studied, the healthcare environment in which the research is conducted, and the particular criteria for identifying PIMs, whether it be the Beers criteria from 2012, 2015, or 2019, or STOPP criteria, any other criteria that are employed.[140]

We are also doing a systematic literature review and meta-analysis to examine the pooled prevalence of PIM use among older adults with dementia or CI attending memory clinics. The secondary objective was to identify frequently implicated PIMs. A total of 11 studies were included in the review.[141] The pooled prevalence of PIMs was 38%, with 95% CIn between 27 to 49%. The Beers criteria and STOPP criteria were the most commonly used explicit criteria. Compared to the results of the Cross-et al. study, which was conducted to explore the use of PIMs related to cognitive impairment (PIMcog), anticholinergic cognitive burden (ACB) and concomitant use of anticholinergic medications with cholinesterase inhibitors (ChEIs) in patients attending memory clinics.[96] Participants in the study were included from community-dwelling patients who had attended nine memory

clinics and had a diagnosis of MCI or dementia. PIMs were identified using Beers 2012 or STOPP 2015 criteria. Anticholinergic cognitive burden (ACB) was defined as a score of ≥ 3 on the ACB scale.[96] At least one PIM was identified in 21.4% (206/967) of the participants, which is less than the prevalence reported in our study using both the criteria, 47.7% (n= 21) and 27.2% (n= 12) based on Beers and STOPP criteria, respectively. Updated versions of the Beers and STOPP criteria might result in changes in the list of identified PIMs. Moreover, Variations in the characteristics of the study samples, such as demographics, health conditions, medications used, and healthcare settings, could influence the prevalence rates of identified PIMs. The most frequently identified PIMs were anticholinergic drugs, benzodiazepines, non-benzodiazepines, and SSRIs, which are similar to PIMs identified in our study.[96]

Highlighting the differences between the Beers and STOPP criteria is crucial, as these two sets of criteria play a pivotal role in assessing the appropriateness of medications for older adults and individuals with specific medical conditions, including dementia. These differences help healthcare providers make well-informed decisions regarding medication management. Here are some key differences from the independent of diagnosis category: According to the Beers Criteria, the use of danazol is considered inappropriate in older adults, except when it is indicated for confirmed hypogonadism with clinical symptoms.[60] Similarly, the Beers Criteria deem the use of sulfonylureas such as gliclazide inappropriate among older adults. Danazol has been associated with cardiovascular side effects, including an increase in blood pressure and an adverse impact on lipid profiles.[142] For older adults, who are already at increased risk for cardiovascular issues, these effects can be concerning. Compared to other medications, sulfonylureas have a greater risk of

hypoglycemia, cardiovascular events, and all-cause mortality.[143] Sulfonylureas could potentially elevate the risk of cardiovascular death and ischemic stroke. In contrast, it's worth noting that the STOPP Criteria do not categorize the utilization of danazol or gliclazide as inappropriate for older adults.[143] These differences reflect how each set of criteria has distinct considerations based on geographic origins, focuses, and specific medical conditions.

It is important to note that there are more drugs identified as inappropriate from independent of diagnosis category for Beers criteria than STOPP criteria. The important thing to highlight is there are seven medications identified as inappropriate for older adults with dementia and/or CI as per Beers criteria. In contrast, no medications were identified as inappropriate for this population in the "independent of diagnosis" category in the STOPP Criteria. This difference in recommendations underscores that the Beers Criteria may have more specific and condition-related considerations for older adults with dementia and cognitive impairment. The inclusion of more diagnosis categories in the STOPP Criteria compared to the Beers Criteria signifies the broader scope of the STOPP Criteria in addressing DRPs in older adults. This comprehensive approach allows the STOPP Criteria to encompass various medical conditions and considerations that may impact medication appropriateness.[144] Examples include the consideration of timolol use as inappropriate among older adults with bradycardia, which is included in the STOPP Criteria but not in the Beers Criteria. Additionally, the presence of diagnosis categories like insomnia and constipation in the STOPP Criteria, which are not present in the Beers Criteria, further underscores the extended coverage of medical conditions in the STOPP Criteria.[145]

There is a marked variability in the drug-drug interactions (DDI) identified using both criteria. There is not a single DDI common in both the criteria. More DDI were identified using Beers criteria than STOPP criteria. Any combination of ≥3 Central nervous system (CNS-active) drugs was identified as a PIM as per Beers criteria but not in the STOPP criteria. Additionally, out of 7 DDI identified using Beers criteria, 4 of them involve the use of opioids with other agents such as pregabalin, lorazepam, and gabapentin. The interaction between opioids and other CNS-active medications can increase the risk of adverse effects, including excessive sedation, respiratory depression, falls, and CI.[146] Given their increased susceptibility to medication-related side effects and interactions, these risks are especially significant in older adults. However, the identification of a potential DDI related to anti-dementia drugs, specifically donepezil (an acetylcholinesterase inhibitor), in combination with bisoprolol (a beta-blocker known to induce persistent bradycardia), as a risk for cardiac conduction failure, syncope, and injury is a significant finding from the STOPP Criteria.

Only one PIM was identified in kidney function and estimated Glomerular Filtration Rate (eGFR) level category of Beers criteria and STOPP criteria, respectively. Both criteria identified different PIMs. For example, gabapentin use was considered inappropriate as per Beer's criteria if the patient's creatinine clearance was less than 60ml/min. The medication identified as inappropriate using STOPP criteria was the use of celecoxib in a patient with an eGFR level of 40 ml/min/1.73m^2.

Some agreement between two sets of criteria, the Beers Criteria and the STOPP Criteria, in identifying cardiovascular and anti-thrombotic agents like amiodarone and rivaroxaban

as inappropriate for certain situations highlights the importance of these medications' appropriateness concerns. Some agreement between two sets of criteria, the Beers Criteria and the STOPP Criteria, in identifying cardiovascular and anti-thrombotic agents like amiodarone and rivaroxaban as inappropriate for certain situations highlights the importance of these medications' appropriateness concerns. Additionally, drugs identified as inappropriate in older adults with a history of falls are similar.

It is crucial to consider both the Beers Criteria and the STOPP Criteria for assessing medication appropriateness, especially for older adults and individuals with specific medical conditions like dementia, due to several important reasons. Each set of criteria provides a unique and comprehensive evaluation of medication appropriateness. While there may be some overlap, each set addresses specific issues and considerations the others might not cover. Some criteria, like the Beers Criteria, offer more condition-specific recommendations, such as identifying medications that are inappropriate for older adults with dementia or cognitive impairment. Using both criteria provides a more thorough assessment of a patient's medication regimen and allows for tailored, patient-centered care. Both sets of criteria can complement each other, enhancing the assessment of medication appropriateness and providing a more comprehensive view of a patient's medication profile.[60,144]

By considering both the Beers Criteria and the STOPP Criteria, healthcare providers can make well-informed decisions regarding medication management, ensuring the safest and most appropriate care for older adults, including those with dementia.[60,144]

6.1.4 Classification of drug-related problems

The scoping review revealed a gap in the lack of consistency and standardization in reporting DRPs across studies. The scoping review revealed that different studies used different classification systems to define and report DRPs. The literature review in Chapter 2 revealed that the number of DRPs identified during medication reviews varied widely. For instance, one study utilized the Westerlund system,[32] another employed the ASHP classification from 1996,[97] a third used the Cipolle/Morley/Strand classification,[98] and the fourth adopted the PCNE Classification Version 6.2.[99] Meanwhile, two studies did not apply any standard classification system to define DRPs. It is very important to classify the DRPs using any standardized classification system to ensure that DRPs identified through different tools, such as MedRevCiD and MAI, can be uniformly classified, strengthening the credibility of the research outcomes.

This is the first prospective observational study carried out in Canada to classify DRPs using PCNE version 9 classification and to identify factors associated with the occurrence of DRPs in older adults with dementia and/or CI attending Multispecialty Interprofessional Team (MINT) memory clinics. All the DRPs identified using the MedRevCiD checklist MAI criteria, Beers criteria 2023, and the STOPP criteria 2023 were classified into different domains of PCNE criteria. The PCNE classification consists of three domains for DRPs: Treatment effectiveness, treatment safety, and others.

After classifying the DRPs as per PCNE criteria, most of the DRPs were categorized under the Treatment Safety P2 category. P2.1 Treatment safety (patient suffers, or could suffer, from an adverse drug event) was the most dominant primary domain leading to DRPs, which are similar to the results reported in previous studies.[54,147] The result indicates

pharmacists' unique role in memory clinics in Canada in ensuring the safe use of medications for patients in the clinics. In our study, drug selection and dose selection accounted for approximately 81% of the underlying causes of the DRPs, which is consistent with the cause of the DRPs identified in previous studies.[123] Inappropriate medication, according to the MedRevCiD checklist, MAI criteria, Beers criteria, or STOPP criteria were the major subcategories in the drug selection domain, followed by inappropriate combinations of drugs.

No indication for medications was also identified as a common cause of DRPs, which usually leads to unnecessary drug therapy. For example, if a patient has been prescribed aspirin without a clear medical indication for its use, this would be considered unnecessary drug therapy. If a patient is prescribed ezetimibe when they do not have hypercholesterolemia or any other medical condition that warrants cholesterol-lowering treatment, it would also be an example of unnecessary drug therapy. In both cases, prescribing these medications can expose patients to potential risks and side effects without providing clear benefits.

No or incomplete drug treatment, despite existing indications, was also identified as a cause of DRPs from the drug selection category. An example of this subcategory is that some patients had low vitamin B12 levels but were not started with any supplementation. It is vital to detect untreated health conditions and instances where valuable medications are not prescribed sufficiently, especially in older adults, and this is even more critical when dealing with individuals with dementia because some of the untreated medical conditions can interfere with cognition and mimic dementia.

Moreover, it's crucial to consider DDI as these interactions carry significant importance, as they have the potential to result in adverse drug events and may even serve as the primary cause of hospital admissions.[148] Within the inappropriate combination of drugs, all the DDI identified using Beers and STOPP criteria were classified as a cause of DRP in this subcategory.

In the domain of dose selection, the subcategory of dosage being either too high or too low emerged as the most prevalent issue. It's important to note that many medications necessitate dosage adjustments for patients with impaired kidney function. Incorrect medication dosages in older adults with dementia can have far-reaching consequences, including the potential for adverse effects, inadequate treatment, and a worsening of symptoms. High dosages can lead to an increased risk of side effects, while low dosages may not effectively manage their underlying medical conditions, potentially allowing these conditions to deteriorate. Identifying and maintaining appropriate medication dosages in older adults with dementia is essential for their safety, well-being, and overall management of their health conditions.[149]

Non-adherence accounted for only 7/119 (5.8%) of the DRPs found in this study. Even a mild level of cognitive impairment can exert a significant negative influence on the adherence of healthy elderly individuals to their prescribed drug therapies.[150] As compared to a previously published study by Pfister et al., a total of 310 DRPs were reported in 66% (140/212) of the patients. Out of 310 DRPs, four DRPs were identified as related to non-adherence.[54] Another study by Liu et al. in the neurology unit of a tertiary hospital in China didn’t report any DRPs related to non-adherence.[123] The difference in the number of DRPs

reported related to non-adherence between our study and the other study could be attributed to several factors. The utilization of the MedRevCiD domain, explicitly focusing on medication adherence, in our study has enabled a more comprehensive assessment of non-adherence issues compared to other studies that possibly employed different frameworks or criteria for DRP identification. Additionally, variations in patient populations, healthcare settings, or methodologies across studies can contribute to discrepancies in identifying non-adherence related DRPs.

In our study, a total of 53 recommendations were proposed by the pharmacist for the study participants. The most common recommendations were taken at the drug level for the study participants, and the most common recommendation was discontinuation of drug therapy. A detailed example of a pharmacist's recommendation for a patient with multiple comorbidities and medication-related issues is described in Appendix E.

6.1.5 Predicting factors associated with DRPs and PIMs use

Our study also explored the factors that might be associated with DRP use by the study population. Bivariate logistic regression showed a significant association between the number of comorbidities, number of medications per day, nervous system drug use and DRP identified using the MAI criteria. There was a significant association between DRPs identified using MAI criteria and the number of comorbidities, with an odds ratio of 1.86. This suggests that as the number of comorbid conditions increases, there is a higher likelihood of DRPs being assessed by the MAI. On the other hand, the analysis did not demonstrate a statistically significant association between comorbidities and DRPs identified using MedRevCiD. A significant association was observed between the number

of medications taken per day and DRPs assessed by MAI, with an odds ratio of 1.20. This implies that as the number of medications increases, there is an increased likelihood of encountering medication-related problems, according to the MAI.

Additionally, Wucherer et al., reported another association—between the total number of DRPs and the quantity of drugs taken—based on a multivariate Poisson regression analysis.[89] The coefficient (b = 0.07) with a 95% Confidence Interval of 0.05–0.09 and a p-value less than 0.001 indicates that for each unit increase in the number of drugs taken, there's an associated 0.07 increase in the total number of DRPs identified.

These findings collectively emphasize a clear correlation between the quantity of medications taken and the occurrence of medication-related issues, providing valuable insights into the factors influencing drug-related problems among the participants studied. However, there was no significant association between the number of medications and DRPs identified using MedRevCiD checklist. The odds ratio for patients using nervous system drugs is 14, and the p-value is 0.019. In this case, the p-value suggests that there is a statistically significant association between the use of nervous system drugs and a higher likelihood of medication-related problems, as assessed by the MAI.

Clinical significance of the study

Pharmacists play a pivotal role in identifying, assessing, and resolving DRPs, leveraging their clinical experience and expertise to navigate complex medication scenarios across different domains of patient care. Pharmacists' proficiency in identifying DRPs is instrumental in providing patient-centric care, optimizing therapeutic outcomes, and

mitigating potential medication risks. Their role extends beyond dispensing medications, encompassing a proactive and holistic approach to medication management that significantly contributes to patient well-being.

The MedRevCiD checklist, focusing on diverse aspects of medication management and its impact, highlights the multifaceted responsibilities of pharmacists in addressing DRPs. The clinical significance of this study lies in its comprehensive exploration of Drug-Related Problems (DRPs) using various criteria, including MedRevCiD, MAI, Beers Criteria, and STOPP Criteria in older adults, particularly those with CI or dementia. This study holds significant implications for clinical practice, offering insights and recommendations for improved patient care.

The study's findings provide valuable insights into the diverse DRPs encountered in this vulnerable population. Detailed identification of DRPs within specific domains enables targeted interventions. Pharmacists and healthcare professionals can devise personalized strategies to address non-adherence, minimize adverse drug reactions, and optimize medication regimens based on patient needs and clinical conditions.

The identified DRPs shed light on specific areas requiring attention in medication management, especially for older adults and individuals with cognitive impairment or dementia. This insight allows healthcare professionals, including pharmacists and physicians, to tailor medication regimens to individual patients' needs, minimizing risks and maximizing therapeutic benefits. For instance, DRPs related to cognitive side effects emphasize the need to focus on medications that might exacerbate cognitive impairment. For example, drugs like gabapentin or hydromorphone, known to have potential mental

impacts, warrant careful consideration. Recognizing DRPs related to drug-induced cognitive impairment enables healthcare professionals to make informed decisions regarding medication selection. This includes avoiding medications known to exacerbate mental issues and selecting alternatives with fewer cognitive side effects.

Identification of potentially inappropriate medications (PIMs) through criteria like Beers and STOPP Criteria highlights medications that may pose risks to older adults or those with cognitive impairment. This knowledge empowers healthcare providers to mitigate these risks, reducing adverse events and promoting patient safety.

The study's findings contribute to optimizing medication management strategies for older adults with cognitive impairment. The study's results necessitate a patient-centered approach to medication management, promoting tailored therapies, interdisciplinary collaboration, patient education, continuous monitoring, adherence to guidelines, and cost-effective care. Tailoring drug regimens based on the identified DRPs ensures that medications are effective and safer, enhancing the overall quality of care. These implications guide healthcare practitioners toward optimizing care for older adults with cognitive impairment or dementia, ensuring safer and more effective medication use and overall improved patient outcomes.

Identifying DRPs certainly offers valuable insights into medication management, but there are downsides or challenges associated with this process. Identifying a high number of DRPs might overwhelm patients, caregivers, or even healthcare providers. It could lead to confusion about prioritization, implementation of interventions, or managing multiple changes in medication plans simultaneously. Interventions to resolve DRPs might lead to

unintended consequences. Adjusting medications or discontinuing certain drugs could impact the patient differently than anticipated, leading to new or exacerbated issues.

6.2 Strength and Limitations

To the best of our knowledge, this is the first study that has analyzed and compared the DRPs using the MedRevCiD checklist and MAI criteria in older adults with dementia and/or CI. This is the first prospective observational study conducted in Canada to classify DRPs using PCNE version 9 classification and to identify factors associated with the occurrence of DRPs in older adults with dementia and/or CI attending MINT memory clinics in Canada. Moreover, we employed the American Geriatric Society (AGS) Beers criteria 2023 and the European Geriatric Society (EGS) STOPP criteria 2023 to identify the PIMs among this population. As the latest criteria released in 2023, our study will be among the first to report PIMs using these updated guidelines worldwide. Future research might be designed using the project's findings to further test MedRevCiD in other practice settings such as family health clinic teams, nursing homes, and hospitals.

Several limitations of this study must be considered. First, the study was conducted only in older adults receiving care at the MINT memory clinic in the Kitchener-waterloo area; therefore, the findings may not be generalizable to older patients receiving care at nursing homes or hospitals. One of the important limitations was the pharmacist's involvement in developing the MedRevCiD checklist and conducting medication reviews for the patient population being studied poses a potential bias in the research. When a tool or methodology developer is directly involved in its application or evaluation, there's a risk of bias due to their familiarity, attachment, or vested interest in its success. This scenario can lead to

subconscious influences on the study results. For instance, the pharmacist might have a preconceived notion of the effectiveness or utility of the MedRevCiD checklist, potentially impacting how they conduct the medication reviews or interpret the outcomes. The involvement of the pharmacist's graduate student (RS) in conducting the study under the pharmacist's guidance raises concerns about potential biases. When student conducts research under the guidance of a mentor who has developed the methodology or tool being studied, there's a risk of inheriting or being influenced by the mentor's biases, perspectives, or preferences. Another limitation identified was the short duration of the study and follow-up. Pharmacist recommendations aimed at resolving DRPs may require ongoing monitoring and support. The study's short duration may not allow for assessing these recommendations' long-term outcomes. Some pharmacist recommendations may involve medication changes or discontinuations. The short follow-up duration may not allow for a comprehensive assessment of the outcomes of these adjustments, including whether they successfully resolved the identified DRPs.

6.3 Future recommendations

The results of this thesis project provide data regarding DRPs encountered among older adults with dementia and/or CI. Moreover, there is a need for a full-scale implementation study outside of MINT memory clinics to include a more diverse patient population. Different healthcare settings, such as primary care, nursing homes, or community health centers, cater to a wider range of patients with varying levels of dementia, comorbidities, and sociodemographic backgrounds. Furthermore, testing the MedRevCiD checklist in diverse healthcare settings allows for validating its effectiveness and relevance in different contexts. It helps confirm whether the checklist is a robust and adaptable tool for

identifying and addressing DRPs in patients with dementia across various care settings. Different healthcare settings may present unique challenges and opportunities regarding DRPs. Using the MedRevCiD checklist in a wider range of settings, researchers can identify DRPs that may not have been apparent in specialized memory clinics. This can lead to more tailored interventions and recommendations.

This is the first study using MedRevCiD in the clinical setting. There is a need for more studies to do additional validation studies to assess the tool's sensitivity and specificity further. In terms of the validity and reliability of the MedRevCiD tool, investigate the predictive validity of the tool by examining whether the identification of DRPs and using MedRevCiD leads to improved patient outcomes, such as reduced adverse events, improved cognitive function, or enhanced quality of life.

Moreover, there is a need for a study evaluating inter-rater reliability and intra-rater reliability to support the tool's credibility in identifying medication-related problems in older adults with dementia and/or CI. Lastly, studies need to examine the link between the identification and resolution of DRPs and clinical outcomes, including cognitive function, falls, hospitalizations, and mortality. Assess whether addressing DRPs leads to improved patient well-being and quality of life.

6.4 Conclusion

The MedRevCiD checklist has shown its potential as a sensitive tool for identifying DRPs, especially in the context of dementia care. Its unique categorization into different domains has allowed for a comprehensive assessment of medication-related issues, encompassing aspects often overlooked by other criteria sets. Moreover, the study has not only identified DRPs but has also proposed recommendations to resolve the DRPs, offering a practical

approach to enhancing medication management and patient safety. The study sets the stage for future research, including large-scale implementation studies outside of MINT memory clinics, to validate the findings and extend the impact to a broader population. Future studies should also explore the specificity, sensitivity, content, and construct validity of the MedRevCiD checklist and assess its reliability in clinical practice. This study has provided valuable insights into the prevalence of PIMs in older adults with dementia and/or CI attending MINT memory clinics in Canada.

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Appendix A

Scoping review

Appendix A-1:- Search Strategy

OVID Medline

#	Search strategy	Medline hits
1	exp Aged/	3372444
2	((older$ or elderly or geriatric) adj2 (adult$ or people$ or patient$ or in patient$ or in-patient$ or inpatient$)).ti,ab,kw	291927
3	(aged or frail elderly or (health services adj3 aged) or community dwelling older adults).ti,ab,kw	648093
4	or/1-3	3857586
5	exp Dementia/ or exp Alzheimer Disease/ or exp Dementia, Vascular/ or exp Frontotemporal Dementia/	187161
6	exp Cognition Disorders/ or exp Cognition/ or exp Memory Disorders/	297449
7	exp Lewy Body Disease/	3864
8	exp Korsakoff Syndrome/	545
9	(dement$ or (alzheimer or (lewy adj2 bod$) adj2 diseas$) or (chronic adj2 cerebrovascular)).ti,ab,kw	142515
10	(organic brain disease or organic brain syndrome).ti,ab,kw	796
11	(cerebr$ adj2 (deteriorat$ or insufficien$) or binswanger$ or (pick$ disease)).ti,ab,kw	5962
12	(behavio?r$ adj2 (modif$ or chang$ or improv$)).ti,ab,kw	74553
13	or/5-12	555768
14	4 and 13	175244
15	exp Medication Reconciliation/ or exp Medication Adherence/	25488
16	((prescription$ or prescribing or medication$ or medicine$ or drug therapy or pharmac$ or drug regime$ or drug therap$ or pharmaceutical care or dosage$ or dose$) adj3 (review$ or assess$ or audit$ or monitor$ or reconcil$ or manag$ or monitor$ or plan or record or adher$ or concord$)).ti,ab,kw	113529

17	15 or 16	128535
18	14 and 17	1857
19	Limit 18 to English language	1772

OVID Embase

#	search strategy	Medline hits
1	exp Aged/	3316437
2	((older$ or elderly or geriatric) adj2 (adult$ or people$ or patient$ or in patient$ or in-patient$ or inpatient$)).ti,ab,kw	418145
3	(aged or frail elderly or (health services adj3 aged) or community dwelling older adults).ti,ab,kw	896078
4	or/1-3	4036298
5	exp Dementia/ or exp Alzheimer Disease/ or exp multiinfarct dementia/ or exp Frontotemporal Dementia/ or exp frontal variant frontotemporal dementia/ or pick presenile dementia/ or semantic dementia/ or senile dementia/ or presenile dementia/	399376
6	exp cognitive defect/ or exp Memory Disorders/	598959
7	exp diffuse Lewy body disease/	10136
8	exp Korsakoff psychosis/	1550
9	(dement$ or (alzheimer or (lewy adj2 bod$) adj2 diseas$) or (chronic adj2 cerebrovascular)).ti,ab,kw	210743
10	(organic brain disease or organic brain syndrome).ti,ab,kw	1040
11	(cerebr$ adj2 (deteriorat$ or insufficien$) or binswanger$ or (pick$ disease)).ti,ab,kw	7535
12	(behavio?r$ adj2 (modif$ or chang$ or improv$)).ti,ab,kw	96104
13	or/5-12	719253
14	4 and 13	201783
15	exp Medication Reconciliation/ or exp Medication compliance/	51136

16	((prescription$ or prescribing or medication$ or medicine$ or drug therapy or pharmac$ or drug regime$ or drug therap$ or pharmaceutical care or dosage$ or dose$) adj3 (review$ or assess$ or audit$ or monitor$ or reconcil$ or manag$ or monitor$ or plan or record or adher$ or concord$)).ti,ab, kw	188256
17	15 or 16	214686
18	14 and 17	3329
19	Limit 18 to English language	3240

SCOPUS

#	search strategy	Scopus
#1	TITLE-ABS-KEY ((*older** OR *"elderly"* OR *"geriatric"*) W/2 (*adult** OR *people** OR *patient** OR *"in patient"* OR *"in-patient"* OR *"inpatient"*))	416,837
#2	TITLE-ABS-KEY (*"aged"* OR *"frail elderly"* OR (*"health services"* W/3 *"aged"*) OR *"community dwelling older adults"*)	5,766,189
#3	#1 OR #2	5,887,136
#4	TITLE-ABS-KEY (*"Dementia"* OR *"Alzheimer Disease"* OR "Alzheimer disorder" OR *"multiinfarct dementia"* OR *"Frontotemporal Dementia"* OR *"frontal variant frontotemporal dementia"* OR *"Pick presenile dementia"* OR *"semantic dementia"* OR *"senile dementia"* OR *"presenile dementia"*)	371,317
#5	TITLE-ABS-KEY (*"Cognition disorder"* OR *"Cognition"* OR *"Memory disorder"*)	448,722
#6	TITLE-ABS-KEY (*"Lewy body disease"*)	8,237
#7	TITLE-ABS-KEY (*"Korsakoff Syndrome"* OR *"Korsakoff psychosis"*)	2,703
#8	TITLE-ABS-KEY (*"Chronic"* W/2 *"cerebrovascular"*)	1,306
#9	TITLE-ABS-KEY (*"organic brain disease"* OR *"organic brain syndrome"*)	3,587
#10	TITLE-ABS-KEY (*cerebr** W/2 (*deteriorat** OR *insufficien**) OR *binswanger** OR *pick** AND *disease*)	2,446

#11	TITLE-ABS-KEY (*behavio?r** W/2 (*modif** OR *chang** OR *improv**))	61,824
#12	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11	819,232
#13	#3 AND #12	249,393
#14	TITLE-ABS-KEY ((*prescription** OR *"prescribing"* OR *medication** OR *medicin** OR *"drug therapy"*) W/3 (*review** OR *assess** OR *audit** OR *monitor**))	48,267
#15	TITLE-ABS-KEY ((*prescription** OR *"prescribing"* OR *medication** OR *medicin** OR *"drug therapy"*) W/3 (*reconcil** OR *manag** OR *monitor** OR *plan*))	45,140
#16	TITLE-ABS-KEY ((*prescription** OR *"prescribing"* OR *medication** OR *medicin** OR *"drug therapy"*) W/3 (*"record"* OR *adher** OR *concord**))	41,616
#17	TITLE-ABS-KEY ((*pharmac** OR *"drug regimen"* OR *"pharmaceutical care"* OR *dosage** OR *dose**) W/3 (*review** OR *assess** OR *audit** OR *monitor**))	75,683
#18	TITLE-ABS-KEY ((*pharmac** OR *"drug regimen"* OR *"pharmaceutical care"* OR *dosage** OR *dose**) W/3 (*reconcil** OR *manag** OR *monitor** OR *plan*))	46,372
#19	TITLE-ABS-KEY ((*pharmac** OR *"drug regimen"* OR *"pharmaceutical care"* OR *dosage** OR *dose**) W/3 (*"record"* OR *adher** OR *concord**))	8,372
#20	#14 OR #15 OR #16 OR #17 OR #18 OR #19	216,220
#21	#13 AND #20	3,470
#22	LIMIT-TO (LANGUAGE , "English")	3,333

Appendix A-2: Definitions of types of care settings, pharmacist care interventions, drug related problems (DRPs) and drug related interventions (DRIs)

	Care settings	**Description**
Type of care settings	Community	Patients receiving primary healthcare services outside of a designated accommodation facility while living independently or with family members[76]
	Hospital	Facility that is distinguishable from a long-term care facility due to well established differences in the type and duration of specialist medical treatment[76]
	Long-term care facility	Patients receiving primary healthcare services at the nursing homes/skilled nursing facilities/assisted living/residential living homes[75]
	Class	**Description of main categories**
Type of Pharmacist Care Interventions	Cognitive Pharmacy Services (CPS)	Comprehensive Medication Management • With medications prescribed from another health care professional. Subdivided into 3 steps: 1) Clinical assessment[76,81,84,86] • Collect general medication history and other key clinical information • Conduct medication review • Identify drug related problems (DRPs) 2) Care Plan Creation and Implementation[84,86] • Recommend interventions and solutions for DRPs 3) Evaluation[76,84,86] • Follow-up and monitor results
	Educational and Advisory Services[84,104]	Secondary Patient Care Services • Perform additional patient care services, e.g., administer drugs via injection Management of Minor Conditions

		• Assessment and diagnosis, triage/referral, treatment, monitor and follow-up Patients, Family members, and Caregivers • Provide drug counselling services Health Care Professionals • Provide advice and explanations on drug information and rationale for medication use Other health care workers e.g., staff workers at facilities • Provide advice and explanations on drug information and rationale for medication use
	Source	**Type of DRPs**
Type of DRPs	Westerlund classification system,[32] ASHP classification 1996,[97] Cipolle/Morley/Strand classification,[98] PCNE Classification V 6.2[99]	• Non-conformity to guidelines / contra-indication • Drug without indication • Improper administration • Supratherapeutic dosage • Untreated indication • Subtherapeutic dosage • Unnecessary Drug Therapy • Needs Additional Therapy • Ineffective/Inappropriate drug • Too High Dosage • Drug use process errors: DRPs that occur due to inappropriate administration by a care provider • Drug monitoring • Drug interaction • Adverse drug reaction • Failure to receive drug • Length • Schedule • Failure to receive the full benefit of prescribed therapy • Drug-disease that are clinically significant • Lack of understanding of the medication

		• Inappropriate dose renal impairment • Dosage form
	Source	**Type of DRIs**
Type of DRIs	Pharmaceutical Care Network Europe Classification for Drug related problems[71]	• No intervention • At prescriber level • At patient level • At drug level • Other intervention (e.g., side effect monitoring, health, and medicine monitoring)

Appendix A-3: Characteristics of included studies (n= 22) of the scoping

Study	Study characteristics		Participant characteristics							
	Design; follow up; medication review conducted by	Type of care setting; single center/multicenter	Sample size (N=)	Study population	Age	Sex	Classification of dementia	Secondary conditions	Evaluation of medication use	Other
Canada										
1. Wilchesky et al., 2018[82]	Observational pre-post study; 104 days; Clinical pharmacist	LTC; Multicenter	44	Nursing home residents 65 years of age or older with diagnosis of severe dementia	86.9 (6.9) (mean (SD))	70.5% F 29.5% M	NR	7.45 (2.46) (mean (SD)) Charlson Comorbidity Score	7.86 (3.78) (mean (SD)) Number of Medication per patient	Level of Agitation and Pain
United States										
2. Dong et al., 2021[70]	Retrospective study; NR; Clinical pharmacist	Community, LTC, Hospital; Multicenter	129,820 (Intervention= 32,455; comparison group= 97,365)	Aged 65 years or older had AD	79.04 (7.37) (mean (SD))- intervention 78.93 (7.86) (mean	34.18% M 65.82% F intervention 34.18% M	NR	NR	NR	Proportions of nonadherent beneficiaries

					(SD))-comparison	65.82% F comparison				
3. Pearson et al., 2021[84]	Retrospective study; NR; Clinical pharmacist	Community (Academic geriatric primary care clinics); Multicenter	40	Community-dwelling patients with dementia	82.4 (67-98) (mean (range))	37.5% M 62.5% F	NR	NR	Donepezil Monotherapy (n= 3) Donepezil + Memantine (n= 4) Rivastigmine + Memantine (n= 2) Galantamine + Memantine (n= 1) Memantine Monotherapy (n= 7)	
4. Bach et al., 2017[90]	Prospective study; NR; Clinical pharmacist	LTC (Nursing homes); Multicenter	20	Nursing home residents diagnosed with dementia	87.1 (7.9) (mean (SD))	90% F 10% M	NR	NR	13.3 (5.5) (mean (SD)) number of medications Olanzapine 25% Quetiapine 60% Risperidone 15%	
5. Levine et al., 2021[85]	Retrospective study; NR; Clinical pharmacist	Community (Living home); Single center	29	Older adults aged ≥ 65 years, living at home with dementia	78.9 (7.2) (mean (SD))	48.3% F 51.7% M	NR	3.21 (1.5) Average comorbidities per patient	8.3 (3.9) (mean (SD)) number of medications Memory agents 41.7% Acetylcholinesterase inhibitors 43.3%	

									NMDA antagonist 38.95% Central nervous system agents 10.7% Antidepressants 9.6% Anxiolytics 4.2% Anticonvulsants 26.7% Antiparkinsonian agents 28.6% Anticholinergic agents 10%	
6. Melville et al., 2020[86]	Retrospective study; NR; Geriatric clinical pharmacist	Community (Tertiary care Veterans Affairs health care system Outpatients); Single center	104	Older Adults with dementia attending Outpatients in a tertiary care Veterans Affairs health care system	81 (65-99) (mean (range))	4% F 96% M	NR	NR	NR	
United Kingdom										

6. Aziz et al., 2018[90]	Audit study; NR; Consultant Pharmacist	Hospital (Cwm Taf UHB); Multicenter	58 first audit 47 re-audit	Psychiatric in-patients with dementia	78.33 (2.74) (mean (SD)) first audit 78.72 (3.11) re-audit	53.5% F 46.5% M first audit 63% F 37% M Re-audit	Alzheimer's dementia (n= 18) Vascular dementia (n= 21) Dementia with Lewy bodies (n= 5) Mixed Alzheimer's/vascular dementia (n= 7) Other dementia (n= 6)	6.23 (1.52) Average comorbidities per patient- first audit 5.73 (1.02) re-audit	10.88 (1.27) Average number of prescriptions per patient- first audit 10.15 (0.58) re-audit	
7. Ballard et al., 2016[77] (primary study)	Randomized controlled trial; NR; Therapist	LTC (Nursing Care homes);	277 (Residents on anti-psychot	People with dementia living in	85.26 (7.02) (mean (SD))	74% F 26% M	NR	NR	NR	Cohen-Mansfield Agitation Inventory score,

Ballard et al., 2017[78] (secondary study)		Multicenter	ic review 146; Residents not on anti-psychotic review = 131)	nursing homes						Neuropsychiatric Inventory score, quality of life
8. Maidment et al., 2020[95]	Feasibility study; 6 months; Specialist dementia care pharmacist	LTC (Residents in care homes); Multicenter	29	People living with moderate to severe dementia	83.6 (9.3) (mean (SD)) 66- 100 (range)	62.1% F 37.9% M	NR	NR	medication involved in medication reviews, citalopram (n= 6) Sertraline (n= 4) Mirtazapine (n= 4) Antihistamines (n= 3) Trimipramine (n= 1) Amisulpride (n= 1)	Neuropsychiatric Inventory score, quality of life
Netherlands										
9. Smeets et al., 2021[79] (primary study) Van Der Spek et al.,	Randomized controlled trial; 18 months; Elderly care physician, pharmacist,	LTC; Multicenter	222	Nursing home residents living in the participating dementia	84 (7.4) (mean (SD)) 55–99 (range)	78% F 22% M	Alzheimer's dementia 41% Vascular		Any antipsychotic, antidepressant, hypnotic, and/or anxiolytic:- 48% Antipsychotics25% Antidepressants 25%	Cohen-Mansfield Agitation Inventory score, Neuropsychiat

2018[80] (secondary study)	nurse (assistant)			special care units (DSCUs)			dementia 12% Mixed Alzheimer's/vascular dementia 10% Another dementia 37%		Hypnotics (14%) Anxiolytics (14%)	ric Inventory score
Slovenia										
10. Stuhec et al., 2021[81]	Observational pre–post study; NR; Clinical pharmacist	Community; Multicenter	19	Elderly patients aged 65 years or above diagnosed with dementia	NR	NR	NR	NR	NR	
France										
12. Novais et al., 2021[87]	Retrospective study; NR; Senior pharmacists or resident pharmacists	Hospital (Cognitive-behavioral unit); Single center	543	Elderly patients admitted in a cognitive-behavioral unit with	79.0 (9.5) (mean (SD))	NR	NR	NR	NR	Economic, and organizational impact

				Alzheimer's disease and Related Dementia (ADRD))						
Spain										
13. Weeks et al., 2019[88]	Retrospective study; 4 weeks; Carers, nursing staff, physicians, physical & leisure therapists, and administrators	LTC (Nursing homes); Multicenter	606		NR	NR	NR	NR	NR	
14. Massot et al., 2019[83]	Prospective, observational pre-post study; 6 months; Neurologist, a psychiatrist, a geriatrician, 2 primary	LTC (Nursing homes associated with a single primary care team); Multicenter	240	Institutionalized patients diagnosed with dementia	87.9 (6.8) (mean (SD))	75% F 25% M	NR	NR	2.71 (1.47) average number psychotropic drugs/patient	

	care general practitioners and 4 pharmacists,									
15. Hernandez et al., 2020[91]	Prospective study; NR; Pharmacist and a geriatrician	LTC (long-term care psychogeriatric unit (21 beds) in an intermediate care hospital); Single center	65	Patients with dementia admitted controlling behavioral and psychological symptoms	84.9 (6.7) (mean (SD))	60% F 40% M	Alzheimer's dementia 30.8% Vascular dementia 7.7% Dementia with Lewy bodies 7.7% Mixed Alzheimer's/vascular dementia 4.6% Other dementia 6.2%	Diseases of the circulatory system 83.1% Endocrine, nutritional, and metabolic diseases 60% genitourinary system 32.3% musculoskeletal system and connective tissue 29.2% nervous system 27.7% Neoplasms 16.9% Injury, poisoning, and certain other consequences 26.2%	9.0 (3.1) average number psychotropic drugs/patient Antipsychotics 78.5% hypnotics and sedatives)/anxiolytics 47.7% antidepressants 53.9% analgesics 66.2% anti-dementia drugs 30.9% antiepileptic drugs 12.3% anti-Parkinson drugs 4.6%	Anticholinergic burden

								digestive system 23.1% eye and adnexa 16.9% blood and blood-forming organs 15.4% Mental and behavioral disorders 15.4% respiratory system 12.3% skin and subcutaneous tissue 1.5%		
16. Molist et al., 2014[67]	Observational pre-post study; NR; Two geriatricians and a clinical pharmacist	Hospital (advanced dementia admitted to acute geriatric unit); Single center	73	Patients with advanced dementia	86.1 (5.73) (mean (SD)) 72–100 (range)	79.45% F 20.55% M	NR	Trauma 35.61% Infection 36.98% Respiratory infections 44.34% Urinary tract infections 33.26% Cardiovascular disease 20.54%	7.27 average of medications prior to hospitalization	
Taiwan										

17. Liang et al., 2017[45]	Prospective study; 12 months; Dementia specialist, a special nurse with expertise in dementia care, a pharmacist, a dietician, a physical therapist, an occupational therapist, a clinical psychologist, and social workers	LTC and Community (intervention in Jia-Li Veterans Home and usual care model in the community (Memory clinic)); Multicenter	61	Participants aged 65 years and older with mild-to-moderate dementia	85.8 (5.6) (mean (SD))	NR	NR	NR	Use of anti-dementia drug included acetylcholinesterase inhibitor and memantine 88.5%	Delaying cognitive and physical decline, and improvement or prevention of geriatric syndromes during 1-year follow up
Australia										
18. Cross et al., 2020[96]	Pre- and post-intervention feasibility study; 6 months; Two consultant pharmacists	Community (outpatient memory clinics); Single center	50	Patients attending the memory clinics	80.5 (71.5-85.0) (median (IQR))	36% F 64% M	Alzheimer's dementia 16% Mixed dementia 14% Mild cognitive	4.94 (1.89) (mean (SD)) Charlson comorbidity index	11 (8-13.25) (median (IQR)) Median number of medications at home visit	Quality of life (EQ-5D), tool for adherence behavior screening Adherence

							impairment 26% Not confirmed diagnosis 26%			
Northern Sweden										
19. Gustafsson et al., 2017[44] (primary study) Gustafsson et al., 2018[55] (secondary study)	Randomized controlled trial; 6 months; Three clinical pharmacists	Hospital (Patients admitted to acute internal medicine wards at the Skellefteå County Hospital and Umea University Hospital and to the orthopedic ward); Multicenter	212	65 years or older and had dementia	83.1 (6.6) (mean (SD))	63% F 37% M	Alzheimer's dementia 30% Vascular dementia 20% Other or unspecified dementia 47.6%	Heart failure 34% Hypertension 55% Cardiac arrhythmia 29% Diabetes mellitus 29% Chronic obstructive pulmonary disease 8% Malignant disease 13% Myocardial infarction 17% Stroke, past 24%	8.4 (3.6) average number of drugs	Drug-related readmissions

Pfister et al., 2017[54] (secondary study)			140 People with DRPs 72 People without DRPs		83.7 (6.6) (mean (SD)) People with DRPs 82.0 (6.3) People without DRPs	62.9% F 37.1% M People with DRPs 62.5% F 37.5% M People without DRPs	NR	People with DRPs: Heart failure 35.7% Cardiac arrhythmia 28.6% Diabetes mellitus 30.7% Chronic obstructive pulmonary disease 7.1% Stroke, past 31.4% People without DRPs: Heart failure 30.6% Cardiac arrhythmia 30.6% Diabetes mellitus 25% Chronic obstructive pulmonary disease 8.3%	People with DRPs: - 9.3 (3.4) average number of drugs at randomization People without DRPs: - 6.8 (3.4) average number of drugs at randomization	

								Stroke, past 12%		
Abramsson et al., 2020[56] (secondary study)			153 Patients with DRPs identified by STOPP/START 59 Patients without DRPs identified by STOPP/START		83.7 (6.3) (mean (SD)) People with DRPs identified by STOPP/START 81.6 (7.1) Patients without DRPs identified by STOPP/START	64.7% F 35.3% M People with DRPs identified by STOPP/START 57.6% F 42.4% M Patients without DRPs identified by STOPP/START	NR	People with DRPs identified by STOPP/START: - Heart failure 38.6% Cardiac arrhythmia 32.7% Diabetes mellitus 29.4% Stroke, past 26.1% Patients without DRPs identified by STOPP/START: - Heart failure 22% Cardiac arrhythmia 20.3% Diabetes mellitus 27.1%	9.1 (3.5) (mean (SD)) average number of drugs prescribed- People with DRPs identified by STOPP/START 6.8 (3.2) (mean (SD)) average number of drugs prescribed- People without DRPs identified by STOPP/START	

								Stroke, past 16.9%		
Germany										
20. Wucherer et al., 2017[89]	Retrospective study; NR; Clinical pharmacists	Community; Multicenter	446 Total (without DRP + With DRP)	Community-dwelling primary care patients screened positive for dementia	79.8 (5.4) (mean (SD))	57.6% F 42.4% M	NR	Formal diagnosis of dementia 37.2% Diagnosis of mental and behavioral disorders 25.9% Depression 16.1% 12.1 (7.3) average comorbid diagnoses	6.4 (3.2) average number of drugs prescribed	Degree of cognitive impairment
Denmark										
21. Tang et al., 2016[92]	Prospective study; NR; Clinical pharmacists	Long-Term Care Facility (Nursing homes); Single center	12	Nursing home above 65 years of age diagnosed with dementia	87 (77-96) (mean (range))	42% M 58% F	NR	4.4 (range 2–8) average number of diagnoses per patient was	83 total number of prescription in 12 patients	Pain intensity, pain symptoms
Hong Kong										

22. Wong et al., 2016[93]	Prospective study, NR; Clinical pharmacists	Hospital; Single center	54	Elderly with dementia	NR	NR	NR	NR	NR	

Note: - LTC, Long-term care facility; SD, standard deviation; F, Female; M, Male; NR, Not reported; AD, Alzheimer's disease; NMDA, N-methyl-D-aspartate; DRPs, Drug-related problems.

Appendix A-4: Summary of interventions with reported outcomes

	Study																					
Reported outcomes	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
Medication Prescription Processing (MPP)																						
1. Comprehensive Medication Management- Clinical Assessment[76,81,84,86]																						
a) Collect general medication history and other key clinical information					X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
b) Conduct medication review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
c) Identify drug related problems (DRPs)			X		X	X					X	X			X			X	X	X		X
2. Comprehensive Medication Management- Care Plan Creation and Implementation[84,86]																						
a) Recommend interventions and solutions for DRPs			X		X					X	X	X			X	X			X		X	
3. Comprehensive Medication Management- Evaluation[76,84,86]																						
a) Follow-up and monitor results									X	X	X	X		X	X			X	X			
Educational and Advisory Services[76,86]																						
1. Secondary Patient Care Services																						
a) Perform additional patient care services, e.g. administer drugs via injection																						
2. Management of Minor Conditions																						
a) Assessment and diagnosis, triage/referral,																			X			

treatment, monitor and follow-up																						
3. Patients, Family members, and Caregivers																						
a) Provide drug counselling services																						X
4. Health Care Professionals																						
a) Provide advice and explanations on drug information and rationale for medication use						X		X						X				X				
5. Other health care workers e.g., staff workers at facilities																						
a) Provide advice and explanations on drug information and rationale for medication use																						
Evaluation of medication use	X	X	X	X	X	X	X	X	X			X	X	X	X	X	X				X	
Cost/time effectiveness								X				X										
Drug Related Interventions																						
a) At prescriber level				X							X	X			X			X	X			
b) At patient level																						
c) At drug level			X								X	X			X			X	X			
d) Other intervention or activity										X												
Proposed intervention			49	12						3	248	543			175			261			17	
Accepted intervention			14	4						3	110	269			152			136			1	
Secondary outcomes (Cohen-Mansfield Agitation Inventory score, Neuropsychiatric Inventory	X						X	X	X						X			X	X	X		

score, Anticholinergic burden, Drug-related readmissions)																						
Other outcomes							X	X				X					X	X			X	

Other outcomes such as quality of life, improvement, or prevention of geriatric syndromes during 1-year follow up, Pain intensity

Appendix A-5: Overview of medication review and important clinical outcomes reported

Study	Group	Before medication review	After medication review	Important outcomes reported
Wilchesky et al., 2018[82]	Total number of regular medications	372	327	A significant 12.1% reduction (OR: 0.81; 95% CI: 0.70–0.92) in overall medication burden
	Total number of "sometimes" appropriate medications	194	167	Decreased (from 194 pre to 167 post-intervention)
	The mean number of regular medications per resident	7.86 (3.78) (mean (SD))	6.82 (3.75) (mean (SD))	Decreased from 7.86 to 6.81 (p = 0.007))
Dong et al., 2021[70]	Proportions of nonadherent beneficiaries	Intervention: - Medication for Diabetes 13.1% Medication for Hypertension 16.39% Medication for Hyperlipidemia 18.69% Comparison: - Medication for Diabetes 10.84% Medication for Hypertension 13.57% Medication for Hyperlipidemia 16.06%	Intervention: - Medication for Diabetes 9.78% Medication for Hypertension 12.5% Medication for Hyperlipidemia 11.72% Comparison: - Medication for Diabetes 12.08% Medication for Hypertension 17.25% Medication for Hyperlipidemia 17.83%	Following a medication review, the percentage of non-adherent beneficiaries in the intervention group for each prescription category reduced, but they grew in the comparison group over time.
Pearson et al., 2021[84]	180-day reduction in baseline PIM usage	1.5 PIMs per patient	0.9 PIMs per patient	Decrease from 1.5 PIMs per patient to 0.9 PIMs per patient in the patients living with dementia group

Aziz et al., 2018[94]	Average number of prescriptions per patient	10.88 (1.27)- first audit	10.15 (0.58)- re-audit	The average number of prescriptions per patient significantly decreased, according to the results of the t-test (8% reduction), t (1) = 28.808, P = 0.022, 95% CI = 5.877–15.153.
	Number of patients receiving polypharmacy	51/58- first audit	39/47- re-audit	No difference in the number of patients receiving polypharmacy, t (1) = 7.500, P = 0.084. The audit revealed that polypharmacy has decreased overall by 24%.
	Average comorbidities per patient	6.23 (1.52)- first audit	5.73 (1.02)- re-audit	The average number of comorbidities between the two audits significantly decreased, according to the t-test results (7% reduction), t (1) = 23.920, P = 0.027, 95% CI = 2.803–9.157.
Ballard et al., 2016[77,78]	Antipsychotic use by patients	20- Residents on anti-psychotic review 20- Residents not on anti-psychotic review	13- Residents on anti-psychotic review 23- Residents not on anti-psychotic review	Overall, the review group's use of antipsychotics was much lower than that of the non-review group (odds ratio 0.17, 95%CI 0.05 to 0.60, p=0.006)
	Quality-of-life score for people with dementia (proxy) (DEMQOL Proxy)	106.51 (9.14) Residents on antipsychotic review 102.69 (15.22) Residents not on antipsychotic review	102.11 (13.41) Residents on antipsychotic review 105.79 (10.53) Residents not on antipsychotic review	People receiving antipsychotic review showed a 4.54 (95% confidence interval (CI) 9.26 to 0.19) point worsening (p= 0.06) in their DEMQOL-Proxy scores, which

				approached statistical significance.
Massot et al., 2019[83]	Number of psychotropic drugs prescribed	636	458	Reduced by 28% (from 636 before to 458 after the intervention).
	Mean number of psychotropic drugs prescribed per patient	2.71 (1.47)	1.95 (1.24) 1-month postintervention 2.06 (1.36) 6-month postintervention	Decreased from 2.71 at baseline to 1.95 at 1-month postintervention and 2.01 at 6 months ($p < 0.001$ for both time points). Antipsychotics were the drug class showing the highest reduction rate (49.66%)
Hernandez et al., 2020[91]	PRISMA extension for scoping reviews by Medication Appropriateness Index (MAI) mean score	4 (4.6)	0.5 (2.6)	Significant differences ($p<0.001$) between the mean (SD) MAI scores at admission and post-intervention (4 (4.6) vs 0.5 (2.6))
	mean (SD) anticholinergic burden per patient	1.38 (0.7)	1.08 (0.7)	Statistically significant differences were found between pre- and post-intervention (p1 was 30 (DBI range 0.3–2.6).
	the number of patients who presented with an anticholinergic burden >1 (considered high-risk burden limit)	44 (DBI range 0.3–3)	30 (DBI range 0.3–2.6)	
Molist et al., 2014[67]	average of medications per person	7.27 prior to hospitalization	4.8 at discharge	66.85% reduction, ($P < 0.05$)
				multiple Cox regression model

Gustafsson et al., 2017[44,54-56]				revealed that after adjustment for heart failure, the intervention significantly reduced the risk of drug-related readmissions (HR 0.49, 95% CI 0.27–0.90, p = 0.02).
	People with DRPs (n= 140) People without DRPs (n= 72)			DRPs were more common among people taking a higher number of drugs (OR, 1.255 [95% CI, 1.137-1.385])
				DRPs were more common among people with an earlier stroke (OR, 5.042 [95% CI, 2.032-12.509]) people with heart failure (OR, 2.66 [95% CI, 1.64–4.30]), diabetes mellitus (OR, 2.32 [95% CI, 1.41–3.81]),
	Number of patients using anticholinergic drugs; NSAIDs; exposed to PIMs	15 (7.1%) at admission; 7 (3.3%) at admission; 43 (20.3%) at admission	7 (3.3%) at discharge 2 (0.9%) at discharge 30 (14.2%) at discharge	Anticholinergic drugs use decreased significantly from 7.1% to 3.3 % (p = 0.005) the use of NSAIDs decreased from 3.3% to 0.9% (p = 0.025) PIMs decreased significantly from 20.3% to 14.2% (p = 0.002)
Wucherer et al., 2017[89]				In the multivariate Poisson regression analysis, the total number of drugs taken (b = 0.07; 95% CI: 0.05–0.09; p < 0.001)

				and the presence of a diagnosis of mental and behavioral disorders (b = 0.09; 95% CI: 0.03–0.15; p = 0.003) were associated with total number of DRPs (significant regression model: $F(11,89) = 6.18$, $p < 0.001$)

Note: - PIM, potentially inappropriate medication; LWD, Living with dementia; DBI, Drug burden index; HR, Hazard ratio; OR Odds ratio; DRPs, Drug-related problems; NSAIDs, non-steroidal anti-inflammatory drugs

Appendix B

Data collection form

Patient ID:	Date of data collection:
Age: Gender: Marital status:	
Medical problems:	
Allergies:	
Total memory clinic visits (if reported:	
Social history Alcohol: Smoking, recreational drug use/Cannabis:	

Past medical history:
Recent history of falls:

Medication	**Indication**	**Remarks**

Drug-related problems identified as per MAI					
Type of MRP	**Medication related to MRP**	**Resolution for drugs a**	**Resolution for drugs b**	**Resolution for drugs c**	**Resolution for drugs d**
1. Treatment effectiveness a) No effect of drug treatment despite correct use b) Effect of drug treatment not optimal					

c) Untreated symptoms or indication					
2. Treatment safety a) Adverse drug event (possibly) occurring					
3. Other a) Unnecessary drug-treatment b) Unclear problem/complaint.					
The Causes (including possible causes for potential problems)					
1. Drug selection a) Inappropriate drug b) No indication for drug c) Inappropriate combination of drugs, or drugs and herbal medications, or drugs and dietary supplements d) Inappropriate duplication of active ingredient e) No or incomplete drug treatment despite existing indication f) Too many different drugs/active ingredients prescribed for indication					
2. Drug form a) Inappropriate drug form					
3. Dose selection a) Drug dose too low b) Drug dose too high c) Dosage regimen not frequent enough d) Dosage regimen too frequent e) Dose timing instructions wrong, unclear or missing					
4. Treatment duration a) Duration of treatment too short b) Duration of treatment too long					
5. Dispensing a) Prescribed drug not available					

b) Necessary information not provided or incorrect advice provided c) Wrong drug, strength or dosage advised (OTC) d) Wrong drug or strength dispensed					
6. Drug use process a) Inappropriate timing of administration or dosing intervals b) Drug under-administered c) Drug over-administered d) Drug not administered e) Wrong drug administered f) Drug administered via wrong route					
7. Patient related a) Patient intentionally uses/takes less drug than prescribed or does not take the drug at all for whatever reason b) Patient uses/takes more drug than prescribed c) Patient abuses drug (unregulated overuse) d) Patient decides to use unnecessary drug e) Patient takes food that interacts f) Patient stores drug inappropriately g) Inappropriate timing or dosing intervals h) Patient unintentionally administers/uses the drug in a wrong way					
8. Other a) No or inappropriate outcome monitoring (incl. TDM) b) Other cause; specify c) No obvious cause					

Beers criteria	STOPP criteria
1. Independent of diagnosis	

2. Dependent of diagnosis	
3. Used with caution	
4. Drug-drug interaction	

5. PIM according to creatinine clearance	

Planned interventions
No intervention
At prescriber level ☐ Prescriber informed only ☐ Prescriber asked for information ☐ Intervention proposed to prescriber ☐ Intervention discussed with prescriber
At patient level ☐ Patient (drug) counselling ☐ Written information provided (only) ☐ Patient referred to prescriber ☐ Spoken to family member/caregiver
At drug level

- ☐ Drug changed to …
- ☐ Dosage changed to …
- ☐ Formulation changed to …
- ☐ Instructions for use changed to …
- ☐ Drug paused or stopped
- ☐ Drug started

Appendix C: Ethics Clearance

UNIVERSITY OF WATERLOO

Notification of Ethics Clearance to Conduct Research with Human Participants

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Principal Investigator: Tejal Patel (School of Pharmacy)

Study coordinator: Sarah Abu Fadaleh (School of Pharmacy)

Student investigator: Rishabh Sharma (School of Pharmacy)

Study coordinator: Jessica Ivo (School of Pharmacy)

Other: Sadaf Faisal (School of Pharmacy)

Co-Investigator: Feng Chang (School of Pharmacy)

Co-Investigator: Linda Lee (McMaster University)

File #: 44673

Title: Medication Review in Cognitive Impairment and Dementia: Comparison of Instruments

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The Clinical Research Ethics Board is pleased to inform you this study has been reviewed and given ethics clearance.

Initial Approval Date: 12/07/22 (m/d/y)

University of Waterloo Research Ethics Boards are composed in accordance with, and carry out their functions and operate in a manner consistent with, the institution's guidelines for research with human participants, the Tri-Council Policy Statement for the Ethical Conduct for Research Involving Humans (TCPS, 2nd edition), International Conference on Harmonization: Good Clinical Practice (ICH-GCP), the Ontario Personal Health Information Protection Act (PHIPA), the applicable laws and regulations of the province of Ontario. Both Boards are registered with the U.S. Department of Health and Human Services under the Federal Wide Assurance, FWA00021410, and IRB registration number IRB00002419 (HREB) and IRB00007409 (CREB).

This study is to be conducted in accordance with the submitted application and the most recently approved versions of all supporting materials.

Expiry Date: 12/08/23 (m/d/y)

Multi-year research must be renewed at least once every 12 months unless a more frequent review has otherwise been specified. Studies will only be renewed if the renewal report is received and approved before the expiry date. Failure to submit renewal reports will result in the investigators being notified ethics clearance has been suspended and Research Finance being notified the ethics clearance is no longer valid.

Level of review: Delegated Review

Signed on behalf of the Clinical Research Ethics Board

Appendix D

Information letter

Study Title: Medication Review in Cognitive Impairment and Dementia: Comparison of Instruments

Faculty Supervisor: Dr. Tejal Patel, Clinical Associate Professor, University of Waterloo School of Pharmacy. Phone: 1-519-888-4567 ext. 21337, Email: tejal.patel@uwaterloo.ca

Student Investigator: Rishabh Sharma, MSc (candidate), School of Pharmacy, University of Waterloo, Email: r367shar@uwaterloo.ca

PARTICIPANT'S INFORMATION/CONSENT LETTER

This letter is an invitation to participate in a project led by Dr. Tejal Patel the University of Waterloo School of Pharmacy. To help you make an informed decision regarding your participation, this letter will explain what the study is about, the expected risks and benefits, and your rights as a research participant. If you do not understand something in the letter, please ask one of the research team members prior to providing your consent to participate to the study.

What is the study about?

We are inviting you to participate in a research study investigating drug-related problems (DRP) while receiving care at MINT memory clinic. The objective of this study is to identify DRPs using Medication Review in Cognitive Impairment and Dementia (MedRevCiD) checklist and Medication appropriateness index (MAI) in older adults with cognitive impairment or dementia receiving care at primary care.

What does participation involve?

If you agree to take part in this study, you will allow the researcher to review your medical records to abstract information on your background, your social history, your current medical problems, your drug-therapy information, information on your diagnostic testing and imaging, and information on clinical measurements and cognitive test scores. You will be asked information about your experience with managing your medication and adherence.

A medication review will be conducted by a researcher (RS) in collaboration with the pharmacist for the included participants. After obtaining all the needed information, the researcher, pharmacist, and participants will be able to discuss the medications currently being taken by the participants based on their medical and medication history. Following the

discussion process, the researcher will review patients' medications to identify DRPs using MedRevCiD Checklist and MAI. You will only meet the researcher once during your visit to MINT Memory clinic. The meeting time for the interview will be during your scheduled appointments.

Follow-up involves the chart review of the patient will be completed at 1-month post-implementation of the medication review process to report on recommendation acceptance (recommendation accepted, recommendation not accepted) and status of the DRP (problem solved, a problem not solved, problem partially solved).

Who may participate in the study?

You are eligible to participate in this research study if you are a patient (all genders) age ≥ 65 years receiving care at MINT memory clinic and prescribed one or more medications (prescription and over-the-counter medicine). You will not be able to participate if you are under the age of 65 years or are taking only natural health products. You have been given this information letter based on your eligibility as a patient.

Is participation in the study voluntary?

Yes. Participation in this study is voluntary and you are under no obligation to participate. In addition, you may choose to decline to answer any question that you do not wish to answer. Furthermore, you may withdraw your participation from this study by simply informing the researcher of your decision.

Will I receive anything for participating in the study?

No, you will not receive any form of renumeration for participation in the study.

What are the possible risks associated with the study?

There are no known or anticipated risks associated with participation in this study. If a question, or the discussion, makes you uncomfortable, you can choose not to answer.

What are the possible benefits of the study?

There are no direct benefits of participating in this study. However, using the MedRevCiD checklist and MAI in MINT memory clinics across Kitchener-Waterloo region will help us to identify DRPs in this population. The potential impact of an effective MedRevCiD checklist and MAI is the identification and possible resolution of important medication related problems that frequently arise in patients with cognitive impairments and/or dementia.

Will my information be kept confidential?

Your participation in this study will be considered confidential and identifying information will be removed from the data that is collected and stored separately. Information obtained during the medication review will be coded. All the data will be summarized, and no individual will be able to be identified from these summarized results. The data collected from this study will be securely stored in a locked office and/or on a password protected computer for a minimum of seven years. De-identified data related to your participation may be submitted to an open access repository or journal (i.e., the data may be publicly available). These data will be completely de-identified/anonymized prior to submission by removing all personally identifying information (e.g., names, email addresses, and certain identifying demographic information) and will be presented in aggregate form in publications. This process is integral to the research process as it allows other researchers to verify results and avoid duplicating research. Other individuals may access these data by accessing the open access repository.

What are the limitations to withdrawal?

You may withdraw your consent and request that your data be removed from the study by contacting the researchers within this time period. Please note that it is not possible to remove your data once results have been analyzed and results have been submitted for publication.

Who is sponsoring/funding this study?

This study is not sponsored and will not be receiving funding.

Has the study received ethics clearance?

This project has been reviewed and received ethics clearance through the University of Waterloo Research Ethics Board (ORE# 44673). Should you have any comments or concerns resulting from your participation in this study, please contact the Office of Research Ethics, at 519-888-4567 ext. 36005 or reb@uwaterloo.ca.

Who should I contact if I have questions regarding my participation in the study?

Should you have any questions about the study or would like additional information to assist you in reaching a decision about participation, please contact Dr. Tejal Patel, Rishabh Sharma, using the contact information listed below.

Dr. Tejal Patel, Clinical Associate Professor, University of Waterloo School of Pharmacy. Phone: 1-519-888-4567 ext. 21337, Email: tejal.patel@uwaterloo.ca

Rishabh Sharma, MSc student, University of Waterloo School of Pharmacy. Email: r367shar@uwaterloo.ca

Consent Form

By signing this consent form, you are not waiving your legal rights or releasing the investigator(s) or involved institution(s) from their legal and professional responsibilities.

Study Title: Medication Review in Cognitive Impairment and Dementia: Comparison of Instruments

I have read the information presented in the information letter about a study being conducted by Rishabh Sharma, under the supervision of Dr. Tejal Patel, School of Pharmacy, University of Waterloo. All the procedures and any risks and benefits relating to my participation have been explained. I have had the opportunity to ask any questions related to this study (if any), to receive satisfactory answers to my questions, and any additional details I wanted.
I am aware that:

- □ I may withdraw my consent for any of the above statements or withdraw my study participation at any time without penalty by advising the researcher.
- □ I agree to the use of anonymous quotations in any paper or publication resulting from this study

This project has been reviewed and received ethics clearance through the University of Waterloo Research Ethics Board (ORE# 44673). Should you have any comments or concerns resulting from your participation in this study, please contact the Office of Research Ethics, at 519-888-4567 ext. 36005 or reb@uwaterloo.ca.

With full knowledge of all foregoing, I agree, of my own free will, to participate in the study titled Medication Review in Cognitive Impairment and Dementia: Comparison of Instruments

□Agree □Disagree

Participant's Name	Signature and Date
Person obtaining consent' Name	Signature and Date

Consent Form for Caregiver

Your signature on this form indicates that you have understood to your satisfaction the information regarding participation in the research project and agree to allow the person you represent to participate. In no way does this waive the participant's legal rights nor release the investigators or involved institutions from their legal and professional responsibilities. You are free to withdraw the participant from the study at any time.

Study Title: Medication Review in Cognitive Impairment and Dementia: Comparison of Instruments

I have read the information presented in the information letter about a study being conducted by Rishabh Sharma, under the supervision of Dr. Tejal Patel, School of Pharmacy, University of Waterloo. All the procedures and any risks and benefits relating to participant participation have been explained. I have had the opportunity to ask any questions related to this study (if any), to receive satisfactory answers to my questions, and any additional details I wanted.

I am aware that:

- □ I may withdraw my participant consent for any of the above statements or withdraw study participation at any time without penalty by advising the researcher.
- □ I agree to the use of anonymous quotations in any paper or publication resulting from this study

This project has been reviewed and received ethics clearance through the University of Waterloo Research Ethics Board (ORE# 44673). Should you have any comments or concerns resulting from your participation in this study, please contact the Office of Research Ethics, at 519-888-4567 ext. 36005 or reb@uwaterloo.ca.

Participant's Name	
Caregiver's Name	Signature and Date
Person obtaining consent' Name	Signature and Date

Verbal script

Hello,

My name is [Rishabh Sharma] and I am a master's student working under the supervision of [Dr. Tejal Patel] in the Department of Pharmacy at the University of Waterloo. As part of my master's degree, I am conducting a research study on [Medication Review in Cognitive Impairment and Dementia: Comparison of Instruments]. This study, identify drug-related problems using the MedRevCiD checklist and Medication appropriateness index (MAI) in older adults with cognitive impairment (CI) or dementia.

If you decide to participate in this study, your participation will consist of a medication review that will take approximately 45 to 60 minutes of your time. A medication review will be conducted by a researcher (RS) in collaboration with the MINT Memory clinic pharmacist for the included participants. During the review, we will need to review your medical records and you will be asked questions to collect information on your background, your social history, your current medical problems, your drug-therapy information, information on your diagnostic testing and imaging, and information on your memory, attention, thinking, learning skills, language skills, problem solving skills, and other abilities related to mental functioning.. This information will guide our understanding to effectively identify any DRPs and help achieve optimal medication management. You are not required to do any additional visits to the MINT memory clinic pertaining to the study.

Participation in this study is voluntary and you are under no obligation to participate. In addition, you may choose to decline to answer any question that you do not wish to answer. Furthermore, you may withdraw your participation from this study by simply informing the researcher of your decision.

In appreciation of your time, you will receive a Thank you letter for participating in the study.

This project has been reviewed and received ethics clearance through the University of Waterloo Research Ethics Board (ORE# 44673). Should you have any comments or concerns resulting from your participation in this study, please contact the Office of Research Ethics, at 519-888-4567 ext. 36005 or ore-ceo@uwaterloo.ca

Please read the attached Information Letter for more details regarding what participation will involve. If you would like to participate, or you require additional information to assist you in deciding on participation, please do not hesitate to contact me at [r367shar@uwaterloo.ca]. You may also contact my supervisor at [tejal.patel@uwaterloo.ca].

Thank you for your assistance in this project.

Sincerely,

Rishabh Sharma

Thank you letter

Study Title: Medication Review in Cognitive Impairment and Dementia: Comparison of Instruments

Dear Participant,

Thank you for taking part in our study titled "**Medication Review in Cognitive Impairment and Dementia: Comparison of Instruments"**

As a reminder, the purpose of this study is to identify drug-related problems using the Medication Review in Cognitive Impairment and Dementia (MedRevCiD) checklist and the Medication appropriateness index (MAI) in older adults with cognitive impairment (CI) or dementia.

Please remember that any data about you as an individual participant will be kept confidential. The results of the study may be published for scientific purposes. However, data will be completely de-identified/anonymized prior to submission by removing all personally identifying information (e.g., names, email addresses, and certain identifying demographic information) and will be presented in aggregate form in publications. If you would like any further information about the study, including a copy of our findings when they become available, please contact us using the information below.

If you have any questions about the study, please contact Dr. Tejal Patel at the University of Waterloo School of Pharmacy at (519) 888-4567 ext. 21337, or via email at t5patel@uwaterloo.ca for assistance.

This project has been reviewed and received ethics clearance through the University of Waterloo Research Ethics Board (ORE# 44673). Should you have any comments or concerns resulting from your participation in this study, please contact the Office of Research Ethics, at 519-888-4567 ext. 36005 or ore-ceo@uwaterloo.ca.

Sincerely,

Tejal Patel, BScPharm, PharmD
Clinical Associate Professor
School of Pharmacy
University of Waterloo
E-mail: t5patel@uwaterloo.ca
Phone: 519-888-4567 ext. 21337

Appendix E

Results appendices

Appendix E-1:- Distribution of Drug-drug interactions

Drug combination	Potential effect	N= 225
Major DDI		**1 (0.4)**
Timolol (Beta blockers, non-selective) + Symbicort (Budesonide and Formoterol)	Beta blocker may dimmish the broncho dilatory effect of Symbicort	1 (0.4)
Moderate DDI		**31 (13.4)**
Oxycodone (Opioid analgesic) + Pregabalin (CNS depressant)	CNS depressants may enhance the CNS Depressant effect of Oxycodone	1 (0.4)
Bilastine (CNS depressant) + Oxycodone (Opioid analgesic)	CNS depressants may enhance the CNS Depressant effect of Oxycodone	1 (0.4)
Bilastine (CNS depressant) + Tapentadol	CNS depressants may enhance the CNS Depressant effect of Tapentadol	1 (0.4)
Bromazepam/Lorazepam + Oxycodone (Opioid analgesic)	CNS depressants may enhance the CNS Depressant effect of Oxycodone	1 (0.4)
Bromazepam/Lorazepam + Tapentadol	CNS depressants may enhance the CNS Depressant effect of Tapentadol	1 (0.4)
Cyclobenzaprine + Oxycodone (Opioid analgesic)	CNS depressants may enhance the CNS Depressant effect of Oxycodone	1 (0.4)
Cyclobenzaprine + Tapentadol	CNS depressants may enhance the CNS Depressant effect of Tapentadol	1 (0.4)
Doxepin + Oxycodone (Opioid analgesic)	CNS depressants may enhance the CNS Depressant effect of Oxycodone	1 (0.4)
Doxepin + Tapentadol	CNS depressants may enhance the CNS Depressant effect of Tapentadol	1 (0.4)
Oxycodone (Opioid analgesic) + Tapentadol	CNS depressants may enhance the CNS Depressant effect of Oxycodone	1 (0.4)

Zopiclone + Oxycodone (Opioid analgesic)	CNS depressants may enhance the CNS Depressant effect of Tapentadol	1 (0.4)
Zopiclone + Tapentadol	CNS depressants may enhance the CNS Depressant effect of Tapentadol	1 (0.4)
Gliclazide (Sulfonylurea) + Liraglutide (GLP-1 Agonists)	GLP-1 may enhance the hypoglycemic effects of Gliclazide	1 (0.4)
Insulin Glargine + Liraglutide	Liraglutide may enhance the hypoglycemic effects of Insulin	1 (0.4)
Brimonidine and timolol (alpha-2 agonists) + Metoprolol (Beta-blocker)	Alpha-2 agonists may enhance the AV-blocking of Metoprolol	1 (0.4)
Amlodipine + Simvastatin	Amlodipine may increase the serum concentration of Simvastatin	1 (0.4)
Gabapentin (CNS Depressants) + Hydromorphone (Opioid agonists)	CNS Depressants may enhance the CNS depressant effect of Opioid Agonists	1 (0.4)
Hydromorphone (Opioid agonists) + Robaxacet (Acetaminophen and Methocarbamol) (CNS depressant)	CNS Depressants may enhance the CNS depressant effect of Opioid Agonists	1 (0.4)
Linagliptin (Dipeptidyl peptidase IV inhibitor) + Insulin glargine (Toujeo Doublestar)	Dipeptidyl Peptidase-IV Inhibitors may enhance the hypoglycemic effect of Insulins	1 (0.4)
Allopurinol + Warfarin (Vitamin k antagonist)	Allopurinol may enhance the anticoagulant effect of Vitamin K Antagonists	1 (0.4)
Hydromorphone (Opioid analgesic) + Mirtazapine (CNS Depressant)	CNS Depressants may enhance the CNS depressant effect of Opioid Agonists	1 (0.4)
Hydromorphone (Opioid analgesic) + Trazodone (CNS Depressant)	CNS Depressants may enhance the CNS depressant effect of Opioid Agonists	1 (0.4)
Gabapentin (CNS Depressant) + Oxycodone (Opioid analgesic)	CNS Depressants may enhance the CNS depressant effect of Oxycodone	1 (0.4)
Insulin Lispro + Semaglutide (GLP-1 Agonists)	GLP-1 Agonists may enhance the hypoglycemic effect of Insulins	1 (0.4)

Insulin Lispro + Empagliflozin (SGLT 2 Inhibitors)	SGLT2 Inhibitors may enhance the hypoglycemic effect of Insulins	1 (0.4)
Lamotrigine (CNS Depressant) + Oxycodone (Opioid analgesic)	CNS Depressants may enhance the CNS depressant effect of Oxycodone	1 (0.4)
Ibuprofen (Nonsteroidal Anti-Inflammatory Agents (Nonselective) + Aspirin (Salicylates)	Nonsteroidal Anti-Inflammatory Agents (Nonselective) may enhance the adverse/toxic effect of Salicylates. An increased risk of bleeding may be associated with the use of this combination. Nonsteroidal Anti-Inflammatory Agents (Nonselective) may diminish the cardioprotective effect of Salicylates. Salicylates may decrease the serum concentration of Nonsteroidal Anti-Inflammatory Agents (Nonselective).	1 (0.4)
Dapagliflozin (SGLT2 Inhibitors) + Insulin Degludec	SGLT2 Inhibitors may enhance the hypoglycemic effect of Insulins	1 (0.4)
Dapagliflozin (SGLT2 Inhibitors) + Insulin Aspart	SGLT2 Inhibitors may enhance the hypoglycemic effect of Insulins	1 (0.4)
Semaglutide (GLP-1 Agonists) + Insulin Degludec	Glucagon-Like Peptide-1 Agonists may enhance the hypoglycemic effect of Insulins	1 (0.4)
Semaglutide (GLP-1 Agonists) + Insulin Aspart	Glucagon-Like Peptide-1 Agonists may enhance the hypoglycemic effect of Insulins	1 (0.4)
Minor DDI		193 (86)
Aspirin (Salicylates) + Perindopril (ACE inhibitors)	Salicylates may enhance the nephrotoxic effect of Angiotensin-Converting Enzyme Inhibitors	5 (2.2)
Aspirin + Sertraline	SSRI enhance the antiplatelet effect of Aspirin	4 (1.7)
Aspirin + Citalopram (SSRI)	Selective Serotonin Reuptake Inhibitors may enhance the antiplatelet effect of Aspirin	4 (1.7)
Metformin + Perindopril (ACE Inhibitors)	Angiotensin-Converting Enzyme Inhibitors may enhance the adverse/toxic effect of Metformin	3 (1.3)
Bisoprolol + Furosemide	Furosemide may enhance the hypotensive effect of antihypertensive agents	2 (0.8)
Oxycodone (Opioid analgesic) + Sertraline (Serotonergic agents)	Oxycodone may enhance the serotonergic effect of sertraline	2 (0.8)

Bisoprolol + Donepezil	Acetyl cholinesterase inhibitor may enhance the bradycardic effect of Bisoprolol	2 (0.8)
Bisoprolol + Tamsulosin	Bisoprolol may enhance the hypotensive effects of hypotensive associated agent (Tamsulosin)	2 (0.8)
Levothyroxine + Salbutamol (Sympathomimetics)	Levothyroxine may enhance the adverse/toxic effect of sympathomimetics)	2 (0.8)
Tamsulosin + Mirabegron (CYP2D6 Inhibitors)	CYP2D6 inhibitors may increase the serum concentration of tamsulosin	2 (0.8)
Furosemide (Diuretics) + Hydromorphone (Opioid agonists)	Opioid Agonists may enhance the adverse/toxic effect of Diuretics	2 (0.8)
Fluoxetine/Sertraline (SSRI) + Levothyroxine	SSRI may diminish the therapeutic effect of levothyroxine	2 (0.8)
Aspirin + Ramipril (ACE Inhibitors)	Aspirin may enhance the nephrotoxic effect of ACE inhibitors	2 (0.8)
Furosemide (Diuretic) + Salbutamol (Beta-2 agonists)	Beta2-Agonists may enhance the hypokalemic effect of Loop Diuretics	2 (0.8)
Gabapentin (CNS Depressants) + Acetaminophen and Methocarbamol (CNS depressant)	CNS Depressants may enhance the adverse/toxic effect of other CNS Depressants	2 (0.8)
Citalopram (SSRI) + Hydrochlorothiazide (thiazide and thiazide like diuretic)	SSRI may enhance the hyponatremic effect of Thiazide and Thiazide-Like Diuretics	2 (0.8)
Aspirin + Duloxetine (SNRI)	Serotonin/Norepinephrine Reuptake Inhibitors may enhance the antiplatelet effect of Aspirin	2 (0.8)
Ezetimibe + Fenofibrate	Fenofibrate and Derivatives may enhance the adverse/toxic effect of Ezetimibe	2 (0.8)
Insulin Aspart (Hypoglycemia associated agents) + Insulin Degludec (Hypoglycemia-associated agents)	Hypoglycemia-Associated Agents may enhance the hypoglycemic effect of other Hypoglycemia-Associated Agents	2 (0.8)
Bisoprolol (BP lowering agents) + Nitroglycerin (Hypotension-associated agents)	BP Lowering Agents may enhance the hypotensive effect of Hypotension-Associated Agents	2 (0.8)

Tamsulosin + Tadalafil	tamsulosin may enhance the hypotensive effect of tadalafil	1 (0.4)
Candesartan + Furosemide	Monitor for changes in blood pressure and renal function, due to the risk of hypotension and decreased renal function	1 (0.4)
Candesartan + Spironolactone	Angiotensin II receptor blocker may enhance the hyperkalemic effect of potassium sparing diuretic	1 (0.4)
Bisoprolol + Empagliflozin	Bisoprolol may enhance the hypoglycemic effect of antidiabetic agents	1 (0.4)
Bisoprolol + Digoxin	Bisoprolol (Bradycardia causing agent) may enhance the effect of another bradycardia causing agent	1 (0.4)
Bisoprolol + Quetiapine	Bisoprolol may enhance the hypotensive effects of antipsychotic agents (Quetiapine)	1 (0.4)
Tamsulosin + Quetiapine	Tamsulosin may enhance the hypotensive effects of antipsychotic agents (Quetiapine)	1 (0.4)
Donepezil + Digoxin	Donepezil (Bradycardia causing agent) may enhance the effect of another bradycardia causing agent	1 (0.4)
Empagliflozin + Furosemide	Empagliflozin may enhance the hypotensive effect of loop diuretic	1 (0.4)
Digoxin + Furosemide	Furosemide may enhance the adverse toxic effect of cardiac glycosides. Specially, digoxin toxicity may be enhanced by the hypokalemic and hypomagnesemia effect of loop diuretics	1 (0.4)
Digoxin + Spironolactone	Spironolactone may increase the serum concentration of digoxin	1 (0.4)
Furosemide + Spironolactone	Furosemide may enhance the hypotensive effect of spironolactone	1 (0.4)
Bilastine (Anticholinergic) + Cyclobenzaprine (Anticholinergic)	Anticholinergics enhance the adverse/toxic effect of another Anticholinergic	1 (0.4)
Bilastine (Anticholinergic) + Doxepin (Anticholinergic)	Anticholinergics enhance the adverse/toxic effect of another Anticholinergic	1 (0.4)
Bilastine (Anticholinergic) + Nabilone (Cannabinoid containing product)	AC agents enhance the tachycardic effect of Cannabinoid containing products	1 (0.4)

Bilastine (CNS depressant) + Bromazepam/Lorazepam (CNS depressant)	CNS depressant may enhance the adverse/toxic effect of another CNS depressant	1 (0.4)
Bilastine (CNS depressant) + Zopiclone (CNS depressant)	CNS depressant may enhance the adverse/toxic effect of another CNS depressant	1 (0.4)
Bromazepam (CNS depressant) + Cyclobenzaprine (CNS depressant)	CNS depressant may enhance the adverse/toxic effect of another CNS depressant	1 (0.4)
Bromazepam (CNS depressant) + Doxepin (CNS depressant)	CNS depressant may enhance the adverse/toxic effect of another CNS depressant	1 (0.4)
Bromazepam (CNS depressant) + Lorazepam (CNS depressant)	CNS depressant may enhance the adverse/toxic effect of another CNS depressant	1 (0.4)
Bromazepam (CNS depressant) + Nabilone (Cannabinoid containing products)	CNS depressant may enhance the adverse/toxic effect of another CNS depressant	1 (0.4)
Bromazepam (CNS depressant) + Zopiclone (CNS depressant)	CNS depressant may enhance the adverse/toxic effect of another CNS depressant	1 (0.4)
Celecoxib (Methemoglobinemia associated agents) + Lidocaine (Local anesthetic)	Celecoxib may enhance the adverse/toxic effect of local anesthetic	1 (0.4)
Celecoxib (NSAID, COX-2) + Sertraline (SSRI)	SSRI may enhance the antiplatelet effect of NSAIDS	1 (0.4)
Aspirin + Sertraline (SSRI)	SSRI may enhance the antiplatelet effect of aspirin	1 (0.4)
Cyclobenzaprine + Doxepin (Serotonergic agents)	Cyclobenzaprine may enhance the serotonergic effect of Serotonergic Agents (High Risk)	1 (0.4)
Cyclobenzaprine + Sertraline (Serotonergic agents)	Cyclobenzaprine may enhance the serotonergic effect of Serotonergic Agents (High Risk)	1 (0.4)
Cyclobenzaprine (CNS depressant) + Nabilone (Cannabinoid containing products)	AC enhance the tachycardic effect of Nabilone CNS depressant may enhance the adverse/toxic effect of another CNS depressant	1 (0.4)

Cyclobenzaprine (CNS depressant) + Zopiclone (CNS depressant)	CNS depressant may enhance the adverse/toxic effect of another CNS depressant	1 (0.4)
Doxepin (AC) + Nabilone (Cannabinoid containing products)	AC enhance the tachycardic effect of Nabilone CNS depressant may enhance the adverse/toxic effect of another CNS depressant	1 (0.4)
Doxepin (CNS depressant) + Zopiclone (CNS depressant)	CNS depressant may enhance the adverse/toxic effect of another CNS depressant	1 (0.4)
Doxepin + Synthroid	Thyroid product may enhance the arrhythmogenic effect of doxepin	1 (0.4)
Doxepin + Ventolin	Doxepin may enhance the adverse/toxic effect of Ventolin	1 (0.4)
Oxycodone (Methemoglobinemia associated agents) + Lidocaine (Local anesthetic)	Methemoglobinemia associated agents may enhance the adverse/toxic effect of local anesthetic	1 (0.4)
Zopiclone (Methemoglobinemia associated agents) + Lidocaine (Local anesthetic)	Methemoglobinemia associated agents may enhance the adverse/toxic effect of local anesthetic	1 (0.4)
Nabilone (Cannabinoid containing agent) + Oxycodone (Opioid analgesic) (CNS depressant)	CNS depressant may enhance the CNS depressant effect of Cannabinoid containing agent	1 (0.4)
Nabilone (Cannabinoid containing agent) + Tapentadol (CNS depressant)	CNS depressant may enhance the CNS depressant effect of Cannabinoid containing agent	1 (0.4)
Nabilone (Cannabinoid containing agent) + Zopiclone (CNS depressant)	CNS depressant may enhance the CNS depressant effect of Cannabinoid containing agent	1 (0.4)
Nabilone + Ventolin (Sympathomimetics)	Nabilone may enhance the tachycardic effect of sympathomimetics	1 (0.4)
Ondansetron + Sertraline (Serotonergic agents)	Ondansetron may enhance the serotonergic effect of serotonergic agents	1 (0.4)
Ondansetron + Tapentadol	Ondansetron may diminish the analgesic effect of Tapentadol	1 (0.4)
Sertraline + Synthroid	Sertraline may diminish the therapeutic effect of Synthroid	1 (0.4)

Sertraline (Serotonergic) + Tapentadol (Opioid)	Tapentadol may enhance the serotonergic effect of serotonergic agents	1 (0.4)
Tamsulosin + Lisinopril	Tamsulosin may enhance the hypotensive effects of hypotension associated agents	1 (0.4)
Tamsulosin (Hypotension associated agents) + Ramipril (BP Lowering agents)	Tamsulosin may enhance the hypotensive effects of hypotension associated agents	1 (0.4)
Lisinopril + Quetiapine	Lisinopril may enhance the hypotensive effects of antipsychotic agents (Quetiapine)	1 (0.4)
Risperidone + Quetiapine	Enhance QTc prolongation	1 (0.4)
Quetiapine + Warfarin	Quetiapine may enhance the anticoagulant effect of Warfarin	1 (0.4)
Citalopram (Agents with antiplatelet properties) + Clopidogrel (Agents with antiplatelet properties)	Increase risk of antiplatelet effect /bleeding risk	1 (0.4)
Rosuvastatin + Clopidogrel	Clopidogrel may increase serum concentration of rosuvastatin (monitor for rosuvastatin toxicities)	1 (0.4)
Mirabegron + Solifenacin	Mirabegron may enhance the adverse/toxic effect of Solifenacin	1 (0.4)
Mirabegron + Trazodone	Trazodone may enhance the CNS depressant effect of Mirabegron	1 (0.4)
Sertraline (SSRI) + Trazodone (Serotonergic non-opioid CNS depressant)	Selective Serotonin Reuptake Inhibitors may enhance the serotonergic effect of Serotonergic Non-Opioid CNS Depressants	1 (0.4)
Brimonidine and timolol (CNS depressant) + Trazodone (CNS depressant)	CNS depressant may enhance the adverse/toxic effect of another CNS depressant	1 (0.4)
Duloxetine (SNRI) + Trazodone	Trazodone may enhance the serotonergic effect of Serotonin/Norepinephrine Reuptake Inhibitors	1 (0.4)
Aspirin + Lisinopril	Salicylates may enhance the nephrotoxic effect of Lisinopril	1 (0.4)
Celecoxib + Hydrochlorothiazide	Hydrochlorothiazide may enhance the nephrotoxic effect of Celecoxib	1 (0.4)

Celecoxib + Latanoprost	Celecoxib may diminish the therapeutic effects of prostaglandins (latanoprost)	1 (0.4)
Celecoxib + Lisinopril	Lisinopril may enhance the adverse/toxic effect of Celecoxib Combination may result in a significant decrease in renal function	1 (0.4)
Celecoxib + Metformin	Celecoxib may enhance the adverse/toxic effect of Metformin	1 (0.4)
Gliclazide + Hydrochlorothiazide (Hyperglycemia associated agent)	Hydrochlorothiazide may diminish the therapeutic effect of Gliclazide	1 (0.4)
Gliclazide + Insulin Glargine (Toujeo Solo Star)	Gliclazide may enhance the hypoglycemic effect of Insulin glargine (hypoglycemic associated agent)	1 (0.4)
Gliclazide (Hypoglycemic associated agent) + Metformin (Antidiabetic)	Metformin may enhance the hypoglycemic effect of hypoglycemia associated agents	1 (0.4)
Hydrochlorothiazide (hyperglycemia associated agent) + Metformin (Antidiabetic agent)	Hydrochlorothiazide may diminish the therapeutic effect of Metformin	1 (0.4)
Hydrochlorothiazide (hyperglycemia associated agent) + Insulin Glargine (Toujeo Solo Star)	Hydrochlorothiazide may diminish the therapeutic effect of Insulin Glargine	1 (0.4)
Hydrochlorothiazide (hyperglycemia associated agent) + Liraglutide (Antidiabetic agent)	Hydrochlorothiazide may diminish the therapeutic effect of Liraglutide	1 (0.4)
Hydrochlorothiazide + Ipratropium	Ipratropium may increase the serum concentration of Hydrochlorothiazide	1 (0.4)
Hydrochlorothiazide + Lisinopril	Hydrochlorothiazide may enhance the hypotensive effect of Lisinopril	1 (0.4)
Lisinopril + Metformin	Lisinopril may enhance the adverse/toxic effect of Metformin	1 (0.4)

Aspirin (Salicylates) + Metformin (Agents with blood glucose lowering effects)	Salicylates may enhance the hypoglycemic effect of Agents with Blood Glucose Lowering Effects	1 (0.4)
Metformin (Antidiabetic agent) + Insulin Glargine (Hypoglycemia associated agent)	Metformin may enhance the hypoglycemic effect of hypoglycemia associated agents)	1 (0.4)
Bupropion (CYP2D6 Inhibitors) + Duloxetine	CYP2D6 may increase the serum concentration of duloxetine	1 (0.4)
Duloxetine + Telmisartan (BP Lowering agents)	BP lowering agents may enhance the hypotensive effect of Duloxetine	1 (0.4)
Levothyroxine + Symbicort (Sympathomimetics)	Levothyroxine may enhance the adverse/toxic effect of Symbicort	1 (0.4)
Metoprolol (Beta blocker) + Symbicort (Beta-2 agonist)	Beta-Blockers (Beta1 Selective) may diminish the broncho dilatory effect of Beta2-Agonists	1 (0.4)
Metoprolol (BP Lowering agents) + Nitroglycerin (Hypotension associated agents)	Blood Pressure Lowering Agents may enhance the hypotensive effect of Hypotension-Associated Agents	1 (0.4)
Nitroglycerin (Hypotension associated agents) + Ramipril (BP Lowering agents)	Blood Pressure Lowering Agents may enhance the hypotensive effect of Hypotension-Associated Agent	1 (0.4)
Nitroglycerin (Hypotension associated agents) + Tamsulosin (BP Lowering agents)	Blood Pressure Lowering Agents may enhance the hypotensive effect of Hypotension-Associated Agents	1 (0.4)
Apixaban + Duloxetine (Agents with antiplatelet properties)	Agents with Antiplatelet Properties may enhance the adverse/toxic effect of Apixaban	1 (0.4)
Darifenacin (Anticholinergic agents) + Donepezil (Acetyl cholinesterase inhibitor)	Anticholinergic Agents may diminish the therapeutic effect of Acetylcholinesterase Inhibitors	1 (0.4)
Apixaban + Levetiracetam	Levetiracetam may diminish the therapeutic effect of Apixaban	1 (0.4)
Hydrochlorothiazide (thiazide like diuretic) + Ramipril (ACE Inhibitor)	Thiazide and Thiazide-Like Diuretics may enhance the hypotensive effect of Angiotensin-Converting Enzyme Inhibitors	1 (0.4)

Atenolol (Beta-blockers (beta 1 selective + Metformin (Antidiabetic agents)	Beta-Blockers (Beta1 Selective) may enhance the hypoglycemic effect of Antidiabetic Agents	1 (0.4)
Galantamine (Acetylcholinesterase inhibitor) + Risperidone (Antipsychotics agents) (Anticholinergic agents)	Acetylcholinesterase Inhibitors (Central) may enhance the neurotoxic (central) effect of Antipsychotic Agents Anticholinergic Agents may diminish the therapeutic effect of Acetylcholinesterase Inhibitors	1 (0.4)
Perindopril and Indapamide (BP Lowering agents) + Risperidone (Antipsychotic agent) (Anticholinergic agent)	Blood Pressure Lowering Agents may enhance the hypotensive effect of Antipsychotic Agents	1 (0.4)
Fluticasone and Salmeterol (Beta- 2 agonists) + Furosemide (Loop diuretic)	Beta2-Agonists may enhance the hypokalemic effect of Loop Diuretics	1 (0.4)
Fluticasone and Salmeterol (Sympathomimetics) + Salbutamol (Sympathomimetics)	Sympathomimetics may enhance the adverse/toxic effect of other Sympathomimetics	1 (0.4)
Cannabidiol (Cannabinoid containing product) + Gabapentin (CNS depressant)	CNS Depressants may enhance the CNS depressant effect of Cannabinoid-Containing Products	1 (0.4)
Cannabidiol (Cannabinoid containing product) + Hydromorphone (CNS depressant)	CNS Depressants may enhance the CNS depressant effect of Cannabinoid-Containing Products	1 (0.4)
Cannabidiol (Cannabinoid containing product) + Acetaminophen and methocarbamol (CNS depressant)	CNS Depressants may enhance the CNS depressant effect of Cannabinoid-Containing Products	1 (0.4)
Domperidone (Gastrointestinal agents) + Hydromorphone (Opioid agonists)	Opioid Agonists may diminish the therapeutic effect of Gastrointestinal Agents	1 (0.4)

Furosemide (Diuretic) + Triamcinolone (Corticosteroid systemic)	Corticosteroids (Systemic) may enhance the hypokalemic effect of Loop Diuretics	1 (0.4)
Aspirin + Diltiazem (CCB)	Calcium Channel Blockers (Nondihydropyridine) may enhance the antiplatelet effect of Aspirin	1 (0.4)
Atorvastatin + Diltiazem (CYP3A4 Inhibitor)	CYP3A4 Inhibitors (Moderate) may increase the serum concentration of Atorvastatin	1 (0.4)
Citalopram (SSRI) + Linagliptin (Agents with blood glucose lowering effects)	Selective Serotonin Reuptake Inhibitors may enhance the hypoglycemic effect of Agents with Blood Glucose Lowering Effects	1 (0.4)
Citalopram (SSRI) + Mirtazapine (Serotonergic non opioid CNS depressant)	Selective Serotonin Reuptake Inhibitors may enhance the serotonergic effect of Serotonergic Non-Opioid CNS Depressants	1 (0.4)
Citalopram (SSRI) + Insulin glargine (Agents with blood glucose lowering effects)	SSRI may enhance the hypoglycemic effect of Agents with Blood Glucose Lowering Effects	1 (0.4)
Diltiazem (BP Lowering agents) + Nitroglycerin (Hypotension associated agents)	BP Lowering agents may enhance the hypotensive effect of Hypotension-Associated Agents	1 (0.4)
Duloxetine + Tamsulosin (BP Lowering agents)	BP Lowering Agents may enhance the hypotensive effect of Duloxetine	1 (0.4)
Amlodipine (BP Lowering agent) + Nitroglycerin (Hypotension associated agents)	BP Lowering Agents may enhance the hypotensive effect of Hypotension-Associated Agents	1 (0.4)
Amlodipine (BP Lowering agent) + Sinemet (Levodopa and carbidopa) (Hypotension associated agents)	BP Lowering Agents may enhance the hypotensive effect of Hypotension-Associated Agents	1 (0.4)
Nitroglycerin (BP Lowering agents) + Sinemet (Hypotension associated agents)	BP Lowering Agents may enhance the hypotensive effect of Hypotension-Associated Agents	1 (0.4)
Nitroglycerin (Hypotension associated agents) + Perindopril (BP Lowering agent)	BP Lowering Agents may enhance the hypotensive effect of Hypotension-Associated Agents	1 (0.4)

Perindopril (BP Lowering agent) + Sinemet (Hypotension associated agents)	BP Lowering Agents may enhance the hypotensive effect of Hypotension-Associated Agents	1 (0.4)
Allopurinol + Furosemide (Loop diuretic)	Loop Diuretics may enhance the adverse/toxic effect of Allopurinol	1 (0.4)
Bisoprolol + Dabigatran	Bisoprolol may increase the serum concentration of Dabigatran Etexilate	1 (0.4)
Bisoprolol (Beta blocker) + Dapagliflozin (Antidiabetic agent)	Beta-Blockers (Beta1 Selective) may enhance the hypoglycemic effect of Antidiabetic Agents	1 (0.4)
Bisoprolol (Beta blocker) + Semaglutide (Antidiabetic agent)	Beta-Blockers (Beta1 Selective) may enhance the hypoglycemic effect of Antidiabetic Agents	1 (0.4)
Bisoprolol (Beta blocker) + Salbutamol (Beta-2 agonist)	Beta-Blockers (Beta1 Selective) may diminish the broncho dilatory effect of Beta2-Agonists	1 (0.4)
Colchicine + Rosuvastatin (HMG CoA reductase inhibitors)	Colchicine may enhance the myopathic (rhabdomyolysis) effect of HMG-CoA Reductase Inhibitors (Statins)	1 (0.4)
Dabigatran (Anticoagulants) + Warfarin (Vitamin K antagonists)	Anticoagulants may enhance the anticoagulant effect of Vitamin K Antagonists	1 (0.4)
Dapagliflozin (Antidiabetic agent) + Furosemide (Hyperglycemia associated agents)	Hyperglycemia-Associated Agents may diminish the therapeutic effect of Antidiabetic Agents	1 (0.4)
Furosemide + Semaglutide	Furosemide may diminish the therapeutic effect of Semaglutide	1 (0.4)
Furosemide (BP Lowering agents + Tamsulosin (Hypotension associated agents)	BP Lowering Agents may enhance the hypotensive effect of Hypotension-Associated Agents	1 (0.4)
Levothyroxine (Thyroid product) + Warfarin (Vitamin K antagonists)	Thyroid Products may enhance the anticoagulant effect of Vitamin K Antagonists	1 (0.4)
Rosuvastatin (HMG- CoA reductase inhibitor) + Warfarin (Vitamin K antagonist)	HMG-CoA Reductase Inhibitors (Statins) may enhance the anticoagulant effect of Vitamin K Antagonists	1 (0.4)

Amlodipine and Atorvastatin (BP Lowering agents) + Duloxetine	BP Lowering Agents may enhance the hypotensive effect of Duloxetine	1 (0.4)
Aspirin + Ramipril and hydrochlorothiazide (ACE Inhibitor)	Salicylates may enhance the nephrotoxic effect of Angiotensin-Converting Enzyme Inhibitors Salicylates may diminish the therapeutic effect of Angiotensin-Converting Enzyme Inhibitors	1 (0.4)
Amlodipine (Antihypertensive agents) + Furosemide (Loop diuretics)	Loop Diuretics may enhance the hypotensive effect of Antihypertensive Agents	1 (0.4)
Mirtazapine + Trazodone	Trazodone may enhance the CNS depressant effect of Mirtazapine Trazodone may enhance the serotonergic effect of Mirtazapine	1 (0.4)
Gabapentin (CNS Depressant) + Lamotrigine (CNS Depressant)	CNS Depressants may enhance the adverse/toxic effect of other CNS Depressants	1 (0.4)
Insulin Lispro (Agents with blood glucose lowering effects) + Sertraline (SSRI)	SSRI may enhance the hypoglycemic effect of Agents with Blood Glucose Lowering Effects.	1 (0.4)
Semaglutide (Agents with blood glucose lowering effects) + Sertraline (SSRI)	SSRI may enhance the hypoglycemic effect of Agents with Blood Glucose Lowering Effects	1 (0.4)
Sertraline (SSRI) + Empagliflozin and Metformin (Agents with blood glucose lowering effects)	SSRI may enhance the hypoglycemic effect of Agents with Blood Glucose Lowering Effects	1 (0.4)
Bisoprolol (Beta-blocker) + Empagliflozin (Antidiabetic agent)	Beta-Blockers (Beta1 Selective) may enhance the hypoglycemic effect of Antidiabetic Agents	1 (0.4)
Bisoprolol (BP lowering agents) + Risperidone (Antipsychotic agents)	BP Lowering Agents may enhance the hypotensive effect of Antipsychotic Agents (Second Generation [Atypical])	1 (0.4)
Candesartan (BP lowering agents) + Nitroglycerin (Hypotension-associated agents)	BP Lowering Agents may enhance the hypotensive effect of Hypotension-Associated Agents	1 (0.4)

Candesartan (BP lowering agents) + Risperidone (Antipsychotic agents)	BP Lowering Agents may enhance the hypotensive effect of Antipsychotic Agents (Second Generation [Atypical])	1 (0.4)
Empagliflozin (Antidiabetic agent) + Risperidone (Hyperglycemia associated agents)	Hyperglycemia-Associated Agents may diminish the therapeutic effect of Antidiabetic Agents	1 (0.4)
Amiloride and Hydrochlorothiazide (Thiazide and thiazide like diuretic) + Citalopram (SSRI)	SSRI may enhance the hyponatremic effect of Thiazide and Thiazide-Like Diuretics	1 (0.4)
Amiloride and Hydrochlorothiazide (Thiazide and thiazide like diuretic) + Perindopril (ACE Inhibitors)	Thiazide and Thiazide-Like Diuretics may enhance the hypotensive effect of ACE Inhibitors	1 (0.4)
Aspirin (Salicylates) + Clopidogrel (Agents with antiplatelet properties)	Agents with Antiplatelet Properties may enhance the adverse/toxic effect of Salicylates. Increased risk of bleeding may result	1 (0.4)
Atorvastatin (HMG-CoA reductase inhibitor) + Colchicine	Colchicine may enhance the myopathic (rhabdomyolysis) effect of HMG-CoA Reductase Inhibitors (Statins). Colchicine may increase the serum concentration of HMG-CoA Reductase Inhibitors (Statins). HMG-CoA Reductase Inhibitors (Statins) may increase the serum concentration of Colchicine.	1 (0.4)
Ibuprofen (NSAIDs) + Perindopril (ACE Inhibitors)	ACE Inhibitors may enhance the adverse/toxic effect of NSAIDs. Specifically, the combination may result in a significant decrease in renal function. NSAIDs may diminish the antihypertensive effect of ACE Inhibitors	1 (0.4)
Ibuprofen (NSAIDs) + Indapamide (Thiazide like diuretic)	Thiazide and Thiazide-Like Diuretics may enhance the nephrotoxic effect of NSAIDs. NSAIDs may diminish the therapeutic effect of Thiazide and Thiazide-Like Diuretics	1 (0.4)
Dapagliflozin (Antidiabetic agents) + Perindopril and Indapamide (Hyperglycemia associated agents)	Hyperglycemia-Associated Agents may diminish the therapeutic effect of Antidiabetic Agents.	1 (0.4)

	Thiazide and Thiazide-Like Diuretics may diminish the therapeutic effect of Antidiabetic Agents.	
Metformin (Antidiabetic agents) + Insulin Degludec (Hypoglycemia associated agents)	Antidiabetic Agents may enhance the hypoglycemic effect of Hypoglycemia-Associated Agents	1 (0.4)
Metformin (Antidiabetic agents) + Insulin Aspart (Hypoglycemia associated agents)	Antidiabetic Agents may enhance the hypoglycemic effect of Hypoglycemia-Associated Agents	1 (0.4)
Semaglutide (Antidiabetic agents) + Perindopril (Hyperglycemia-associated agents)	Hyperglycemia-Associated Agents may diminish the therapeutic effect of Antidiabetic Agents	1 (0.4)
Semaglutide (Antidiabetic agents) + Indapamide (Thiazide like diuretic)	Thiazide and Thiazide-Like Diuretics may diminish the therapeutic effect of Antidiabetic Agents	1 (0.4)
Perindopril and Indapamide (BP Lowering agents) + Sildenafil (Phosphodiesterase 5 inhibitor)	Phosphodiesterase 5 Inhibitors may enhance the hypotensive effect of BP Lowering agents	1 (0.4)
Perindopril and Indapamide (Hyperglycemia associated agents) + Insulin Degludec/Insulin Aspart (Antidiabetic agent)	Hyperglycemia-Associated Agents may diminish the therapeutic effect of Antidiabetic Agents	1 (0.4)
Amiodarone + Levothyroxine (Thyroid product)	Amiodarone may diminish the therapeutic effect of Thyroid Products	1 (0.4)
Amiodarone (Bradycardia-causing agents) + Donepezil (Bradycardia-causing agents)	Bradycardia-Causing Agents may enhance the bradycardic effect of other Bradycardia-Causing Agents QT-prolonging Agents (Indeterminate Risk - Caution) may enhance the QTc-prolonging effect of QT-prolonging Agents	1 (0.4)
Amiodarone (Hypotension-associated agents) +	BP Lowering Agents may enhance the hypotensive effect of Hypotension-Associated Agents	1 (0.4)

Amlodipine (BP Lowering agents)		

Appendix E-2:- Distribution of the Number of Medications Among Study Participants, With and Without DRPs, at the Drug Level

Prescribed medication according to the ATC classes and codes	Total prescribed (375 total prescribed to 44 patients) n (%)	DRP (N= 59) n (%)	Without DRP (N= 316) n (%)
G GENITO URINARY SYSTEM AND SEX HORMONES			
1. G04C Drugs used in benign prostatic hypertrophy	12 (3.2)	0 (0)	12 (3.8)
• Tamsulosin	7 (1.8)	0 (0)	7 (2.2)
• Dutasteride	3 (0.8)	0 (0)	3 (0.9)
• Alfuzosin	1 (0.2)	0 (0)	1 (0.3)
• Finasteride	1 (0.2)	0 (0)	1 (0.3)
2. G04BE Drugs used in erectile dysfunction	1 (0.2)	0 (0)	1 (0.3)
• Tadalafil	1 (0.2)	0 (0)	1 (0.3)
3. G03C Estrogens	1 (0.2)	1 (1.6)	0 (0)
• Premarin (Estrogen derivative)	1 (0.2)	1 (1.6)	0 (0)
4. G03X Oother sex hormones and modulators of the genital system	1 (0.2)	1 (1.6)	0 (0)
• Danazol	1 (0.2)	1 (1.6)	0 (0)
5. G04B Urologicals	7 (1.8)	3 (5)	4 (1.2)
• Mirabegron	4 (1)	1 (1.6)	3 (0.9)
• Solifenacin	1 (0.2)	1 (1.6)	0 (0)
• Darifenacin	1 (0.2)	1 (1.6)	0 (0)
• Sildenafil	1 (0.2)	0 (0)	1 (0.3)
6. G03B Androgens	1 (0.2)	0 (0)	1 (0.3)
• Testosterone	1 (0.2)	0 (0)	1 (0.3)
7. G01A Antiinfectives and antiseptics, excl. combinations with corticosteroids	1 (0.2)	0 (0)	1 (0.3)
• Clotrimazole vaginal cream	1 (0.2)	0 (0)	1 (0.3)
Total	24 (6.4)	5 (8.4)	19 (6)
A ALIMENTARY TRACT AND METABOLISM			
1. A11C Vitamin A and D, incl. combinations of the two	19 (5)	0 (0)	19 (6)
• Vitamin D analog	19 (5)	0 (0)	19 (6)
2. A02B Drugs for peptic ulcer and gastro-esophageal reflux disease	16 (4.2)	1 (1.6)	15 (4.8)

• Rabeprazole	5 (1.3)	0 (0)	5 (1.5)
• Pantoprazole	9 (2.4)	1 (1.6)	8 (2.5)
• Esomeprazole	1 (0.2)	0 (0)	1 (0.3)
• Omeprazole	3 (0.8)	0 (0)	3 (0.9)
3. A10B Blood glucose lowering drugs, excl. insulins	14 (3.8)	0 (0)	14 (4.4)
• Empagliflozin	3 (0.8)	0 (0)	3 (0.9)
• Liraglutide	1 (0.2)	0 (0)	1 (0.3)
• Metformin	3 (0.8)	0 (0)	3 (0.9)
• Gliclazide	1 (0.2)	0 (0)	1 (0.3)
• Linagliptin	1 (0.2)	0 (0)	1 (0.3)
• Dapagliflozin	2 (0.5)	0 (0)	2 (0.6)
• Semaglutide	3 (0.8)	0 (0)	3 (0.9)
4. A06A Drugs for constipation	3 (0.8)	0 (0)	3 (0.9)
• Docusate sodium	2 (0.5)	0 (0)	2 (0.6)
• Senna glycosides	1 (0.2)	0 (0)	1 (0.3)
5. A04A Antiemetics and antinauseants	2 (0.5)	1 (1.6)	1 (0.3)
• Nabilone	1 (0.2)	1 (1.6)	0 (0)
Ondansetron	1 (0.2)	0 (0)	1 (0.3)
6. A11D Vitamin B1, plain and in combination with vitamin B6 and B1	4 (1)	0 (0)	4 (1.2)
• Thiamine Hydrochloride	1 (0.2)	0 (0)	1 (0.3)
• Vitamin B1 (Thiamine)	2 (0.5)	0 (0)	2 (0.6)
7. A10A Insulins and analogues	7 (1.9)	0 (0)	7 (2.2)
• Insulin Glargine	2 (0.5)	0 (0)	2 (0.6)
• Insulin Aspart	2 (0.5)	0 (0)	2 (0.6)
• Insulin Degludec	2 (0.5)	0 (0)	2 (0.6)
• Insulin Lispro	1 (0.2)	0 (0)	1 (0.3)
8. A11G Ascorbic acid (vitamin C), incl. combinations	3 (0.8)	0 (0)	3 (0.9)
• Vitamin C	3 (0.8)	0 (0)	3 (0.9)
9. A12C Other mineral supplements	2 (0.5)	0 (0)	2 (0.6)
• Magnesium	1 (0.2)	0 (0)	1 (0.3)
10. A03F Propulsives	1 (0.2)	0 (0)	1 (0.3)
• Domperidone	1 (0.2)	0 (0)	1 (0.3)
11. A11A Multivitamins, combinations	1 (0.2)	0 (0)	1 (0.3)
• Multivitamin	1 (0.2)	0 (0)	1 (0.3)
12. A07E Intestinal antiinflammatory agents	1 (0.2)	0 (0)	1 (0.3)
• Budesonide	1 (0.2)	0 (0)	1 (0.3)
13. A12A Calcium	2 (0.5)	0 (0)	2 (0.6)
• Calcium	2 (0.5)	0 (0)	2 (0.6)

Total	75 (20)	2 (3.3)	73 (23.1)
B BLOOD AND BLOOD FORMING ORGANS			
1. B03B Vitamin B12 and folic acid	14 (3.8)	0 (0)	14 (4.4)
• Vitamin B12	13 (3.4)	1 (1.6)	12 (3.8)
2. B01A Antithrombotic agents	29 (7.7)	5 (8.4)	24 (7.6)
• Rivaroxaban	2 (0.5)	1 (1.6)	1 (0.3)
• Aspirin	22 (5.8)	2 (3.3)	20 (6.3)
• Clopidogrel	2 (0.5)	0 (0)	2 (0.6)
• Apixaban	2 (0.5)	1 (1.6)	1 (0.3)
• Dabigatran	1 (0.2)	1 (1.6)	0 (0)
3. B03A Iron preparations	1 (0.2)	0 (0)	1 (0.3)
• Ferrous gluconate	1 (0.2)	0 (0)	1 (0.3)
4. B03X Other antianemic preparations	1 (0.2)	0 (0)	1 (0.3)
• Darbepoetin	1 (0.2)	0 (0)	1 (0.3)
5. B01AA Vitamin K antagonists	1 (0.2)	1 (1.7)	0 (0)
• Warfarin	2 (0.5)	1 (1.6)	1 (0.3)
6. B05X I.V. Solution additives	1 (0.2)	0 (0)	1 (0.3)
• Potassium chloride	1 (0.2)	0 (0)	1 (0.3)
7. B02B Vitamin K and other hemostatics	1 (0.2)	0 (0)	1 (0.3)
• Collagen	1 (0.2)	0 (0)	1 (0.3)
Total	48 (12.8)	6 (10.1)	42 (13.2)
C CARDIOVASCULAR SYSTEM			
1. C10A Lipid modifying agents	32 (8.5)	1 (1.6)	31 (9.8)
• Atorvastatin	13 (3.4)	0 (0)	13 (4.1)
• Simvastatin	2 (0.5)	0 (0)	2 (0.6)
• Ezetimibe	6 (1.6)	1 (1.6)	5 (1.5)
• Rosuvastatin	9 (2.4)	0 (0)	9 (2.8)
• Lovastatin	1 (0.2)	0 (0)	1 (0.3)
• Fenofibrate	2 (0.5)	0 (0)	2 (0.6)
• Pravastatin	1 (0.2)	0 (0)	1 (0.3)
2. C09A ACE inhibitors	10 (2.6)	1 (1.6)	9 (2.8)
• Perindopril	5 (1.3)	0 (0)	5 (1.5)
• Lisinopril	2 (0.5)	0 (0)	2 (0.6)
• Ramipril	3 (0.8)	1 (1.6)	2 (0.6)
3. C07A Beta blocking agents	9 (2.4)	2 (3.2)	7 (2.2)
• Bisoprolol	5 (1.3)	1 (1.6)	4 (1.2)
• Metoprolol	3 (0.8)	1 (1.6)	2 (0.6)
• Atenolol	1 (0.2)	0 (0)	1 (0.3)
4. C01A Cardiac glycosides	1 (0.2)	0 (0)	1 (0.3)
• Digoxin	1 (0.2)	0 (0)	1 (0.3)
5. C03C High-ceiling diuretics	4 (1)	0 (0)	4 (1.2)
• Furosemide	4 (1)	0 (0)	4 (1.2)

6. C03D Aldosterone antagonists and other potassium-sparing agents	2 (0.5)	1 (1.6)	1 (0.3)
• Spironolactone	1 (0.2)	0 (0)	1 (0.3)
• Amiloride and Hydrochlorothiazide	1 (0.2)	0 (0)	1 (0.3)
7. C09C Angiotensin II receptor blockers (ARBs)	10 (2.6)	2 (3.2)	8 (2.5)
• Candesartan	7 (1.8)	1 (1.6)	6 (1.9)
• Telmisartan	1 (0.2)	0 (0)	1 (0.3)
• Irbesartan	1 (0.2)	0 (0)	1 (0.3)
• Valsartan	1 (0.2)	0 (0)	1 (0.3)
8. C08C Selective calcium channel blockers with mainly vascular effects	8 (2.1)	0 (0)	8 (2.5)
• Nifedipine	1 (0.2)	0 (0)	1 (0.3)
• Amlodipine	7 (2)	0 (0)	7 (2.2)
9. C08D Selective calcium channel blockers with direct cardiac effects	1 (0.2)	0 (0)	1 (0.3)
10. C03A Low-ceiling diuretics, thiazides	3 (0.8)	0 (0)	3 (0.9)
• Hydrochlorothiazide	2 (0.5)	0 (0)	2 (0.6)
• Diltiazem	1 (0.2)	0 (0)	1 (0.3)
• Chlorthalidone	2 (0.5)	0 (0)	2 (0.6)
11. C01D Vasodilators used in cardiac diseases	5 (1.3)	0 (0)	5 (1.5)
• Nitroglycerin	5 (1.3)	0 (0)	5 (1.5)
12. C09D Angiotensin II receptor blockers (ARBs), combinations	1 (0.2)	0 (0)	1 (0.3)
• Candesartan and Hydrochlorothiazide	1 (0.2)	0 (0)	1 (0.3)
13. C09B ACE inhibitors, combinations	4 (1)	0 (0)	4 (1.2)
• Perindopril and Indapamide	2 (0.5)	0 (0)	2 (0.6)
• Ramipril and Hydrochlorothiazide	1 (0.2)	0 (0)	1 (0.3)
• Lisinopril and Hydrochlorothiazide	1 (0.2)	0 (0)	1 (0.3)
14. C10B Lipid modifying agents, combinations	2 (0.5)	0 (0)	2 (0.6)
Amlodipine and atorvastatin	2 (0.5)	0 (0)	2 (0.6)
15. C01B Antiarrhythmics, class I and III	1 (0.2)	1 (1.6)	0 (0)
• Amiodarone	1 (0.2)	1 (1.6)	0 (0)
Total	93 (24.8)	8 (13.5)	85 (26.8)
S SENSORY ORGANS			
1. S01E Antiglaucoma preparations and miotics	5 (1.3)	1 (1.6)	4 (1.2)
• Azarga eye drop (Brinzolamide + Timolol)	1 (0.2)	1 (1.6)	0 (0)

• Vistitan	1 (0.2)	0 (0)	1 (0.3)
• Latanoprost	2 (0.5)	0 (0)	2 (0.6)
• Brimonidine and timolol	1 (0.2)	0 (0)	1 (0.3)
2. S01X Other ophthalmologicals	1 (0.2)	0 (0)	1 (0.3)
• Refresh Lacri-Lube (Artificial tears)	1 (0.2)	0 (0)	1 (0.3)
Total	6 (1.6)	1 (1.6)	5 (1.5)
N NERVOUS SYSTEM			
1. N06D Anti-dementia drugs	20 (5.3)	4 (6.7)	16 (5)
• Donepezil	13 (3.4)	3 (5)	10 (3.1)
• Memantine	4 (1)	0 (0)	4 (1.2)
• Galantamine	3 (0.8)	1 (1.6)	2 (0.6)
2. N06A Antidepressants	30 (8)	7 (11.8)	23 (7.2)
• Mirtazapine	5 (1.3)	1 (1.6)	4 (1.2)
• Duloxetine	5 (1.3)	3 (5)	2 (0.6)
• Sertraline	5 (1.3)	3 (5)	2 (0.6)
• Citalopram	5 (1.3)	1 (1.6)	4 (1.2)
• Fluoxetine	1 (0.2)	0 (0)	1 (0.3)
• Trazodone	5 (1.3)	0 (0)	5 (1.5)
• Bupropion	2 (0.5)	0 (0)	2 (0.6)
• Escitalopram	2 (0.5)	0 (0)	2 (0.6)
3. N02B Other analgesics and antipyretics	11 (2.9)	5 (8.4)	6 (1.8)
• Pregabalin	1 (0.2)	1 (1.6)	0 (0)
• Acetaminophen	7 (2)	1 (1.6)	6 (1.8)
• Gabapentin	3 (0.8)	3 (5)	0 (0)
4. N02A Opioids	7 (1.8)	7 (11.8)	0 (0)
• Oxycodone	3 (0.8)	3 (5)	0 (0)
• Tapentadol ER	1 (0.2)	1 (1.6)	0 (0)
• Hydromorphone	2 (0.5)	2 (3.2)	0 (0)
• Codeine	1 (0.2)	1 (1.6)	0 (0)
5. N05B Anxiolytics	2 (0.5)	1 (1.6)	1 (0.3)
• Lorazepam	1 (0.2)	1 (1.6)	0 (0)
• Bromazepam	1 (0.2)	1 (1.6)	0 (0)
• Buspirone	1 (0.2)	0 (0)	1 (0.3)
6. N05C Hypnotics and sedatives	2 (0.5)	2 (3.2)	0 (0)
• Zopiclone	2 (0.5)	2 (3.3)	0 (0)
7. N01B Anesthetics, local	1 (0.2)	0 (0)	1 (0.3)
• Lidocaine	1 (0.2)	0 (0)	1 (0.3)
8. N05A Antipsychotics	4 (1)	3 (5)	1 (0.3)
• Quetiapine	1 (0.2)	1 (1.6)	0 (0)
• Risperidone	3 (0.8)	3 (5)	0 (0)
9. N03A Antiepileptics	3 (0.8)	1 (1.6)	2 (0.6)

• Levetiracetam	1 (0.2)	0 (0)	1 (0.3)
• Cannabidiol	1 (0.2)	0 (0)	1 (0.3)
• Lamotrigine	1 (0.2)	0 (0)	1 (0.3)
10. N04B Dopaminergic agents	1 (0.2)	0 (0)	1 (0.3)
• Sinemet (Carbidopa and levodopa)	1 (0.2)	0 (0)	1 (0.3)
11. N07C Antivertigo preparations	1 (0.2)	0 (0)	1 (0.3)
• Betahistine	1 (0.2)	0 (0)	1 (0.3)
Total	82 (21.8)	30 (50.8)	52 (16.4)
L ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS			
1. L01C Plant alkaloids and other natural products	1 (0.2)	0 (0)	1 (0.3)
• Lutein (Natural product)	1 (0.2)	0 (0)	1 (0.3)
2. L01B Antimetabolites	1 (0.2)	0 (0)	1 (0.3)
• Fluorouracil	1 (0.2)	0 (0)	1 (0.3)
3. L01X Other antineoplastic agents	1 (0.2)	0 (0)	1 (0.3)
• Hydroxyurea	1 (0.2)	0 (0)	1 (0.3)
Total	3 (0.8)	0 (0)	3 (0.9)
H SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES AND INSULINS			
1. H03A Thyroid preparations	7 (1.8)	0 (0)	7 (2.2)
• Levothyroxine	7 (1.8)	0 (0)	7 (2.2)
Total	7 (1.8)	0 (0)	7 (2.2)
R RESPIRATORY SYSTEM			
1. R01B Nasal decongestants for systemic use	1 (0.2)	0 (0)	1 (0.3)
• Pseudoephedrine	1 (0.2)	0 (0)	1 (0.3)
2. R03A Adrenergics, inhalants	9 (2.4)	0 (0)	9 (2.8)
• Salbutamol	7 (1.8)	0 (0)	7 (2.2)
• Symbicort (Budesonide and Formoterol)	1 (0.2)	0 (0)	1 (0.3)
• Fluticasone and Salmeterol	1 (0.2)	0 (0)	1 (0.3)
3. R06A Antihistamines for systemic use	1 (0.2)	1 (1.6)	0 (0)
• Bilastine	1 (0.2)	1 (1.6)	0 (0)
4. R03B Other drugs for obstructive airway diseases, inhalants	3 (0.8)	0 (0)	3 (0.9)
• Ipratropium bromide	1 (0.2)	0 (0)	1 (0.3)
• Omnaris (Ciclesonide)	1 (0.2)	0 (0)	1 (0.3)
• Tiotropium bromide	1 (0.2)	0 (0)	1 (0.3)
5. R03D Other systemic drugs for obstructive airway diseases	1 (0.2)	0 (0)	1 (0.3)
• Montelukast	1 (0.2)	0 (0)	1 (0.3)
Total	15 (4)	1 (1.6)	14 (4.4)
M MUSCULO-SKELETAL SYSTEM			

1. M03B Muscle relaxants, centrally acting agents	3 (0.8)	3 (5)	0 (0)
• Cyclobenzaprine	1 (0.2)	1 (1.6)	0 (0)
• Methocarbamol	2 (0.5)	2 (3.2)	0 (0)
2. M01A Antiinflammatory and antirheumatic products, non-steroids	2 (0.5)	1 (1.6)	1 (0.3)
• Celecoxib	2 (0.5)	1 (1.6)	1 (0.3)
3. M05B Drugs affecting bone structure and mineralization	3 (0.8)	0 (0)	3 (0.9)
• Risedronate	2 (0.5)	0 (0)	2 (0.6)
• Denosumab	1 (0.2)	0 (0)	1 (0.3)
4. M04A Antigout preparations	4 (1)	1 (1.6)	3 (0.9)
• Colchicine	2 (0.5)	0 (0)	2 (0.6)
• Allopurinol	2 (0.5)	1 (1.6)	1 (0.3)
Total	12 (3.2)	5 (8.4)	7 (2.2)
D DERMATOLOGICALS			
1. D04A Antipruritics, incl. antihistamines, anesthetics, etc.	1 (0.2)	1 (1.6)	0 (0)
• Doxepin	1 (0.2)	1 (1.6)	0 (0)
2. D06A Antibiotics for topical use	2 (0.5)	0 (0)	2 (0.6)
• Fusidic acid	1 (0.2)	0 (0)	1 (0.3)
• Mupirocin	1 (0.2)	0 (0)	1 (0.3)
3. D07A Corticosteroids, plain	4 (1)	0 (0)	4 (1.2)
• Triamcinolone	1 (0.2)	0 (0)	1 (0.3)
4. D01A Antifungals for topical use	3 (0.8)	0 (0)	3 (0.9)
• Betamethasone and clotrimazole	1 (0.2)	0 (0)	1 (0.3)
• Terbinafine	1 (0.2)	0 (0)	1 (0.3)
Total	10 (2.6)	1 (1.6)	9 (2.8)

Appendix E-3:- Distribution of patients identified with DRPs and prescribed Nervous system drugs among study participants (PCNE criteria)

N Nervous system	Patient prescribed (N=36) n (%)	Patients with DRP (N=31) n (%)	Patients without DRP (N= 5) n (%)
N06D ANTI-DEMENTIA DRUGS			
o Donepezil	12 (33.3)	8 (25.8)	4 (80)
o Memantine	2 (5.5)	2 (6.4)	0 (0)
o Galantamine and Memantine	1 (2.7)	1 (3.2)	0 (0)
o Galantamine	2 (5.5)	2 (6.4)	0 (0)
o Donepezil and Memantine	1 (2.7)	1 (3.2)	0 (0)
o Total	18 (50)	14 (45.1)	4 (80)
N06A ANTIDEPRESSANTS			
o Mirtazapine	2 (5.5)	1 (3.2)	1 (20)
o Duloxetine	3 (8.3)	3 (9.6)	0 (0)
o Sertraline	4 (11.1)	4 (12.9)	0 (0)
o Citalopram	5 (13.9)	5 (16.1)	0 (0)
o Fluoxetine	1 (2.7)	0 (0)	1 (20)
o Sertraline and trazodone	1 (2.7)	1 (3.2)	0 (0)
o Duloxetine and trazodone	1 (2.7)	1 (3.2)	0 (0)
o Mirtazapine and trazodone	2 (5.5)	2 (6.4)	0 (0)
o Trazodone	1 (2.7)	1 (3.2)	0 (0)
o Escitalopram	1 (2.7)	1 (3.2)	0 (0)
o Duloxetine and bupropion	1 (2.7)	1 (3.2)	0 (0)
o Citalopram and mirtazapine	1 (2.7)	0 (0)	1 (20)
o Escitalopram and bupropion	1 (2.7)	1 (3.2)	0 (0)
o Total	24 (66.6)	21 (67.7)	3 (60)
N02B OTHER ANALGESICS AND ANTIPYRETICS			

o Pregabalin	1 (2.7)	1 (3.2)	0 (0)
o Acetaminophen	7 (19.4)	7 (22.5)	0 (0)
o Gabapentin	3 (8.3)	3 (9.6)	0 (0)
o Total	11 (30.5)	11 (35.4)	0 (0)
N02A OPIOIDS			
o Oxycodone and Acetaminophen	3 (8.3)	3 (9.6)	0 (0)
o Hydromorphone	2 (5.5)	2 (6.4)	0 (0)
o Codeine and Acetaminophen	1 (2.7)	1 (3.2)	0 (0)
o Total	6 (16.6)	6 (19.3)	0 (0)
N05B ANXIOLYTICS			
o Lorazepam or bromazepam	1 (2.7)	1 (3.2)	0 (0)
o Buspirone	1 (2.7)	1 (3.2)	0 (0)
o Total	2 (5.5)	2 (6.4)	0 (0)
N05C HYPNOTICS AND SEDATIVES			
o Zopiclone	2 (5.5)	2 (6.4)	0 (0)
o Total	2 (5.5)	2 (6.4)	0 (0)
N01B ANESTHETICS, LOCAL			
o Lidocaine	1 (2.7)	0 (0)	1 (20)
o Total	1 (2.7)	0 (0)	1 (20)
N05A ANTIPSYCHOTICS			
o Quetiapine	1 (2.7)	1 (3.2)	0 (0)
o Risperidone	2 (5.5)	2 (6.4)	0 (0)
o Total	3 (8.3)	3 (9.6)	0 (0)
N03A ANTIEPILEPTICS			
o Levetiracetam	1 (2.7)	1 (3.2)	0 (0)
o Cannabidiol	1 (2.7)	1 (3.2)	0 (0)
o Lamotrigine	1 (2.7)	1 (3.2)	0 (0)
o Total	3 (8.3)	3 (9.6)	0 (0)
N04B DOPAMINERGIC AGENTS			
o Carbidopa and levodopa	1 (2.7)	0 (0)	1 (20)
o Total	1 (2.7)	0 (0)	1 (20)
N07C ANTIVERTIGO PREPARATIONS			
o Betahistine	1 (2.7)	0 (0)	1 (20)
o Total	1 (2.7)	0 (0)	1 (20)

Appendix E-4:- Distribution of patients identified with DRPs and prescribed Nervous system drugs among study participants (MedRevCiD and MAI)

N Nervous system	Patient prescribed (N=36) n (%)	Patients with DRP as per MedRevCiD (N=30) n (%)	Patients with DRP as per MAI (N= 24) n (%)
N06D ANTI-DEMENTIA DRUGS			
o Donepezil	12 (33.3)	7 (23.3)	5 (20.8)
o Memantine	2 (5.5)	2 (6.6)	2 (8.3)
o Galantamine and Memantine	1 (2.7)	1 (3.3)	0 (0)
o Galantamine	2 (5.5)	2 (6.6)	1 (4.1)
o Donepezil and Memantine	1 (2.7)	1 (3.3)	1 (4.1)
o Total	18 (50)	13 (43.3)	9 (37.5)
N06A ANTIDEPRESSANTS			
o Mirtazapine	2 (5.5)	1 (3.3)	1 (4.1)
o Duloxetine	3 (8.3)	3 (10)	3 (12.5)
o Sertraline	4 (11.1)	4 (13.3)	3 (12.5)
o Citalopram	5 (13.9)	5 (16.6)	3 (12.5)
o Fluoxetine	1 (2.7)	0 (0)	0 (0)
o Sertraline and trazodone	1 (2.7)	1 (3.3)	1 (4.1)
o Duloxetine and trazodone	1 (2.7)	1 (3.3)	1 (4.1)
o Mirtazapine and trazodone	2 (5.5)	2 (6.6)	2 (8.3)
o Trazodone	1 (2.7)	0 (0)	0 (0)
o Escitalopram	1 (2.7)	1 (3.3)	0 (0)
o Duloxetine and bupropion	1 (2.7)	1 (3.3)	1 (4.1)
o Citalopram and mirtazapine	1 (2.7)	0 (0)	0 (0)
o Escitalopram and bupropion	1 (2.7)	1 (3.3)	1 (4.1)
o Total	24 (66.6)	20 (66.6)	16 (66.6)
N02B OTHER ANALGESICS AND ANTIPYRETICS			
o Pregabalin	1 (2.7)	1 (3.3)	1 (4.1)
o Acetaminophen	7 (19.4)	6 (20)	6 (25)
o Gabapentin	3 (8.3)	3 (10)	3 (12.5)

o Total	11 (30.5)	10 (33.3)	10 (41.6)
N02A OPIOIDS			
o Oxycodone and Acetaminophen	3 (8.3)	3 (10)	3 (12.5)
o Hydromorphone	2 (5.5)	2 (6.6)	2 (8.3)
o Codeine and Acetaminophen	1 (2.7)	1 (3.3)	1 (4.1)
o Total	6 (16.6)	6 (20)	6 (25)
N05B ANXIOLYTICS			
o Lorazepam or bromazepam	1 (2.7)	1 (3.3)	1 (4.1)
o Buspirone	1 (2.7)	1 (3.3)	1 (4.1)
o Total	2 (5.5)	2 (6.6)	2 (8.3)
N05C HYPNOTICS AND SEDATIVES			
o Zopiclone	2 (5.5)	2 (6.6)	2 (8.3)
o Total	2 (5.5)	2 (6.6)	2 (8.3)
N01B ANESTHETICS, LOCAL			
o Lidocaine	1 (2.7)	0 (0)	0 (0)
o Total	1 (2.7)	0 (0)	0 (0)
N05A ANTIPSYCHOTICS			
o Quetiapine	1 (2.7)	1 (3.3)	1 (4.1)
o Risperidone	2 (5.5)	2 (6.6)	1 (4.1)
o Total	3 (8.3)	3 (10)	2 (8.3)
N03A ANTIEPILEPTICS			
o Levetiracetam	1 (2.7)	1 (3.3)	1 (4.1)
o Cannabidiol	1 (2.7)	1 (3.3)	1 (4.1)
o Lamotrigine	1 (2.7)	1 (3.3)	1 (4.1)
o Total	3 (8.3)	3 (10)	3 (12.5)
N04B DOPAMINERGIC AGENTS			
o Carbidopa and levodopa	1 (2.7)	0 (0)	0 (0)
o Total	1 (2.7)	0 (0)	0 (0)
N07C ANTIVERTIGO PREPARATIONS			
o Betahistine	1 (2.7)	0 (0)	0 (0)
o Total	1 (2.7)	0 (0)	0 (0)

Appendix E-5:- Distribution of patients identified with PIMs and prescribed Nervous system drugs among study participants (Beers criteria and STOPP criteria)

N Nervous system	Patient prescribed (N=36) n (%)	Patients with PIMs as per Beers criteria (N= 20) n (%)	Patients with PIMs as per STOPP criteria (N= 12) n (%)
N06D ANTI-DEMENTIA DRUGS			
o Donepezil	12 (33.3)	4 (20)	4 (33.3)
o Memantine	2 (5.5)	2 (10)	1 (8.3)
o Galantamine and Memantine	1 (2.7)	1 (5)	0 (0)
o Galantamine	2 (5.5)	1 (5)	0 (0)
o Donepezil and Memantine	1 (2.7)	0 (0)	0 (0)
o Total	18 (50)	8 (40)	5 (41.6)
N06A ANTIDEPRESSANTS			
o Mirtazapine	2 (5.5)	1 (5)	1 (8.3)
o Duloxetine	3 (8.3)	3 (15)	0 (0)
o Sertraline	4 (11.1)	3 (15)	2 (16.6)
o Citalopram	5 (13.9)	4 (20)	2 (16.6)
o Fluoxetine	1 (2.7)	0 (0)	0 (0)
o Sertraline and trazodone	1 (2.7)	1 (5)	0 (0)
o Duloxetine and trazodone	1 (2.7)	1 (5)	1 (8.3)
o Mirtazapine and trazodone	2 (5.5)	0 (0)	0 (0)
o Trazodone	1 (2.7)	0 (0)	0 (0)
o Escitalopram	1 (2.7)	0 (0)	0 (0)
o Duloxetine and bupropion	1 (2.7)	1 (5)	0 (0)
o Citalopram and mirtazapine	1 (2.7)	0 (0)	0 (20)
o Escitalopram and bupropion	1 (2.7)	1 (5)	1 (8.3)
o Total	24 (66.6)	15 (75)	7 (58.3)
N02B OTHER ANALGESICS AND ANTIPYRETICS			
o Pregabalin	1 (2.7)	1 (5)	0 (0)
o Acetaminophen	7 (19.4)	5 (25)	3 (25)
o Gabapentin	3 (8.3)	3 (15)	2 (16.6)

o Total	11 (30.5)	9 (45)	5 (41.6)
N02A OPIOIDS			
o Oxycodone and Acetaminophen	3 (8.3)	3 (15)	2 (16.6)
o Hydromorphone	2 (5.5)	1 (5)	0 (0)
o Codeine and Acetaminophen	1 (2.7)	1 (5)	1 (8.3)
o Total	6 (16.6)	5 (25)	3 (25)
N05B ANXIOLYTICS			
o Lorazepam or bromazepam	1 (2.7)	1 (5)	1 (8.3)
o Buspirone	1 (2.7)	1 (5)	0 (0)
o Total	2 (5.5)	2 (10)	1 (8.3)
N05C HYPNOTICS AND SEDATIVES			
o Zopiclone	2 (5.5)	2 (10)	2 (16.6)
o Total	2 (5.5)	2 (10)	2 (16.6)
N01B ANESTHETICS, LOCAL			
o Lidocaine	1 (2.7)	0 (0)	0 (0)
o Total	1 (2.7)	0 (0)	0 (0)
N05A ANTIPSYCHOTICS			
o Quetiapine	1 (2.7)	1 (5)	0 (0)
o Risperidone	2 (5.5)	2 (10)	1 (8.3)
o Total	3 (8.3)	3 (15)	1 (8.3)
N03A ANTIEPILEPTICS			
o Levetiracetam	1 (2.7)	0 (0)	1 (8.3)
o Cannabidiol	1 (2.7)	1 (5)	0 (0)
o Lamotrigine	1 (2.7)	1 (5)	1 (8.3)
o Total	3 (8.3)	2 (10)	2 (16.6)
N04B DOPAMINERGIC AGENTS			
o Carbidopa and levodopa	1 (2.7)	0 (0)	0 (0)
o Total	1 (2.7)	0 (0)	0 (0)
N07C ANTIVERTIGO PREPARATIONS			
o Betahistine	1 (2.7)	0 (0)	0 (0)
o Total	1 (2.7)	0 (0)	0 (0)

Appendix F

Example of Pharmacist's recommendation for a patient with multiple comorbidities and DRPs

1. **Patient Information**: The patient is an 80-year-old with Mild CI, 10 comorbidities, and is prescribed 21 medications per day.
2. **DRPs and Medication Review**:
    - 20 DRPs were identified in the patient.
    - 11 moderate and 33 minor DDIs were identified.
3. **DRP Identification Tools**:
    - 20 DRPs were identified using the MedRevCiD checklist.
    - 14 DRPs were identified using the MAI criteria.
    - 6 PIMs were identified using the Beers criteria 2023.
    - 7 PIMs were identified using the STOPP criteria.
4. **Pharmacist Recommendations**:

Four pharmacist recommendations were made at the drug level.

- The first recommendation was to discontinue doxepin, and the identified DRPs are:
    1. Drug-induced cognitive impairment or worsening.
    2. DDIs involving doxepin with other medications. Doxepin + Percocet, and Doxepin + Tapentadol, Doxepin (TCA) + Lorazepam (Benzodiazepines) + Tapentadol/Oxycodone (Opioids) +

Cyclobenzaprine (Skeletal muscle relaxant) a Any combination of ≥3 of these CNS-active drugs

3. PIM: - History of falls or fractures: Doxepin >6mg/day (Antidepressant with strong Anticholinergic properties).

- The second recommendation was to wean off bromazepam and zopiclone, each can be weaned by 10- 25% weekly to every 2 weeks, and the identified DRPs are:
    1. Drug-induced cognitive impairment or worsening for both the drugs
    2. Bromazepam use in sleep apnea is not recommended
    3. Concomitant use of Percocet with Benzodiazepine (Bromazepam) may result in profound sedation, respiratory depression, coma, and death
    4. DDIs involving zopiclone with other medications. Zopiclone + Percocet, Zopiclone + Tapentadol, Doxepin (Tricyclic antidepressant) + Lorazepam (Benzodiazepines) + Tapentadol/Oxycodone (Opioids) + Cyclobenzaprine (Skeletal muscle relaxant):- Any combination of ≥3 of these CNS-active drugs
- The third recommendation was to discontinue cyclobenzaprine, and the identified DRPs are:
    1. Drug-induced cognitive impairment or worsening
    2. DDIs involving cyclobenzaprine with other medications. Cyclobenzaprine + Percocet, Cyclobenzaprine + Tapentadol, Doxepin (TCA) + Lorazepam (Benzodiazepines) + Tapentadol/Oxycodone

(Opioids) + Cyclobenzaprine (Skeletal muscle relaxant) Any combination of ≥3 of these CNS-active drugs

3. PIM: - History of falls or fractures: Cyclobenzaprine (Anticholinergic)

- The fourth recommendation was to discontinue celecoxib given patients current renal function, and the identified DRPs are:
    1. Celecoxib (NSAID's, COX-2) in patient with eGFR level 40 ml/min/1.73m2

One pharmacist recommendation was made at the other recommendation or activity

- The pharmacist recommends waiting for MRI results, if there is no ischemic stroke, discontinue aspirin, and the identified DRPs are:
    1. Aspirin use is not recommended in patients with asthma

No pharmacist recommendation was made for the following DRPs

1. Drug-induced cognitive impairment or worsening: Oxycodone, Tapentadol
2. DDIs: Oxycodone + Tapentadol, Doxepin (TCA) + Lorazepam (Benzodiazepines) + Tapentadol/Oxycodone (Opioids) + Cyclobenzaprine (Skeletal muscle relaxant): - Any combination of ≥3 of these CNS-active drugs
3. Duplicate therapy (Oxycodone, Tapentadol)
4. PIM: History of falls: - Opioid analgesic (Oxycodone, Tapentadol)

5. **Outcome of Recommendation**:

- After the pharmacist recommendation, 9 DRPs were totally resolved, 4 DRPs were partially solved, and status of DRPs was not known in 7 DRPs.

In the comprehensive medication review, the pharmacist's recommendations have addressed several critical DRPs in the patient's complex medication regimen; there are a few noteworthy aspects to consider. First, some DRPs indicate the need for ongoing monitoring and assessment to determine the effectiveness of interventions and whether further actions are required. Second, not all identified DRPs received recommendations, which could be due to various factors such as clinical judgment or the complexity of balancing risks and benefits.