

Assessing Medication Adherence in Older Adults with Memory Concerns in a Primary Care-Based Memory Clinic

by

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AUTHOR'S DECLARATION

I hereby declare that I am the sole author of this thesis. This 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

There is an increasing prevalence of cognitive impairment in the rapidly ageing population. Cognitive impairment has been shown to be a unique barrier to medication adherence in older adults coupled with an increased number of chronic conditions and prescription medications. There is a need to identify those who are non-adherent in order to reduce the repercussions related to non-adherence such as hospitalization and increased health care costs. Although several instruments exist to assess adherence, not all can be applied to primary health based setting.

Pharmacists practicing in novel primary care settings such as Center for Family Medicine's Family Health Team's Memory clinic measure adherence using pill count and pharmacy refill data, however which method is more feasible remains unknown. Furthermore, it remains unknown whether the scores obtained using these instruments correlate. There is paucity in the current literature that addresses the aforementioned gaps. In addition, cognitively impaired older adults require assistance in managing medication, however, it remains unclear which adherence aids are being used by the caregivers of these patients seen at the memory clinic. Therefore, the overall objectives of this thesis were: 1) To map and describe the various aspects described in the current literature regarding medication adherence in older patients with memory concerns, and, 2) To determine the most feasible method of assessing adherence in an interdisciplinary, primary care based memory clinic setting.

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DEDICATION

I would like to dedicate this thesis to my late grandpa, Mr. Shahbuddin Budhwani.

To my Aunt, Zarina Budhwani – thank you for being a guardian and my mother away from home.

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LIST OF ABBREVIATIONS

AD	Alzheimer’s disease	HR	Hazard Ratio
ADRD	Alzheimer’s disease and related disorders	LCF	Long Cognitive Function
ANOVA	One-way analysis of variance	LTC	Long Term Care
BP	Blood pressure	MCI	Mild Cognitive Impairment
BPSD	Behavioural and Psychological Symptoms of dementia	MEMS	Medication Event Monitoring System
CAD	Canadian Dollar	MMD	Multi-compartment Medication Devices
CBP	Calendar Blister Packs	MMSE	Mini-Mental State Examination
ChEI	Cholinesterase Inhibitors	MoCA	Montréal Cognitive Assessment
CCB	Calcium Channel Blockers	MPR	Medication Possession Ratio
CDT	Clock Drawing Test	OOP	Out-of-Pocket
CFFM	Center for Family Medicine	OR	Odd’s Ratio
CI	Confidence interval	OTC	Over-the-counter
CRF	Case Report Form	RR	Relative Risk
ER	Extended Release	WHO	World Health Organization
FHT	Family Health Team		
HCF	High Cognitive Function		

CHAPTER 1: INTRODUCTION

*“The physician must not only be prepared to do what is right himself, but also to make the patient, the attendants, and externals cooperate.” –Hippocrates.*¹

In recent decades, an immense amount of research has been devoted to the development of newer drugs leading to advent of more effective therapies with better benefit-to-risk profiles for treating a large number of diseases. This exploration in the field of novel drug discovery has led to a shift towards an increased emphasis on health outcomes research.² Although many of these new treatments have been shown to improve health outcomes, an important aspect of patient behaviour is often ignored; a patient’s medication-taking behaviour. A patient’s medication-taking behaviour is an important component in achieving the intended health outcome (Figure 1).²

Figure 1: Importance of medication-taking behaviour



A patient’s medication-taking behaviour is a complex and individual act. The most appropriate term that defines this concept is debatable. Several definitions including medication compliance, adherence, and concordance are used in the literature interchangeably. Although the terms sound synonymous, certain differences exist and it is necessary to define each term to clarify these differences.

1.1 Terminologies

The most commonly used terminologies are defined below:

1.1.1 Compliance

In terms of health care, compliance is defined as:

“The extent to which a person’s behaviour (in terms of taking medications, following a diet or executing lifestyle changes) coincides with medical or health advice ”³

The term compliance implies a one-sided role of the health care provider in the decision making process and portrays a paternalistic attitude by the prescriber towards the patient. Moreover, “non-compliance” suggests refusal to comply or disobedience and therefore the term carries a negative connotation. The term concordance was introduced to tackle this issue.³

1.1.2 Concordance

Concordance has been defined in medical literature in the following way:

“Concordance is a shared process leading to an agreement between the patient and prescriber about the aims of treatments and how these are achieved. The process enables the patient to participate fully and to influence the outcome ”⁴

Although the term implies that patient and the clinician should be equal partners in the decision making process, it is not clear how one can identify a patient who desires a

participation of this sort. It may also not be possible for all patients to identify the aims of treatments which questions the benefits of involving them in the decision making process.³

1.1.3 Adherence

Aside from compliance and concordance, adherence is a term that is being increasingly used to describe the patient's act of taking their medications. The World Health Organization (WHO) defines adherence as:

“The extent to which a person's behaviour – taking medication, following a diet and/or executing lifestyle changes, corresponds with agreed recommendation from a health care provider”⁵

This definition emphasizes the importance of a patient-prescriber relationship and describes patients' active collaboration in treatment. The term adherence also offers a balance between the responsibility of the prescriber in prescribing a certain therapy and the patient's liberty in accepting a given recommendation. Unlike concordance, this definition does not imply that a patient will be able to identify and understands his/her condition for a successful treatment.³ For this reason, the majority of authors in medical literature prefer the term adherence to describe patients' medication-taking behaviour. For the purpose of this thesis, the terms adherence and non-adherence were chosen because they offer an appropriate relationship balance between the patient choice and prescriber authority. Other terms such as persistence and discontinuation represent a

different paradigm of medication-taking behaviour. Persistence is the time period between the start of a dose to the last dose, which is followed by discontinuation.⁶

1.2 Adherence to medications

Although medication adherence is known to be an important factor that predicts the effectiveness of pharmacotherapy, it is especially crucial for the long-term success of medications used in managing chronic conditions. For example, some of the earliest research regarding medication adherence indicated that improving adherence to antihypertensive treatment improves health outcome by reducing the risk of cardiovascular complexities such as myocardial infarction and stroke.⁷ Sackett and Haynes showed an improvement in blood pressure in their study involving 38 hypertensive Canadian steelworkers who were non-adherent to their antihypertensive treatment.⁷ This cohort of participants was divided into a control and intervention group, where the intervention group received training on blood pressure monitoring and strategies to improve adherence. After a follow up period of six months, the intervention group showed a substantial decrease in blood pressure, whereas the control group showed only a modest decrease in blood pressure.⁷

Poor adherence has shown to result in increased health care costs and hospitalizations.⁸ In fact, poor medication adherence contributes to an estimated one-third to two-thirds of all medication-related hospitalizations in the United States.^{9,10} Furthermore, in 2003, the WHO reported that approximately 50% of patients with chronic conditions do not take their medications as prescribed.⁵ This medication non-adherence causes increased morbidity and death, resulting in a total yearly cost of approximately \$100 billion all over the world. In Canada alone, it was estimated that the

cost related to medication non-adherence was in the range of \$8 to \$10 billion in the year 2006.¹¹

1.3 Prevalence of medication non-adherence

According to the WHO report of 2003, half of the patients suffering from chronic conditions are non-adherent to their medications.⁵ Although the threshold by which one can be considered as non-adherent is debatable, the current consensus among researchers indicates that an adherent person will be consuming medications at least 80% of the time for most common chronic conditions including hypertension, diabetes and hyperlipidemia.¹²⁻¹⁴

The prevalence of medication non-adherence can vary considerably depending on the type or duration of the treatment. A number of clinical trials report adherence rates for patients suffering from chronic conditions to fall within the range of 43-78%.¹⁴ For example, a quantitative review of research on medication adherence over the past 50 years it is suggested that the adherence rates are lower for conditions like sleep disorder (66%) and diabetes (68%), were 50% for heart disease and mental illnesses, and were much higher in case of cancer (79%) or HIV treatments (88%).¹⁵

1.4 Risk factors leading to non-adherence

It is necessary to understand the causes of decreased adherence in order to improve medication adherence. There are several determinants of non-adherence and these causes may in turn be multi-factorial. Many review articles on medication adherence, including the report by WHO, have broadly classified these factors as patient-related, therapy-related, healthcare system-related, socio-economic factor-related and condition-related.^{5,16-18} Patient-related factors including patient demographics, low health literacy,

lack of involvement in the decision-making process, and poor medication management skills are some of the major determinants of non-adherence.¹⁹⁻²¹ Therapy-related factors are also responsible for lower adherence including patient's perception of treatment, past experiences to therapies and decreased motivation.²² Factors associated with health care system include patient-prescriber relationship, accessibility to health centers, long wait times and prior patient experiences during health care appointments.²³ Some of the commonly listed socio-economic barriers are treatment cost, lower understanding of medication instructions, lack of familial support, and low patient income.¹⁷ Lastly, there are some key condition-related factors including disease type, severity of disease, and impaired cognition, which are also known to cause decreased adherence to medications.^{24,25}

1.5 Assessing medication adherence

As medication adherence is an individual patient behaviour and can vary among individuals, it is challenging to assess adherence. Accurate measurement of adherence becomes increasingly difficult due to the absence of a gold standard. A gold standard instrument is a tool that has to be inconspicuous (to avoid patient bias and sensitization), objective (to produce reproducible results) and practical (to easily incorporate into practice with minimal cost).²⁶

Broadly speaking, adherence-assessing instruments are categorized as direct and indirect methods. Direct measurement instruments take an advantage of detecting specific drug related markers or metabolites in blood and urine samples to confirm the consumption of medications.²⁷ Although direct measurement of the drug metabolite/marker levels is the most accurate method, its use is often limited due to

impracticality and higher costs in routine clinical practice and research. As an alternative, there are several indirect tools available to assess adherence.²⁷ Some of the most commonly used indirect methods in the literature include pill counts,²⁸ pharmacy refill dates²⁹ and structured or semi-structured interviews³⁰. The major disadvantages of these indirect techniques are that these methods are a proxy measure of patient adherence and that they do not guarantee the intake of the drug by the patient. Amongst these indirect techniques, the electronic monitoring method is considered to be the closest to a gold standard.²⁸ Electronic monitoring uses a medication event-monitoring system (MEMS) equipped with a microchip that records real-time opening and closing of the pill container. As with other indirect measuring techniques, the use of MEMS is limited due to its inability to measure actual consumption of the medications and furthermore due to its higher cost in comparison to other indirect techniques.²⁷

1.6 Interventions

Several adherence-improving interventions have been suggested in the literature. These include patient and prescriber education on importance of adherence, collaboration between patient and prescriber in the treatment decision-making process, reducing pill burden and simplifying treatment regimens by tailoring it to individual patient's lifestyle, use of reminder aids, and support from family members.³¹⁻³³

Although interventional strategies depend on the patient condition and type of disease being treated, one of the most impactful strategies shown to improve adherence rates is an effective communication between the health care provider and the patient. Effective communication between a patient and prescriber involves verbal and non-verbal communication, expression of concerns, and participation in decision-making.³⁴ For

example, a recent meta-analysis reported an improvement of adherence rate by 19% when there was an effective communication between the physician and the patient.³⁴ The study has also indicated that an effective communication increased the likelihood of patients adhering to their medication by two times.³⁴

1.7 Medication Non-adherence in Older Adults: A Public Health Concern

Over the past 30 years, Canada has seen an increase in the proportion of adults over the age of 65 from 10% in 1984 to 16% in 2014.³⁵ Lower birthrates and longer life expectancy will continue to trend the aging population upwards, with estimates reaching 28% of the total population by 2063. The upward trend in an aging population is concerning, as the presence of chronic conditions increases with age. In 2009 it was reported that 89% of adults over the age of 65 had at least one chronic condition, and older adults are four times more likely to report having a chronic condition compared to the 18-24 year old population.³⁶ The chronic conditions most associated with aging are osteoarthritis, osteoporosis, cardiovascular diseases, cancer, diabetes, Alzheimer's disease and other dementias.³⁶ Older adults also face an increased number of co-chronic conditions, for example, 25% of Canadians aged 65 to 79 years and 37% of those aged 80 years and older reported having four or more chronic conditions.³⁷

Closely related to multiple chronic conditions is an increase in the number of prescription medications among seniors.³⁸ On an average, seniors took three to four prescription medications when they reported one or two chronic conditions and six prescription medications when they reported three or more chronic conditions.³⁸ Self-managing such a large number of medications often becomes challenging to older adults with many noted barriers to chronic disease management including comorbidity and

functional disability.³⁹ Difficulties with self-managing medications and/or the resulting therapeutic regimens ultimately affect an older patient's medication-taking behavior and is commonly known to lead to non-adherence.⁴⁰ This non-adherence to medications is a cause of increasing hospitalization among older adults. In fact, drug non-adherence attributes to an estimated 10% of total hospitalizations worldwide.

Among the many risks associated with co-morbidities faced by older adults such as the consequences of frailty, an increased risk of memory impairment with increasing age also raises concern. The prevalence of cognitive impairment is on the rise with the rising ageing population. This increased prevalence of cognition-related disorders such as mild cognitive impairment, dementia, and Alzheimer's disease further impacts the ability of older adults to carry out their daily activities including managing their medications. This further adds to the risk of non-adherence in this population. In addition, the behavioural and psychological symptoms of dementia (BPSD) increase the burden on the caregiver of the patient, leading to increased caregiver stress and reduced support for these patients. All these factors have been associated with reduced medication non-adherence, making managing medications and adherence a huge challenge in this population. However, most of these factors that may affect adherence in this population are under studied or have not been studied extensively.

In the recent years, a novel approach has been developed and adopted in Southern Ontario to help manage the conditions of older adults with memory concerns. The first clinic dealing with patients in a primary health care setting was established in 2006 at the Center for Family Medicine in Kitchener. This model has since spread to various other cities in Ontario such as Cambridge, London, and Ottawa. These novel practice sites are

commonly known as “memory clinics”. These memory clinics are comprised of an interdisciplinary team consisting of a physician, nurse, pharmacist, social worker and occupational therapist. This team aims to manage several aspects of memory impairment, including the health aspect, therapy aspect, and social aspect. The memory clinic model was developed with the aim to support older adults with memory concerns progressing towards dementia and Alzheimer’s disease. The team focuses on slowing the progression by eliminating some of the risk factors associated with dementing illnesses. In particular, the pharmacist plays a key role in the therapy related aspect of managing the problems related to older adults. This includes the addition or elimination of drugs from the current therapy in order to manage the underlying conditions, and assessing and improving adherence to medications. An important barrier to assessing adherence is the lack of a gold standard. This stands true in memory clinic setting as with other research studies.

^{13,14,27,41} As previously mentioned, there are two major assessment techniques for clinicians to choose from, direct and indirect methods. The use of direct methods is not possible in general practice mainly due to cost and feasibility among other disadvantages. Indirect methods provide a clinician the flexibility to assess adherence without worrying about the cost. Specifically in a memory clinic setting, the pharmacist uses pharmacy refill history and pill count to assess adherence. However, performing both of these methods on all patients can be time-consuming and laborious for the pharmacist, as he/she has other duties entitled to perform. Hence, there is a lack of studies showing the most feasible method among the two in a clinical setting.

To address the aforementioned gaps in the current literature, the overall objectives of this thesis are:

1. To map and describe the various aspects described in the current literature regarding medication adherence in older patients with memory concerns, and,
2. To determine the most feasible method of assessing adherence in an interdisciplinary, primary care based memory clinic setting.

CHAPTER 2: A SCOPING REVIEW ON MEDICATION ADHERENCE IN OLDER ADULTS WITH MEMORY CONCERNS

2.1. Background

Patient adherence is of utmost importance for optimal effectiveness of prescribed medications.¹⁷ Failure to adhere to a prescribed medication regimen can lead to suboptimal clinical outcomes. Previous research has indicated that poor adherence to beta-blockers was associated with a 4.5 times increased risk of coronary heart disease in patients with hypertension compared to those whose adherence was 80% or greater.⁴² Patient behaviours related to adherence are dynamic, vary according to disease states, and are subject to multiple interacting factors such as the number of medications and complexity of prescribed regimens.¹⁴ It becomes more challenging for patients to adhere to their prescribed medications when medication regimens increase in their complexity. For example, the mean adherence in a cohort of older adults was 37%, and was inversely associated with complex drug regimens [Odds ratio (OR)= 7.4, 95% Confidence Interval (CI) 3.2, 16.9].⁴³ Moreover, many older adults consume multiple medications, yet they appear to have adherence estimates that are higher, lower, or comparable to that of younger adults.¹⁷ Nevertheless, this population presents a unique challenge with regards to optimal medication adherence due to the frequency of polypharmacy coupled with the requirement of following a complex set of medication taking instructions. Increased concerns about medications, greater number of chronic medications, higher cost,

decreased mobility and lack of satisfaction with care represents additional barriers that negatively impact medication adherence in older adults.⁴⁴

Cognitive impairment is an important barrier to adherence in older adults over the age of 65 years. The current prevalence of cognitive impairment (includes mild cognitive impairment and Alzheimer's Disease and Related disorders) in Canada is 8% in the age group of 65-74 years old, which increases dramatically to 28-61% among those aged 75+ years.⁴⁵ Cognitive impairment has also been shown to have negative effects on medication adherence.⁴⁶ Patients dealing with cognitive impairment have difficulty remembering to take medications as adherence to medication regimens requires a set of complex cognitive skills such as accessing medications, understanding directions, and scheduling medication taking times.⁴⁷ The aforementioned tasks require verbal memory, working memory, processing speed and reasoning, some or all of which would be expected to be impaired in patients with cognitive impairment.⁴⁷ A major consequence of dementing illnesses is that special attention is required with regards to appropriate medication use, including optimizing adherence.⁴⁸

Accurate estimation of medication adherence is important to determine the success of an intervention to improve adherence or to account for effectiveness of a drug regimen.²⁷ A major challenge in this regard is the lack of a gold standard measure of adherence. A gold standard is an ideal tool or method, which is simple, valid and reliable, with an optimal balance of sensitivity and specificity for assessing medication adherence.²⁷ While numerous methods are available to assess adherence in older people, they are all fraught with limitations.^{17,27}

Unfortunately, there is a dearth of information regarding various aspects of

medication adherence in people with cognitive impairment, such as the prevalence of non-adherence, barriers associated with non-adherence, adherence enhancing methods used by patients, and effectiveness of available interventions aimed at improving adherence. The objective of the scoping review was therefore conducted to map the current literature, to address gaps in the literature, to examine the extent and range of research activity, and finally, to summarize the research findings.

2.2. Methodological framework

The Arksey and O'Malley's framework for scoping reviews was used for the present study.⁴⁹ The following steps were thus undertaken: (1) development of research question, (2) location of relevant publications, (3) screening and selection of publications, (4) data charting, and (5) data analysis and summary of the results. Lavec et. al refer to scoping studies as “mapping”, which is a process of summarizing a range of evidence in order to convey the breadth and depth of a field.⁵⁰ Mapping may act as a blueprint to examine the extent, range and nature of research activity, determine the value of undertaking a full systematic review, summarize and disseminate research findings, or identify research gaps in the existing literature.⁵¹

2.2.1. Step 1: Development of research question

This scoping review focused on mapping the area of medication adherence in patients with cognitive impairment. The research question was “What is known about medication adherence in patients with cognitive impairment?” The focus of this review is on medication adherence in cognitively impaired patients. The working definition for adherence has been given in Chapter 1. Our specific research questions were:

- a) What is the prevalence of non-adherence in patients with cognitive impairment?

- b) What are the most common methods used to assess adherence in cognitively impaired patients?
- c) What are the barriers to adherence in this population?
- d) What interventions are available to improve medication adherence in patients with cognitive impairment?
- e) What is the efficacy of methods identified in d) in improving medication adherence in patients with cognitive impairment

2.2.2. Step 2: Location of relevant publications

In keeping with the methods used for this review, the search strategy was designed to be sufficiently broad in order to decrease the chance of missing key articles. The search strategy was developed in collaboration with the author's supervisor (CF) and a medical librarian (SG). A comprehensive search of electronic databases including Pubmed, MEDLINE (Ovid), EMBASE, CINAHL, IPA and Pyschinfo was conducted during the time period of 1966 to January 2015. Search terms were as follows:

(medication adherence, medication non-adherence, medication compliance, medication non-compliance, medication persistence, drug adherence) AND (dementia, alzheimer, lewy body, lewy bodies, vascular, mixed, cognitive impairment)AND (assess, measur*, evaluat*).*

2.2.3. Step 3: Screening and selection of publications

Two investigators (ZH and CF) screened the titles and abstracts independently with 98.6% inter-reviewer agreement. The publications were reviewed by reading the titles and abstracts of the citations. Studies were included if they examined medication adherence and/or compliance in patients with Alzheimer's disease or related disorders.

All selected studies were included regardless of publication date or language. After screening the titles and abstracts for inclusion, the selected studies deemed eligible for inclusion were read. The disagreements on inclusion/exclusion of studies between the authors were resolved by discussion.

Studies that dealt with persistence and/or discontinuation were excluded, as the working definition for the purpose of this review was adherence. Moreover, studies were excluded when English translation was unavailable (7 articles: 4 Spanish, 2 Japanese & 1 German). In addition, one study was later excluded as it only addressed the complexity of drug regimens and cognitive impairment (Figure 2).

2.2.4. Step 4: Data charting

As per Arksey and O'Malley's framework, each publication was categorized based on the authors, publication year, title of the publications, country (based on the location of the first author), study design, outcome variable, methods used to assess medication adherence, objectives and key findings.⁴⁹

2.2.5. Step 5: Collating, summarizing, and reporting the results

This phase was carried out in three distinct steps. First, the data was extracted based on the general characteristics of the studies, i.e. the publication date, the country (based on the location of the first author), and the adherence assessment methods employed. Second, the results were summarized based on the research question and specific objectives. Thus, the information on prevalence (objective 1), methods to assess adherence (objective 2), barriers (objective 3) and interventions (objective 4&5) was summarized. The results were categorized and described based on the specific objectives. Finally, the clinical and research implications were described.

2.3. Results

The initial search of electronic databases yielded 581 citations, of which 535 remained after removing 46 duplicates (Figure 2). The search strategies for each database and their results can be found in Appendix 1. After reading through each title of the 535 citations, 112 abstracts were selected for screening purposes. After screening these abstracts, 60 full-text studies were reviewed and assessed for eligibility. A total of 42 studies and 2 conference proceedings were deemed eligible for this review.

The publication dates of the papers that were selected for this review are shown in figure (2). A large number (n=27) of studies were published in the last five years and more than half of the research emanated from the United States (n=23).

2.3.1. Prevalence of medication non-adherence in cognitively impaired older adults

Medication non-adherence appears to be common among patients with ADRD, ranging from 2% to 69.9% and varies based on the method used to assess adherence.^{13,21,23,46,48,52-66} For example, using self-reported and/or caregiver reported adherence, non-adherence ranged from 2% to 59%.^{21,23,46,55,62,63,66} By comparison, the proportion of non-adherent patients as assessed by electronic monitoring, refill data, and by pill count ranged from 32% to 48.5%,^{13,52,53,65,67} 19.3 to 66.1%^{48,54,56,57,59-61} and 15.7% to 26.5%, respectively.^{48,53,58,64} The variability in these estimates limits our ability to make cross study comparisons.

2.3.2. Methods to assess medication adherence and their limitations

The most commonly used methods to assess medication adherence included self-reported adherence (32%), Pharmacy refill and claims data (27%), Pill count (14%), health provider's report (14%), electronic monitoring (10%) and clinical health outcomes

(3%).^{13,21,23,46,48,52-66} No direct methods were used in any of the identified studies (Table 1).

Self-report measures utilized standardized questionnaires and structured interviews to assess adherence.^{21,23,46,55,62,63,66} Boada and Arranz⁵⁵ used a standardized questionnaire called the Morisky scale, while others relied on structured interviews for patients and their caregivers.^{21,46,55,62,63,66} Morisky scale is a 4-item self report scale which include questions such as “Do you forget to take your medications?”, “Are you careless about your medications?”, “When you feel better, do you sometimes stop taking your medications?” and “Sometimes if you feel worse when you are on medications, do you stop taking them?”. Reported advantages of self-report methods include ease of administration, but these measures are prone to social desirability bias, recall bias, and error in self-observation, all of which may lead to patients over estimating their degree of adherence.²⁷

Pharmacy refill data was the second most commonly used method to assess adherence (27% of studies).^{48,54,56,57,59-61} This method was reported as an alternative medication adherence assessment method in primary care based clinical settings when pill count was not available.⁶⁸ Based on pharmacy refill data, medication adherence was measured using the medication possession ratio. Medication Possession Ratio (MPR) was defined as the ratio of total days’ supply of medication to the number of days that the patient should have been taking the medication. An MPR value greater than 0.80% was considered as ‘adequate’ adherence in all studies included in this review; thus this value was used as a dichotomous cut-off between adherent and non-adherent patients.⁶⁹ The reported shortcomings of this method include that it does not guarantee the administration

of the medications, nor does reflect the timing of drug consumption. This method might limit assessment of medication adherence in cases where patient were accessing different pharmacies to refill their medications.^{27,53,69}

The third most commonly used method (14%) was pill counts.^{48,53,58,64} Pill count has been reported to be one of the simplest methods to assess adherence. A pill count is performed by counting the pills present in the medication container, then multiplying by the dosage and then dividing the resulting number by the number of pills that should have been consumed as per prescribed dosage and number of days within the analyzed period. (No. of pills dispensed – No. of pills in the container/No. of pills that should have been taken during the given time period) Pill counts have been suggested as an approach that is not subject to recall or social desirability bias and was found to be a method of choice in clinical and research settings.^{27,68} The disadvantage of pill count methods is that they do not guarantee consumption of the medication nor do they reflect the exact timing of medication consumption.²⁷

Some studies utilized electronic monitoring methods to assess adherence (10%).^{13,52,53,65,67} MedTracker™ pillboxes and the Medication Event Monitoring Systems (MEMS) are devices which were used in the included studies.^{13,52} These devices are equipped with microprocessors on the lids, which record the times of every lid opening.⁵² Electronic monitoring has been regarded by some as the closest ‘gold standard’ because it allows researchers to measure adherence in ‘real time’, yet medication consumption is assumed, not verified, and cost is an important limitation.⁶⁷ In addition, use of such devices has been deemed impractical for health care providers in daily practice.²⁷ To date, only one study has compared MEMS with other measures such

as pill count, clinical rating scales of compliance and self-report.⁵³ A weak to moderate correlation between these measures was observed with Kappa correlation ranging from 0.256 to 0.382.⁵³

2.3.3. Barriers to medication adherence

A number of barriers were identified that might contribute to non-adherence in cognitively impaired individuals. These factors were broadly classified in relation to patient, medical conditions, therapy, socioeconomic, and health system barriers (Table 2).

Patient related barriers

Patient factors associated with non-adherence include problem drinking,⁴⁶ non-Caucasian race,⁶¹ younger age,⁶⁰ and female gender.^{53,60} For example, in an *ad hoc* study involving older patients from 11 countries, problem drinking was significantly associated with medication non-adherence [OR= 3.6, 95% CI (1.08, 7.16)].⁴⁶ Non-Caucasian race has also been associated with non-adherence. For example, being Hispanic was associated with lower adherence rates than whites for Dihydropyridine Calcium Channel Blockers (CCBs) [OR= 0.69 95% CI (0.53, 0.89)] and Cholinesterase Inhibitors (ChEI) [OR= 0.77 CI(0.61, 0.96)].⁶¹ On the contrary, other patient related factors such as age, and male gender have been associated positively with medication adherence. In a study showed involving patients on Alzheimer's Disease (AD) medications, patients >86 years were likely to be more adherent as compared to patients on the same medications who were <75 years of age (OR= 1.401, $p < 0.001$).⁶⁰ This study also showed that male gender was more likely to be adherent to AD medications as

compared to female gender (OR= 1.175, $p<0.05$)⁶⁰. Kim also documented a similar association between female gender and adherence.⁵³

Barriers related to medical conditions

Medical conditions-related factors include having good physical health, reduced attention,²³ reduced executive function,⁷⁰ dementia, and cognitive impairment, with the latter^{23,46,59,70} being cited as a key factor associated with medication non-adherence.¹⁷ Indeed, the relative risk of non-adherence increased four times in patients with low cognitive function (Mini Mental State Exam (MMSE) score<23) as compared to patients with high cognitive function (MMSE \geq 23) [RR= 4.1, 95% CI (3.47, 4.78)].⁵² Similar studies showed that cognitively impaired individuals were at higher risk of non-adherence as compared to those who are cognitively intact [Adjusted RR= 2.0, 95% CI (1.4, 2.8)].⁷¹

In addition to cognitive impairment, dementia is also associated with non-adherence.^{59, 23, 70} For example, in a cross sectional study that included older persons living in their homes, it was found that non-adherence was significantly associated with the probability of having dementia [OR= 9.0, 95% CI (1.1, 72.5)].²³ Similar associations were noted in another study where adherence to anti-hypertensive medication was inversely associated with those having psychiatric disorders accompanied by functional impairment such as AD [adjusted OR= 0.865, 95% CI (0.791, 0.945)] and vascular dementia [adjusted OR= 0.785 95% CI (0.672, 0.917)].⁵⁹

Some studies (n=7) identified medication management as a challenge for cognitively impaired individuals. Park *et al.*, noted that managing medications require

components of complex cognition skill sets such as comprehension, working memory, long-term memory, prospective memory and reasoning, thus suggesting that adhering to complex medication regimens might be a challenge for cognitively impaired patients.⁴⁷ This set of complex cognitive skills is required for medication management and have been associated with medication adherence, for example poor treatment adherence in older adults with heart failure was associated with reduced performance on attention executive function, and language.²⁵ Furthermore, the ability to take medications correctly was positively correlated with a high MMSE score.⁷² In contrast, another study showed this correlation to be non-significant. The participants with incorrect Clock Drawing Test (CDT) on MMSE had one or more medication discrepancies as compared to those with accurate CDT (68% vs. 48%, $c^2 = 2.64$, $df = 1$, $p = 0.044$).⁷³ Other practical problems that hamper medication management and drug taking in CI population were difficulties with vision (32.0%), blister opening (12.1%), tablet swallowing (14.8%), tablet splitting (29.7%) and distinction between different drug packages (23.4%).²¹ A Canadian qualitative study found that medication management varied at different stages of dementia. For example, independent management, denial of disease and unwillingness to take medications owing to anger, characterized medication management in patients during the early stages of dementia. Those at a later stage refused to take medications due to delusional thinking or suspicions about the medications.⁷⁴

Health care system related barriers

Health care system barriers associated with medication non-adherence include having poor communication between patient and health care provider,²³ obtaining

prescriptions from more than one physician/prescriber²³ and having one previous occurrence of medication non-adherence.⁶⁶ Poor communication between a patient and a health care provider often leads to non-adherence. For example, Barat *et al.* found a disagreement between drug information regarding doses (in 71% of the population), regimens (in 66% of the population) and drugs (in 22% of the population) collected from non-adherent participants and physicians.²³ Furthermore, the odds of being non-adherent to medications was 2.5 times greater in those patients who had prescriptions from more than one physician [OR= 2.5, 95% CI (1.1, 3.5)].²³ In a prospective study by Thiruchselvam *et al.*, the odds of non-adherence was 2.5 times higher in those patients who have had at least one previous occurrence of medication non-adherence in the past [OR = 2.61; 95% CI (1.18-5.62)].⁶⁶

Socio-economic related barriers

Socio-economic barriers that were found to be associated with medication non-adherence include high medication costs,⁷⁵ poor social support^{46,48,70,71,76} and caregiver stress.⁷⁶ A retrospective study was performed on 6990 AD patients to evaluate the impact of patient's AD medication cost-share on adherence to chronic medications including adrenergic blockers, antiplatelets, antidiabetics and diuretics. AD medication cost-share was defined as the patient's out-of-pocket (OOP) prescription costs. This OOP costs depended on the characteristic of their health plan and formulary status of the AD medications. The study reported that AD patients with high out-of-pocket cost [$>$ Canadian Dollar (CAD) 24.69] had significantly worse adherence to diuretics and beta-adrenergic blockers ($p < 0.05$) than those with low OOP costs [$<$ CAD6.38].⁷⁵

Lack of social support in patients with ADRD was also correlated to medication non-adherence. For example, a study that included patients from 11 countries demonstrated that being unmarried was inversely associated with medication adherence [OR= 2.323, 95% CI (1.089, 4.956)].⁴⁶ There was also an increased risk of non-adherence in patients who lived alone versus those who did not [OR= 2.9, 95% CI (1.2, 7.5)].⁷¹ Foebel *et al.* found that having a caregiver at the same residence reduced the likelihood of medication non-adherence in patients with mild cognitive impairment (MCI).⁷⁶ In many cases, however, the caregiver is the spouse of that patient who may or may not be cognitively intact, which may also negatively impact medication adherence. Indeed, this was observed in a study in which patients with dementia patients with cognitively impaired spouses experienced difficulty complying to medication regimens compared to those with cognitively intact spouses.⁴⁸

Therapy related barriers

A therapy related barrier associated with non-adherence include the increased pill burden:^{23,66} among a random sample of 348 patients aged 75 years, 4% of which had dementia, the use of three or more drugs was found to have a negative impact on medication adherence [OR (for non-adherence)=2.5; 95% CI (1.5,4.1)].²³ These results were consistent with another study of 339 cognitively impaired older patients who lived alone in which a positive association between non-adherence and taking four or more medications [OR=2.58, 95% CI (1.3-5.29)] was observed.⁶⁶

2.3.4. Interventions

Several studies (n=10) have reported interventions to improve medication adherence in cognitively impaired adults (Table 3). For the purpose of this review, these interventions are categorized into alternative dosage forms, multi-compartment pillboxes, and medication reminder aids.

Alternate dosage forms

Alternative dosage forms that have shown improvement in medication adherence include transdermal patches^{55,77-79} and once-daily, higher-dose oral drug products.⁷⁹⁻⁸¹ Rivastigmine transdermal patches were proved clinically effective in improving the condition of patients with probable AD.⁴⁴ An open label evaluation of patients treated with rivastigmine patches showed a modest improvement of MMSE scores after 24-weeks, during screening (19.6 points) and at week 24 (20.9 point).⁷⁷ Rivastigmine patches have shown stabilization in adherence scores. For instance, more patients treated with transdermal patches were adherent versus those treated with capsules (65.0 vs. 41.4%, $p=0.001$).⁵⁵ In addition, caregivers of patients with AD were more satisfied with rivastigmine transdermal patches versus capsules (72% vs 65% ($p=0.001$)).⁵⁵ Blesa *et al.* also found that 72% of caregivers of AD patients preferred rivastigmine patches to the capsule. The reported reasons for preference of patches over capsules were ease of use, ease of following the dosing schedule and less interference with daily life.⁷⁸ Once daily and higher-dose memantine extended release formulation (ER) (28mg) and *Gingko biloba* products may also improve treatment adherence by simplifying the drug regimen for both caregivers and patients with AD.^{80,81} For example, Czeche *et al.* found that

patients receiving *Gingko biloba* 240mg once daily were at lower risk for non-persistence than those receiving 120mg twice daily [Hazard Ratio (HR) = 0.63; 95% CI (0.57, 0.70)].

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Multi-compartment pillboxes and packaging

The use of multi-compartment packaging has been shown to have positive effects on medication adherence. A study conducted by Kakkad *et al.* found that Calendar Blister Packaging (CBP) was associated with 10% higher MPR rates for antihypertensive medications compared to vial use in dementia patients.⁸² Furthermore, a study assessed the ease of use of various Multi-compartment Medication Devices (MMD) (e.g., Venalink™, Nomad Clear™ and Dosette MMDs) in cognitively impaired and cognitively intact individuals. Findings demonstrated that cognitively impaired participants had more difficulty in opening Venalink™ and removing medications from Nomad™ as compared to cognitively intact participants.⁸³ In comparison to Nomad™ and Venalink™, Dosette MMD received the best overall rating by 54% of the participants.

Medication reminder aids

Individualizing memory cues has shown to improve adherence in cognitively impaired patients. For example, Insel *et al.* demonstrated that an intervention using individually tailored memory cues, such as placing medicines in an area routinely used (e.g., dining table, bathroom) by an individual could increase medication adherence.⁶⁵ Specifically medication adherence of 27 older adults (including cognitively impaired

older adults) was electronically monitored for 8 weeks pre-intervention and 8 weeks post-intervention. The number of correct doses taken increased from 64.5% to 78% by the end of the study period.⁶⁵ Medication reminder devices have also been associated with an increase in medication adherence in patients with MCI.⁸⁴ For example, a pilot study was conducted to evaluate the use of an automatic pill dispenser involving 18 cognitively impaired participants. One month after the onset of automatic pill dispenser use, 55.5% (n=10) users showed 100% improvement in adherence scores and 49.9% (n=9) maintained the score until the end of the study (after three months).⁸⁴ Although the study revealed that such devices could improve adherence in CI patients, further research is needed in order to validate the results from the pilot study.

2.4. Discussion

Over the past five years, an increased number of studies have assessed medication adherence among older adults living with cognitive impairment. A large number of these studies emanate from the United States and Europe. As the chances of cognitive impairment increase with age, and because these geographical areas habituate a large aging population, it may explain why many research studies are conducted in the west, including the United States and Europe. Prevalence estimates of non-adherence range from as low as 2% to as high as 69.9% in this population, and as there is no gold standard to assess medication adherence, these findings are not surprising. Each adherence assessment method has advantages and disadvantages. The most commonly used assessment method of self-report is easy to administer in a clinical setting, but is subject to a number of biases, such as social desirability and recall bias. Conversely, electronic monitoring using MEMS supplies a wealth of adherence data but is difficult to administer

in a clinical setting due to its cost. Alternative techniques such as the use of pill count and refill history data are becoming popular methods of choice in primary care clinic settings due to their ease of use and comparably lesser number of biases. These approaches are especially important in settings such as memory clinics, where assessment of medication adherence is part of practice. However, both of these methods do not guarantee the consumption of medications by patients, thereby making it difficult to assess whether patients are actually taking their medications as prescribed. Furthermore, in a study comparing various adherence assessment methods, it was found that there was a poor correlation between these methods.²³

Other objectives of this review were to describe the barriers related to non-adherence and the interventions available to improve adherence in patients with cognitive impairment. In this review, the barriers were categorized into patient related, condition related, health care system related, therapy related and socio-economic related. Some of the barriers that are unique to this population include difficulty in managing medications, reduced cognitive skills and cognitive impairment, presence of dementing illnesses, increased caregiver stress, and presence of a cognitively impaired spouse.^{23,25,46,47,48,59,70-72,76} Some studies described strategies to deal with these barriers and to improve adherence. Interventions have included the use of alternate dosage forms such as a transdermal patch and once-daily higher dose oral products, multi-compartment devices such as CBP, and medication reminder aids.^{50,65,77-84} Transdermal patches and once-daily higher dose drug products have shown to improve adherence by simplifying the medication regimen for patients and their caregivers. Multi-compartment devices have

also shown to be positively associated in improving adherence, but cognitively impaired older adults face difficulty in using such devices.

To our knowledge, this scoping review is the first that encompasses all aspects of medication adherence. We assessed medication adherence in a broader context, addressed medication adherence assessment methods in more detail, at all aspects of adherence and presented an updated literature review on this topic. While other reviews are available on this topic^{16,17} only one systematic, evidence-based review was conducted specific in older adults with dementia.¹⁸ The barriers reported by Campbell et al included difficulty in managing medication and in understanding directions, taking four or more medications, prior history of non-adherence, a caregiver with dementia, and increased overall pill burden.¹⁶ They also reported interventions that attempted to improve adherence in dementia patients. These interventions include the use of reminder cues and organization boxes, and tele-video medication reminders.¹⁸ This review highlighted that barriers to adherence other than impaired cognition should be addressed with equal importance.¹⁸

Although there is an increase in the number of studies pertaining to this population, there are several gaps in the literature that need to be addressed. One of the major difficulties in comparing studies is the large variation in adherence estimates. As there is no gold standard method to assess medication adherence across all populations, which makes it difficult to compare data across studies. A standard method to assess medication adherence that is reproducible and reliable across all populations is needed to better understand and compare data obtained from future studies. Second, assessing medication adherence for these patients is part of practice at many primary care settings. Due to the

number of assessment tools available, it is unknown which method is most feasible that can be applied to a memory clinic setting. A single feasible tool is necessary to allow health care providers to identify adherence patterns in this population, thereby helping them to work collaboratively to develop patient-specific solutions to tackle suboptimal medication adherence. Third, it has been identified that adherence can be affected by cognitively impaired spouses or caregivers.⁴⁸ Spouses of patients are generally in the same age group where there is an increased prevalence of cognitive impairment, and they are therefore also at risk for non-adherence. Unfortunately, there is a dearth of information on how to address adherence issues in cases where both patient and care giver have cognitive impairment.

Lastly, some interventions to improve adherence in cognitively impaired patients have been described. For example, use of rivastigmine transdermal patches and once-daily oral memantine formulations have shown promising results, and have shown to significantly improve adherence to AD medications as compared to capsules.^{77,78} Both these interventions have shown to simplify the therapeutic regimen and improve medication adherence. Transdermal patches are not available for all prescription medications; therefore, making this strategy of limited utility given that older adults consume an average of seven chronic medications. An alternative to the use of transdermal patches could be the use of extended released oral products or use of once daily dosing wherever possible, as Czeche *et al* have shown significant improvement in adherence to once-daily extended release Memantine and *Gingko biloba* products.⁸⁰ Future studies should aim at studying other extended release chronic medications and its effect on adherence in cognitively impaired patients. Other interventions such as the use

of automated pill dispensers and multi-compartment pill-boxes are available and have been studied in the current population, yet, it is unlikely that the issue of medication adherence among patients with cognitive impairment will be satisfactorily addressed by such devices because patients are dependent on their caregivers to set up and operate these devices.

2.5. Limitations of the review

This review has several limitations that should be noted. There is a possibility that some studies with negative results were not published leading to publication bias. To minimize the chance of missing key articles, all online databases were searched for eligible studies and no restriction on the dates was applied during the search. Although the search strategy was not restricted to the English language, some studies had to be excluded, as English translation for these articles was not available. The quantity of data generated was considerable, however, no synthesis of data was performed for this review. It is by design that the framework of scoping studies does not address this issue.^{49,51} Scoping studies are meant to provide a narrative and descriptive account of available literature on a topic over a greater range of study designs in comparison to systematic reviews, which focus on a narrowly defined question.⁴⁹

2.6. Conclusion

The literature on this topic has grown rapidly in the past five years. This scoping review has identified the prevalence of non-adherence in cognitively impaired older adults, adherence assessment techniques, and barriers and interventions available to tackle non-adherence amongst older adults with cognitive impairment. Although there is a growing body of literature, many questions remain unanswered. First of all, there is a

lack of gold standard in assessing adherence. This shortcoming is a challenge because comparison among studies using different assessment tools limits the ability to make cross study comparisons and to draw generalizable conclusions. Secondly, a number of barriers specific to cognitively impaired older adults were identified through this review. Impaired cognition was identified as a key predictor of non-adherence. This predictor is especially important because impaired cognition hampers the ability to manage medications thereby leading to an increased risk of non-adherence. Other barriers such as the presence of a cognitively impaired caregiver, which in most cases is the spouse of the patient, is also a risk factor that facilitates medication non-adherence. Although the spouse of the caregiver is at equal risk of non-adherence, not much work has been done on this topic. Lastly, many interventions tackling medication non-adherence have been studied, however there is a lack of randomized control trials to support the effectiveness of these in cognitively impaired older adults. It is crucial to focus future research on these identified gaps to better describe medication non-adherence problems in this population.

Figure 2: Study flow used in the scoping review

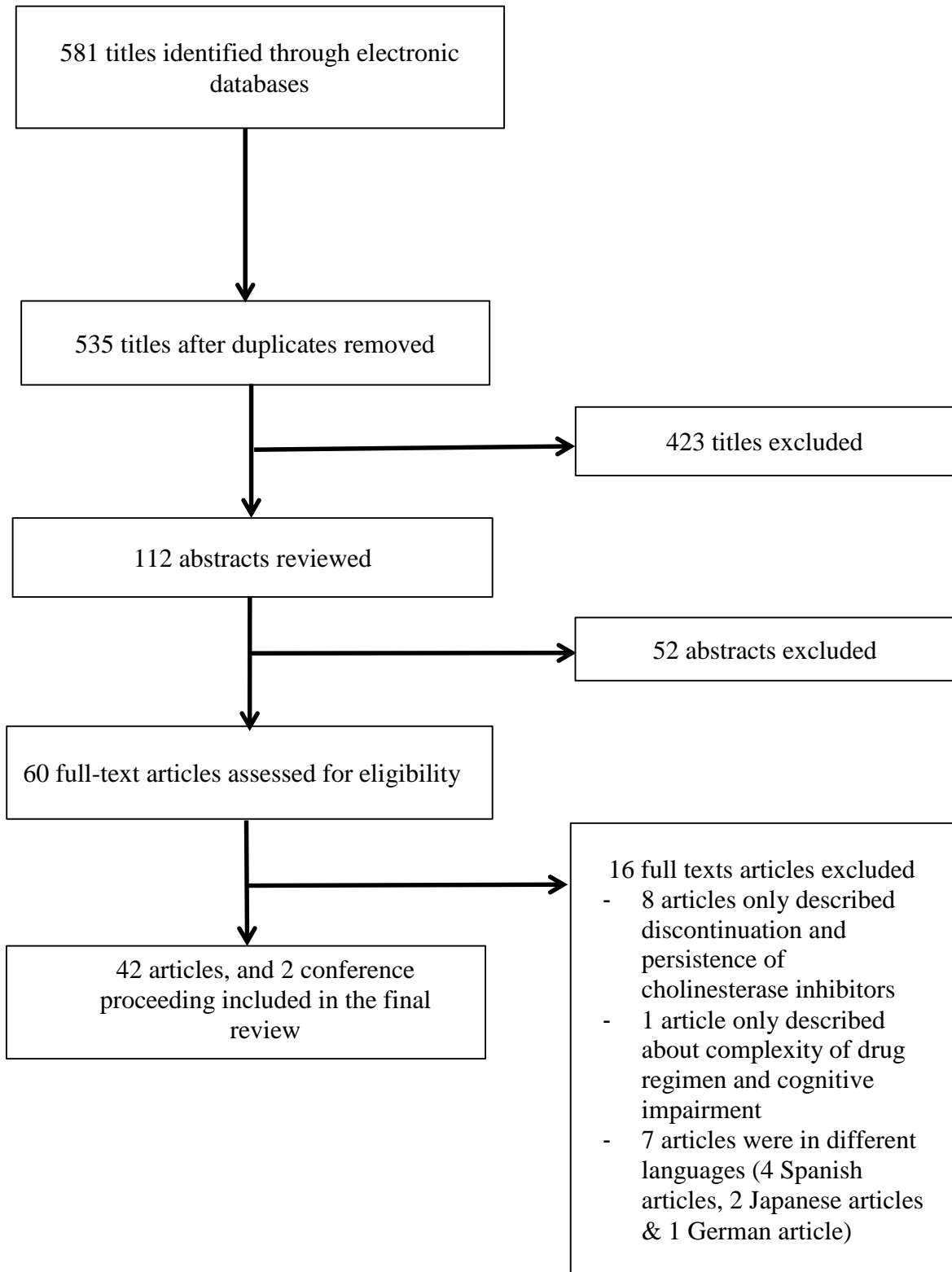


Table 1: Adherence assessment tools used in the literature

Studies	Self-report/care-giver report	Electronic monitoring	Pharmacy refill history	Pill count	Blood/urine medication monitoring	Clinical outcome	Health provider's report
Park et al ⁴⁷		Yes					
Boucher et al ⁴⁸			Yes	Yes			
Barat et al ²³	Yes						Yes
Salas et al ⁷¹			Yes				
Raehl et al ⁷²	Yes						
Cooper et al ⁴⁶	Yes						
Insel et al ⁶⁵		Yes					
Cotrell et al ⁶⁴	Yes			Yes			
Ganguli et al ⁶³	Yes						Yes
Hutchison et al ⁶²	Yes						
Hayes et al ⁵²		Yes					
Poon et al ⁶¹			Yes				
Borah et al ⁶⁰			Yes				
Kim et al ⁵⁹			Yes				
Schwalbe et al ¹³		Yes				Yes	
Jerant et al ⁵⁸				Yes			
Shah et al ⁷⁵			Yes				
Foebel et al ⁷⁶						Yes	
Le Couteur et al ⁵⁷			Yes				
Mehuys et al ²¹	Yes			Yes			Yes
Thiruchselvam et al ⁶⁶	Yes						Yes

Kakkad et al ⁸²				Yes		
Hain et al ⁴⁰	Yes					
Boada et al ⁵⁵	Yes					
Haider et al ⁵⁴				Yes		
Kim. ⁵³	Yes	Yes			Yes	Yes
Sattler et al. ⁶⁹				Yes		
Campbell et al ¹⁸	Yes			Yes		

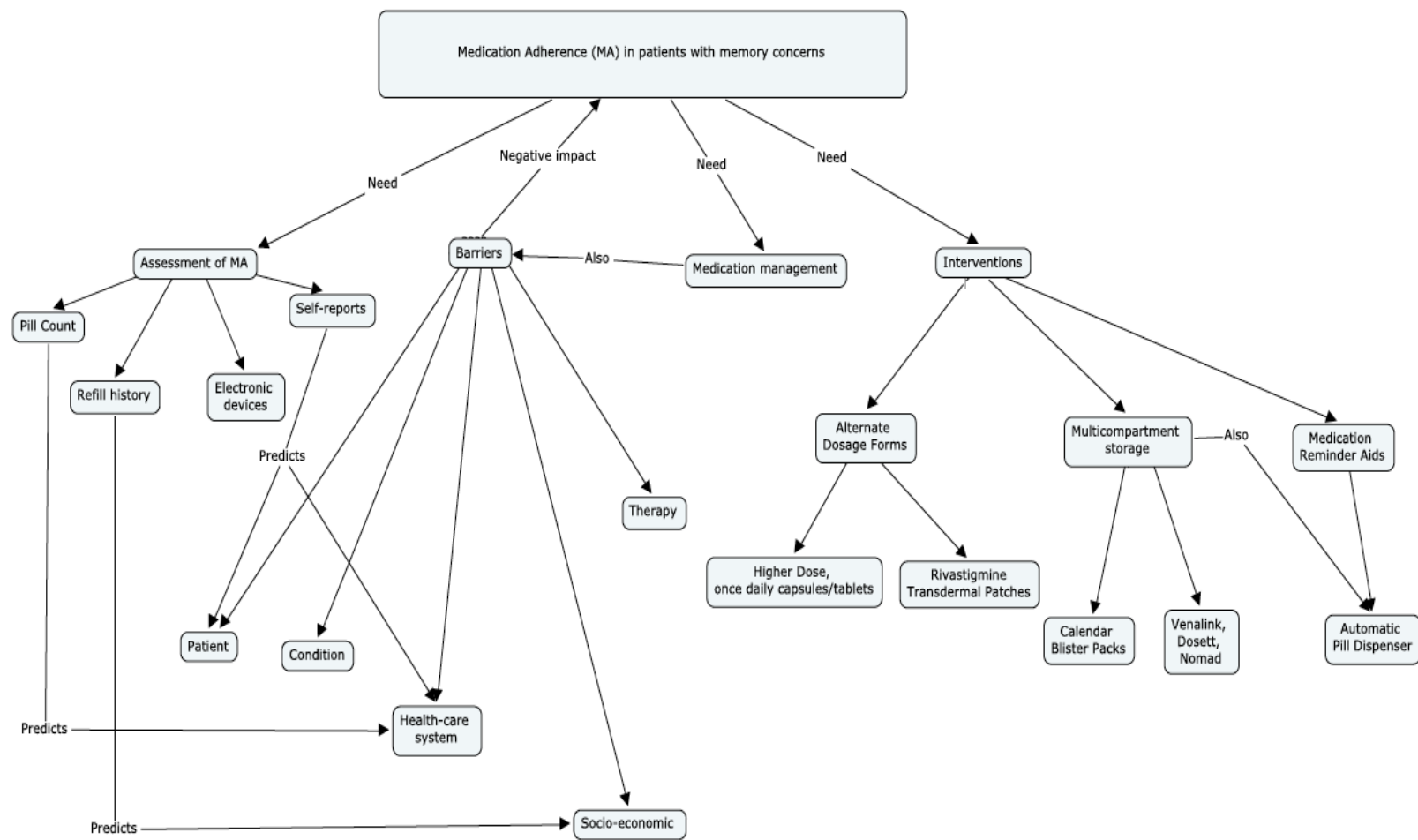


Figure 3: Literature review map

Table 2: Barriers to adherence

Authors	Year	Title	Country	Key findings
Boucher L, Renvall MJ, Jackson JE. ⁴⁸	1996	Cognitively impaired spouses as primary caregivers for demented elderly people.	USA	Dementia patients with cognitively impaired spouses experienced difficulty with medication compliance (p=0.041) compared to cognitively intact spouses
Barat I, Andreassen F, Damsgaard EM. ²³	2001	What doctors believe and patients actually do	Denmark	Positive association was found between non-adherence and the use of three or more drugs [OR 2.5; 95% CI (1.5,4.1)], prescriptions from more than one physician [OR 2.5; 95% CI (1.3,4.8)], and probability of dementia [OR 9.0; 95% CI (1.1,72.5)]
Salas M, In't Veld BA, van der Linden PD, Hofman A, Breteler M, Stricker BH. ⁷¹	2001	Impaired cognitive function and compliance with antihypertensive drugs in elderly: The Rotterdam study.	Netherlands	Increased risk of non-compliance in cognitively impaired older adults [Adjusted RR 2.0; 95% CI (1.4, 2.8)] Increased risk in those who lived alone [OR 2.9; 95% CI (1.2, 7.5)]
Cooper C, Carpenter I, Katona C, et al. ⁴⁶	2005	The AdHOC study of older adults' adherence to medication in 11 countries.	UK	Problem drinking (OR= 3.6), not having a physician review their medication (OR = 3.3), Cognitive impairment (OR=1.4) for every one-point increase in impairment), good physical health (OR = 1.2), being unmarried (OR 2.3)
Ganguli M, Du Y, Rodriguez EG et al. ⁶³	2006	Discrepancies in information provided to primary care physicians by patients with and without dementia: The Steel Valley Seniors survey.	USA	A discrepancy in adherence assessment was found between home visit and chart review in 40.9% of patients with chart dementia diagnosis.
Grocki JH, Huffman KK. ⁷⁰	2007	Medication adherence among older adults.	USA	Medication non-adherence was attributed to: Intentional caregiver neglect (37%)> dementia (24%) > mental illness and family and social support (15%)> theft (6%) > drug abuse (3%) For the oldest men age, 81, dementia was the predominant barrier.
Hayes TL, Larimer N, Adami A, Kaye JA. ⁵²	2009	Medication adherence in healthy elders: Small cognitive changes make a big difference.	USA	Low Cognitive Functioning group were at higher risk of non-adherence as compared to High Cognitive Functioning group [RR = 4.1 CI 95%(3.47, 4.78)].

Poon I, Lal LS, Ford ME, Braun UK. ⁶¹	2009	Racial/ethnic disparities in medication use among veterans with hypertension and dementia: A national cohort study.	USA	<p>Medication adherence was significantly lower in African Americans than whites in all classes except for Angiotensin Receptor Blockers, loop diuretics, and PSDs ($p < 0.05$).</p> <p>Being Hispanic was associated with significantly lower adherence rates than whites for Dihydropyridine CCBs [OR=0.69 CI(0.53, 0.89)] and acetyl cholinesterase inhibitors [OR= 0.77 CI(0.61, 0.96)]</p>
Borah B, Sacco P, Zarotsky V. ⁶⁰	2010	Predictors of adherence among Alzheimer's disease patients receiving oral therapy.	USA	<p>Compared to patients <75 years, patients >86 years were likely to be more adherent (OR= 1.401, $p < 0.001$).</p> <p>Other factors found to be positively associated with the probability of adherence to AD medications were male gender (OR=1.175, $p < 0.05$), overall pill burden (OR= 1.192, $p < 0.001$), and a lower formulary tier status of the AD medication (OR=1.332, $p < 0.001$)</p>
Kim HK, Park JH, Park JH, Kim JH. ⁵⁹	2010	Difference in adherence to antihypertensive medication regimens according to psychiatric diagnosis: Results of a Korean population-based study.	South Korea	<p>Lower MPR was associated with patients with Alzheimer Disease [Adjusted OR= 0.865; 95% CI (0.791, 0.945)] and vascular dementia [Adjusted OR= 0.785; 95% CI(0.672, 0.917)]</p>
Schwalbe O, Scheerans C, Freiberg I, Schmidt-Pokrzywniak A, Stang A, Kloft C. ¹³	2010	Compliance assessment of ambulatory Alzheimer patients to aid therapeutic decisions by healthcare professionals.	Germany	<p>For 10 mg and 5 mg donepezil once-daily dosing, the estimated forgiveness of donepezil was 80% and 90% daily compliance or two and one-dosage omissions at steady state, respectively.</p>
Hawkins LA, Kilian S, Kashner TM, et al. ⁸⁵	2011	Is cognitive impairment associated with medication adherence in outpatients with heart failure?	USA	<p>In patients where pill count could be completed, medication adherence was associated with cognitive impairment ($r=50.24$, p-value 0.004).</p> <p>In outpatient veterans with Heart Failure, previously undiagnosed CI is prevalent and associated with medication adherence</p>

Jerant A, Chapman B, Duberstein P, Robbins J, Franks P. ⁵⁸	2011	Personality and medication non-adherence among older adults enrolled in a six-year trial.	USA	<p>Each five year increment in participant age was associated with a 6.7% greater probability of non-adherence (95% CI [2.4, 11.0]).</p> <p>Lower cognitive function was also associated with non-adherence: a 1 SD decrease in mental status exam score was associated with a 3.0% increase in the probability of non-adherence (95% CI [0.2, 5.9]).</p>
Shah SN, Knoth RL, Margolis J, Alvir J, Lenhart G. ⁷⁵	2011	The effect of Alzheimer's disease medication cost-share burden on chronic disease medication adherence and clinical outcomes.	USA	<p>High AD Out Of Pocket costs (>\$26) had significantly worse adherence and persistence on their diuretics and adrenergic blockers (p<0.05) than those with low OOP costs (<\$6).</p> <p>Increased hospital admissions, inpatient days and ER visits were associated with low AD medication adherence rates (p<0.001).</p>
Alosco ML, Spitznagel MB, van Dulmen M, et al. ²⁵	2012	Cognitive function and treatment adherence in older adults with heart failure.	USA	<p>Reduced performance on attention ($\beta = .26, p = .01$), executive function ($\beta = .18, p = .04$), and language ($\beta = .22, p = .01$) were associated with poorer overall adherence.</p>
Foebel AD, Hirdes JP, Heckman GA. ⁷⁶	2012	Caregiver status affects medication adherence among older home care clients with heart failure	Canada	<p>Among individuals with MCI, having a caregiver at the same residence reduced medication non-adherence. Additionally, caregiver stress was significantly associated with higher rates of non-adherence.</p>
Le Couteur DG, Robinson M, Leverton A et al. ⁵⁷	2012	Adherence, persistence and continuation with cholinesterase inhibitors in Alzheimer's disease.	Australia	<p>Adherence to cholinesterase inhibitors was reasonable after the commencement of the treatment.</p>
Mehuys E, Dupond L, Petrovic M, et al. ²¹	2012	Medication management among home-dwelling older patients with chronic diseases: Possible roles for community pharmacists	Belgium	<p>The overall mean adherence per patient was very high (98.1%). Seventy-six percent (76%) of patients had an acceptable knowledge of the indication for at least seventy-five percent (75%) of their medication.</p> <p>The participants reported several practical problems with drug taking: difficulties with vision (32.0%), blister opening (12.1%), tablet swallowing (14.8%), tablet splitting (29.7%)[represents % of patients who have to split tablets] and distinction between different drug packages (23.4%).</p>

Thiruchselvam T, Naglie G, Moineddin R et al. ⁶⁶	2012	Risk factors for medication nonadherence in older adults with cognitive impairment who live alone.	Canada	Risk of medication non-adherence in patients taking four or more medication [OR 2.58; 95% CI(1.3-5.29)] Risk of medication non-adherence in patients with previous occurrence of non-adherence in past year [OR=2.58; 95% CI (1.18-5.62)]
Haider B, Schmidt R, Schweiger C, Forstner T, Labek A, Lampl C. ⁵⁴	2013	Medication adherence in patients with dementia: An Austrian Cohort study.	Austria	Compliance rate for ChEIs: 28.3%-35.3% At 12 months, highest discontinuation rate was seen in patients taking rivastigmine (67.3%), and memantine had lowest discontinuation rate (45%)
Kim SH. ⁵³	2013	Variables influencing treatment adherence in patients with alzheimer's disease.	South Korea	Poor inter-rater agreement: Kappa coefficients were 0.382 (pill count vs. MEMS), 0.382 (clinician rating scale vs. MEMS) and 0.256 (self-report vs. MEMS). Gender difference was correlated with adherence.

Table 3: Interventions described in literature

Authors	Year	Title	Country	Key findings
Insel KC, Cole L. ⁶⁵	2005	Individualizing memory strategies to improve medication adherence.	USA	Adherence increased from a mean of 64.5% to that of 78% (Z-score = 2.42)
Blesa R, Ballard C, Orgogozo JM, Lane R, Thomas SK. ⁷⁸	2007	Caregiver preference for rivastigmine patches versus capsules for the treatment of Alzheimer disease.	Spain	<p>72% of caregivers preferred the patch to capsules overall.</p> <p>The patch was preferred to capsules because: ease of use (p<0.0001) and ease of following the schedule (p < 0.0001).</p> <p>Caregivers indicated greater satisfaction overall (p <0.0001) and less interference with daily life (p < 0.01) with the patch vs. capsules.</p>
Articus K, Baier M, Tracik F, Kuhn F, Preuss UW, Jurz A. ⁷⁷	2011	A 24-week, multicenter, open evaluation of the clinical effectiveness of the rivastigmine patch in patients with probable Alzheimer's disease	Germany	<p>At week 24, patients treated with the Rivastigmine patch showed improvements on MMSE [During screening (19.6 points) and at week 24 (20.9 point)], Alzheimer's Disease Cooperative Study–Activities of Daily Living (ADCS-ADL) [baseline (50.3 points) and at week 24 (51.4 points)], Alzheimer's Disease Cooperative Study–Clinical Global Impression of Change (ADCS-CGIC) and (Trail Making Test Part A) TMT-A scores.</p> <p>Tolerability: Mean Alzheimer's Disease Caregiver Preference Questionnaire (ADCPQ) scores improved from baseline (12.2 points) at week and at week 24 (30.7 points).</p> <p>Caregivers reported acceptance, preference and satisfaction with the patch.</p>
Kamimura T, Ishiwata R, Inoue T. ⁸⁴	2012	Medication reminder device for the elderly patients with mild cognitive impairment	Japan	Changes in Self Administration Medication Rate (SAMR) 1 month after onset of device use: 10 users (55.5%) showed 100% improvement in SAMR values. The SAMR values for 5 users (27.8%) showed an improvement of <100% (Range: 28.6% - 85.7%).

				Changes in SAMR at 3 months: Nine users (49.9%) maintained SAMR values of 100%, and 1 user (5.6%) showed 100% improvement in SAMR values.
Kakad PP, Harpe SE, Slattum PW. ⁸²	2012	Impact of calendar blister packaging (CBP) on adherence with antihypertensive medications in older adults treated for dementia.	USA	Calendar Blister Packaging use was associated with 10% higher MPR rate as compared to vial use.
Adams R, May H, Swift L, Bhattacharya D. ⁸³	2013	Do older patients find multi-compartment medication devices easy to use and which are the easiest?	UK	Cognitively impaired participants reported more difficulty in opening the Venalink [9(3.5, 10) in CI vs. 7 (2, 8.25) in non impaired] and removing medication from the Nomad [6.5 (3, 9.75) vs. 4.5 (1.75, 8) in non impaired.] Prior of MMDs use made it easier to use: Venalink [-2.03, (-3.94-0.13)], Nomad [-1.56, (-3.11, -0.1)] Best overall rating: Dosett (54%) > Venalink (14%) > Nomad (10%)
Boada M, Arranz FJ. ⁵⁵	2013	Transdermal is better than oral: Observational research of the satisfaction of caregivers of patients with Alzheimer's disease treated with rivastigmine.	Spain	Greater satisfaction with transdermal vs. oral rivastigmine (72.5± 14.1 vs. 65.2± 12.5, p=0.001) Higher adherence with transdermal patch vs. oral (65.0 vs. 41.4%, p=0.001)
Czeche S, Schuessel K, Franzmann A, Burkart M, Schulz M. ⁸⁰	2013	Dosage strength is associated with medication persistence for ginkgo biloba drug products.	Germany	Risk for non-persistence was reduced in patients receiving 240 mg products compared to 120 mg (HR = 0.63; 95% CI 0.57 – 0.70)

CHAPTER 3: FEASIBILITY OF DETERMINING MEDICATION ADHERENCE USING PILL COUNT VERSUS PHARMACY REFILL DATA IN A PRIMARY CARE-BASED MEMORY CLINIC

3.1. Introduction

3.1.1. A brief background on the Center for Family Medicine's Family Health Team's (CFFM FHT) Memory Clinic

The CFFM FHT's memory clinic is a novel primary health care model, which was developed in Kitchener, Ontario to assist the patient's family physician in coping with the complex challenges associated with dementia care and to reduce reliance on specialist referrals to tertiary care centers, which are often inaccessible due to long wait times (6 to 12 months).⁶⁸ The memory clinic team at the Kitchener CFFM FHT is comprised of a physician, nurses, social worker, occupational therapist and pharmacists. Professionals from each discipline work in collaboration to manage the existing comorbidities in patients with dementia, to reduce polypharmacy, and to address the related risks of non-adherence and behavioral and psychological symptoms of dementia.⁶⁸ In particular, the role of the pharmacists is to design and implement appropriate pharmacotherapeutic regimen to manage existing chronic conditions along with a strong emphasis on assessing medication-taking behaviour and promoting medication adherence.⁶⁸ A summary of the model is shown in Figure 3.

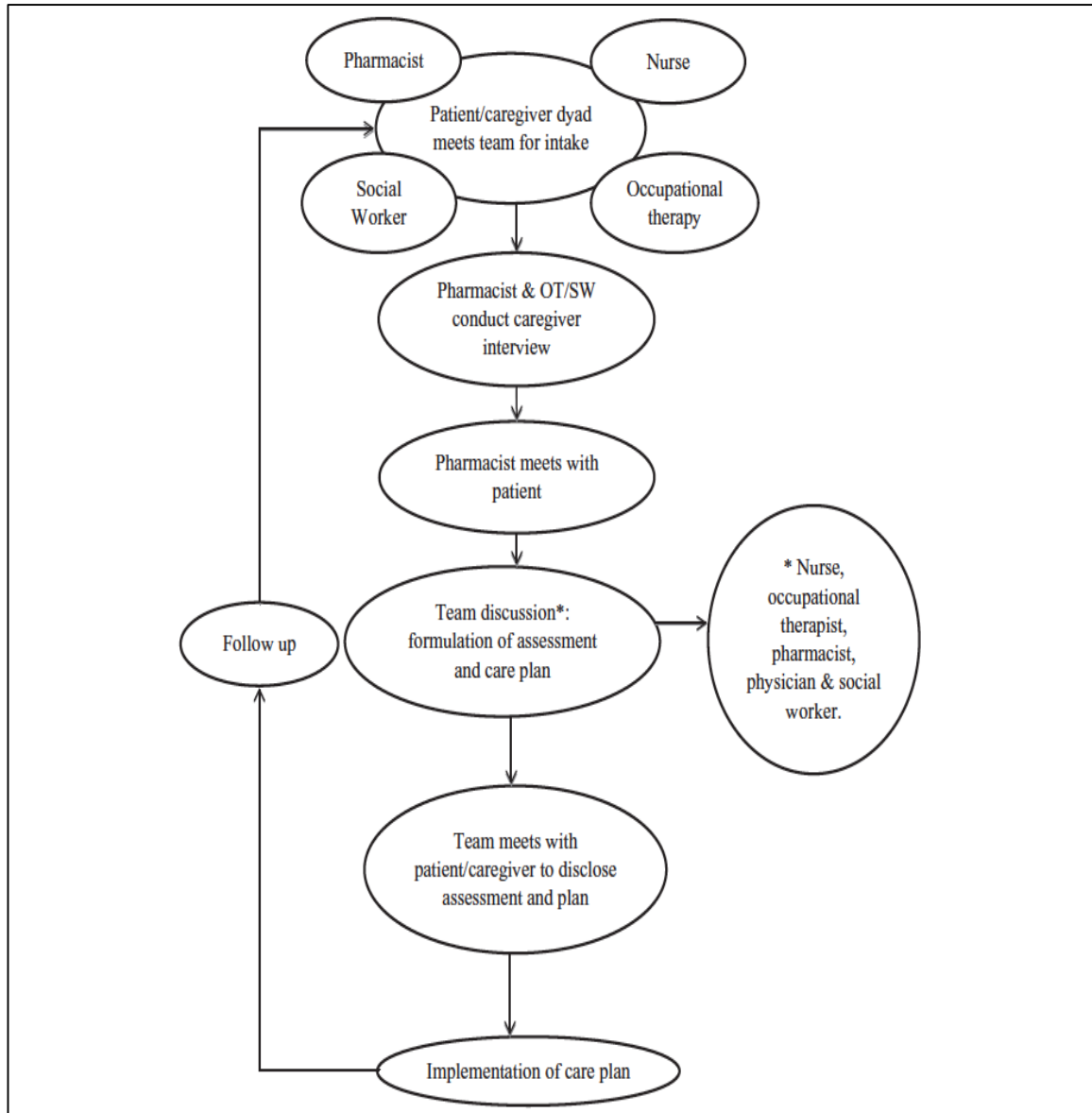
Memory Clinic Operational Model

The clinic operates three to four days a month on average, with six patients scheduled on each clinic day. The patients seen at the clinic are referred by their family physician who has identified memory or cognitive changes, or if there is a family concern regarding changes in memory and cognitive ability or a difficulty in managing a patient with dementia. The referrals are sent electronically using an electronic medical record (EMR) to the memory clinic-scheduling nurse, who in turn, reminds the patient and their caregiver a day or two before their appointment through a phone call. The patient and caregivers are also reminded to bring all prescription medications, vitamins, and over-the-counter medications in their current containers during their visit to the clinic.⁶⁸

On a typical clinic day, the memory clinic team meets the patient and their caregiver at the beginning of the appointment during which time the clinic team is introduced and a history of presenting complaints is gathered. The initial assessments last for 5 to 10 minutes, after which the patient and the caregiver dyad are split into two rooms where the social worker or the occupational therapist and the pharmacist interview the caregiver in one room and the nurse conducts cognitive testing on the patient in the other. During the pharmacist's interview with the caregiver, the pharmacist obtains information regarding the patient's overall function and emotional state and a comprehensive medication history, and assesses medication adherence by pill count, visual examination of blister packs and/or calling the patient's pharmacy to gather past refill history. As the patient is being assessed for cognitive impairment and the degree of impairment is unknown prior to the appointment, he/she may not be able to recall or present insights regarding medication-related concerns, therefore, the interview is carried

out separately with the caregiver. The patient is, however, involved in the decision making process. Once all the relevant data are obtained, the team discusses the case with the physician and input from all the team members is used to obtain a holistic picture of the patient's clinical, functional and social status. The physician then establishes a working diagnosis (e.g., MCI, Alzheimer's disease, mixed dementia, etc.), and a complete treatment plan is developed and optimized with inputs from the pharmacist. In the end, the results are disclosed to the patient and the caregiver, and follow-up visits are scheduled at the memory clinic based on the diagnosis, and type and severity of the problems.⁶⁸

Figure 4: Memory clinic operational model



Used with permission (Appendix 2) 68 Rojas-Fernandez C, Patel T, Lee L. An innovative collaborative practice for clinical pharmacists in an interdisciplinary, primary care based memory clinic in Ontario, Canada. *Ann. Pharmacother.* 2012; 32(10):e262.

3.1.2. Pharmacist's role in a Memory clinic

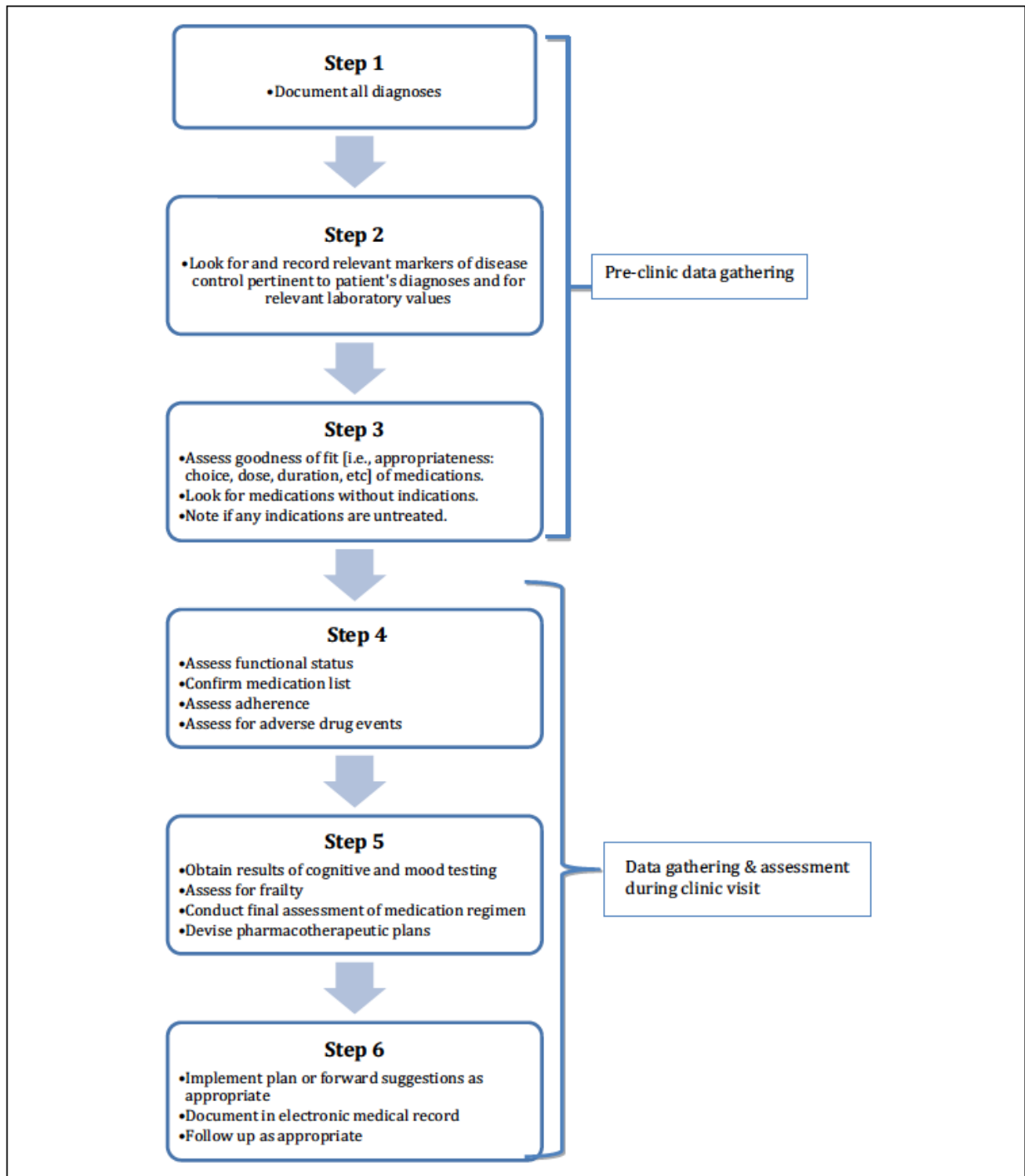
The role of pharmacists has expanded in the recent decades and an increasing number of pharmacists are practicing with well-documented roles in interdisciplinary or multidisciplinary teams, such as heart failure programs, and hypertension clinics.^{86,87} In addition, it has been demonstrated that having a pharmacist on a primary care team can lead to improvement in health outcomes. For instance, a study showed that having a pharmacist on a primary care based hypertension clinic improved blood pressure control in type 2 diabetes patients [OR = 2.6, 95% CI (1.3, 5)].⁸⁶ Recently, Rojas-Fernandez et al described the role of pharmacists practicing in a novel interdisciplinary family health team-based memory clinic.⁶⁸

From a pharmacotherapeutic perspective, a pharmacist practicing in a memory clinic is in a unique position to assess the numerous challenges presented in patients with dementia and/or memory concerns for several reasons.⁶⁸ The most crucial challenge is that dementia commonly exists with other co-morbidities. Managing these complex comorbid conditions require an increased number of pills, which may affect medication management in presence of reduced memory, and this mismanagement of drugs may lead to negative health outcomes. Adverse events as a result of poor management of medications have shown to increase the rate of hospitalization.¹⁰ Other challenges such as the natural progression of cognitive impairment, falls, delirium and polypharmacy also exist in this population. Appropriate medication prescribing is necessary in order to deal with these challenges along with a need to assess the patient's medication-taking behaviour. This requires the pharmacological expertise of a skilled pharmacist because

the clinical guidelines are devised for a single disease state and not for a complex set of diseases.

Furthermore, a pharmacist is also in a unique position to assist in recognizing problems related to medication management and adherence.^{88,89} At the memory clinic, the pharmacist follows a comprehensive, patient-focused method to assess the medication regimens in order to deal with the unique challenges of this complex patient population. To ensure that patient assessment is thorough, it is important to gain an insight about the patient's medication-taking behaviour. Generally, the pharmacist collects data in two broad steps, namely pre-clinic data gathering and data gathering during the clinic visit (Figure 4). In particular, adherence assessment occurs on the appointment day of the patient.

Figure 5: Pharmacist's assessment of patient's medication regimen



Used with permission (Appendix 2) 68 Rojas-Fernandez C, Patel T, Lee L. An innovative collaborative practice for clinical pharmacists in an interdisciplinary, primary care based memory clinic in Ontario, Canada. *Ann. Pharmacother.* 2012.;32(10):e262.

3.1.3. Medication adherence in cognitively impaired older adults

Research on medication non-adherence among older adults has attracted a significant amount of interest in the recent years.⁹⁰ Increased prevalence of chronic conditions coupled with greater pill burden has been cited as a reason for this.⁵ Furthermore, a factor unique to this population is the higher prevalence of cognitive impairment, which has shown to affect medication-taking behaviour of these patients.^{17,18} Although cognitive impairment is a key barrier to medication adherence in older adults, many details of patient behaviour pertaining to taking medications remain untouched, especially in clinical settings. With novel practice sites such as memory clinics now recognizing adherence as a key determinant of health outcomes, it is clear that there is a lack of studies describing various aspects of medication adherence observed in patients seen with cognitive impairment. A major limitation to observing these factors is a lack of gold standard. Furthermore, it becomes increasingly difficult to determine which adherence assessment technique is most suitable in this setting. The literature suggests triangulation of two or more adherence methods to obtain an accurate estimate of patient behaviour.^{27,41} For this reason, the pharmacists practicing in memory clinics use pill count and pharmacy refill data to ascertain patient adherence. However, the role of the pharmacist in the clinic also involves a number of other tasks to ensure a complete and thorough assessment of patients. For this reason, it is crucial to determine which method is most feasible in this clinic. Other aspects such as the interventions used by the caregiver of the patients seen at the memory clinic also remain unanswered.

3.1.4. Pharmacist's assessment of adherence in the memory clinic setting

A number of adherence assessment instruments have been described in the current literature and they have been broadly classified as direct and indirect methods. Direct methods confirm that the patient has consumed the medication, whereas indirect methods are proxy measures and do not demonstrate the consumption of the medication.²⁷

Although several strategies of measurement have been described and studied across various populations, clinicians are faced with a dilemma of choosing the most feasible method in a community setting, as there is no “gold standard” for measuring medication adherence.²⁷

Overall, adherence assessment provides insights that outcome-monitoring alone cannot; yet it remains to be an *estimate* of a patient's true medication-taking behaviour. No single measurement technique is optimal. Although direct measures overcome this limitation by providing true values of actual drug consumption, several factors restrict its use in clinical practice.⁴¹ For example, direct methods such as biological assays are invasive (e.g. blood monitoring), impractical (e.g. analyzing urine samples) and expensive in routine primary care-based practice. Conversely, although indirect adherence measures address some of these limitations of direct methods by providing an economical and practical medium of adherence assessment, they provide only an estimate rather than the true value of patient's behaviour. A multi-method approach combining different measuring techniques has been suggested as a means of identifying non-adherent patients. Currently, the pharmacists at CFFM's FHT's memory clinic uses two common methods of assessing adherence: pharmacy refill data and pill count data. Prior to the visit, all the patients are reminded to bring their pill bottles and/or blister packs to

their appointment. The pharmacy is also contacted to ascertain the refill dates for medication adherence assessment. Although triangulation between adherence methods can improve the accuracy of the measurements, it may not be possible to carry out both techniques in a busy clinic setting. Furthermore, if only one of the aforementioned adherence methods has to be used, there is a need to know whether the scores assessed by both approaches correlate or not. No studies on this topic have been conducted to date.

In addition, the literature points out that cognitively impaired older adults who are aware of their memory impairment have higher adherence rates than those who deny memory impairment.^{48,91} These patients and/or their caregivers are known to use various interventions in order to maintain optimum adherence, for example, use of calendar blister packs and weekly pill boxes.^{16,48} However, there is also a lack of proper studies that describe the interventions used by the caregivers, particularly in a memory clinic setting.

Given the uncertainty regarding the best management of adherence in older adults with cognitive impairment, the primary goal of this project was to determine the most feasible adherence assessment method that could be utilised in a primary care based memory clinic. The specific objectives were to:

- a. Compare the feasibility of using two different methods for assessing medication adherence in older patients with cognitive impairment.
- b. Describe different adherence-enhancing methods used by caregivers, spouses of patients, or by patients.

3.2. Methods

3.2.1. Study design

Before the commencement of the study, ethics clearance was obtained through the Office of Research Ethics at the University of Waterloo (ORE #19939, Appendix 3) and the Physicians' Board of the CFFM FHT.

The study design adopted for this study was a cross-sectional study design. A cross-sectional study design involves sampling patients irrespective of their disease status and is studied at a particular point in time.⁹² This provides a snapshot of both the exposure and outcome at the same time for a given sample of participants.⁹² Cross-sectional studies are mainly used if the purpose of the study is to describe a novel setting or is to determine the prevalence of the outcome of interest for a population at a given point in time.⁹³ As the purpose of the study was to describe the feasibility of assessing adherence in a novel clinic setting, a cross-sectional study was deemed appropriate.

3.2.2. Sample size estimation

Considering the lack of studies on the current topic in the present literature, a $\pm 10\%$ difference in the estimated adherence scores was assumed to facilitate a sample size calculation. The following formula was used to determine the sample size:

$$n = 2[(z_a + z_b) \sigma / \Delta]^2$$

where, σ = standard deviation; Δ = difference between means of pill count and MPR

The estimated sample size was 39, when the $\sigma/\Delta = 2.5$, $\alpha=0.05$ and $\beta=0.2$

3.2.3. Participants

Patients visiting the memory clinic in Kitchener, ON were recruited to take part in this study. Prior to data collection, prospective participants and their caregivers were

invited by the pharmacist or nurse to read an information letter (Appendix 5 and 6) explaining the study rationale and objectives, and were required to indicate their consent to participate by signing a consent form. In a situation where the participant had severe cognitive impairment (if shown in the EMR chart and confirmed by the pharmacist), the caregivers were asked to read the information letter and sign on behalf of the patient in the presence of a witness (usually, the pharmacist or the nurse) (Appendix 7).

Inclusion criteria were laid out in accordance with the objectives of the study. The main objective of the study was to compare two adherence assessment instruments (MPR and pill count) and to determine which is the most feasible in this clinic setting. The study aimed at determining adherence patterns in patients who lived independently, as patients living in long term care usually have their medications managed by the long term care (LTC) nursing staff. Adherence assessment of over-the-counter (OTC) medications was not possible as the adherence assessment methods involved the use of pill count data and pharmacy refill data. The data obtained through these methods do not allow for OTC adherence assessments, as the starting dates of OTC medications are usually unknown. Also, as the clinic specializes in dealing with patients with memory concerns, there was a higher chance that patients with severe impairment could also be scheduled. From an ethical point, it was of importance to obtain consent from the caregiver in addition to the patient. Therefore, the inclusion criteria used for recruiting the participants were:

- a) patients had to live independently,
- b) be 65 years or older,
- c) patients had to have at least one prescription medication and

- d) patients who were able to give consent. In case the patient was severely impaired, their caregiver was asked to consent on the patient's behalf.

Patients were automatically excluded if they:

- a) were residing in long term care units,
- b) were less than 65 years old,
- c) did not report taking any prescription medications or had only reported to take OTC medications and
- d) did not consent to participate.

3.2.4. Data collection

A case report form was designed and developed (CRF) to collect data for the purpose of this study (Appendix 4). Prior to the appointment day, the study participants were contacted through a telephone call as a reminder to bring all their medication pill box/containers (both, prescription and OTC medications).

Pill count data: All the prescribed medications were counted to gather pill count data. This data was applied to a formula (Section 3.2.6).

Pharmacy refill history: Information regarding refill history for all prescription drugs was obtained from the patient's pharmacy. The pharmacies from where participants obtain their medications were contacted through telephone on the same day of their visit to the clinic. The following details were gathered from the pharmacy:

- a. last refill date,

- b. refill date prior to the last filling date and
- c. the total days supply of medication during the refill period

All the aforementioned data were entered in a CRF. Information related to participants was kept anonymous and confidential using a subject code (Month Year Number).

3.2.5. Procedure

The data collected for this project, involved information gathered by the pharmacist as part of routine clinical practice. The variables recorded for this study include patient's demographics (age, sex, marital status, living situation, etc.), Montréal Cognitive Assessment (MoCA) score, Cornell score for depression, diagnosis, medications, and adherence data. The diagnosis and medications taken by the patients were ascertained using the electronic medical record (EMR) of the respective patients.

On the day of regular clinic, the scheduled patients were first reviewed through the EMR to determine the eligibility criteria for inclusion. No data was collected at this point. Only in cases where the subject met all the listed inclusion criteria did the pharmacist or the nurse approach the subject and the caregiver to ask for consent. Patients with severe cognitive impairment were also included in the study, however, the caregiver had to consent on behalf of the patient. All patients and caregivers were provided an information letter explaining the purpose of the study and were asked to read through the letter before signing. In addition, the pharmacist on duty also explained the aim before asking the patient to sign the consent. It should be noted that all the patients visiting the clinic could not be approached as a result of patient irritability, and/or time restrictions on regular clinic days.

Once the consent was obtained, the necessary data was collected from the EMR and adherence data was computed using pharmacy refill history and pill count. The pharmacies of the respective patient were contacted in order to obtain pharmacy refill history. In case a patient did not bring the pill bottles, consent was still obtained in order to ascertain their refill history. MoCA and Cornell testing carried out on the day of appointment by the nurse were collected at the end.

3.2.6. Outcome variables

The primary outcome measure was feasibility, which was defined as the ability to collect the data necessary to compute medication adherence of the patients seen at the memory clinic.

Assessment of adherence using pill count data was considered to be feasible if the participant presented with the pill bottles in order to gather the data required to compute adherence, for example, the number of remaining pills in the pill bottle, the date the drug was filled and the initial quantity of the pills dispensed.

Assessment of adherence using pharmacy refill history was considered to be feasible if all the data (e.g. the last refill date, the refill date prior to the last and the quantity dispensed) necessary to compute adherence could be collected on the phone by calling the participant's pharmacy.

The secondary outcome was patient adherence. Medication adherence using pill count data was estimated using the formula below:

Number of pills dispensed – number of pills present in the bottle / number of pills expected to be taken according to the prescription instructions

- $\geq 80\%$ is considered adherent as per accepted standards.^{27,64,94}

Medication adherence using pharmacy refill data was estimated using the MPR.

MPR is calculated as: ^{27,43,46}

all days supply / the number of days between refills (i.e. days between last prescription dispensed and the appointment day).

- ≥ 0.8 (80%) is considered adherent as per accepted standards. ^{27,43,46}

3.2.7. Analyses

Analysis was carried using IBM's Statistical Package for Social Sciences (SPSS) version 22.0.0.0 for the Macintosh operating system. Analyses consisted of descriptive statistics to describe the patients' baseline characteristics and adherence estimates. Descriptive statistics were used to summarize the feasibility of assessment methods, and the adherence strategies used by patients and/or caregivers. One-way analysis of variance (ANOVA) was conducted to compare the patient demographics in relation to their MPR scores. Pearson's correlation analysis was used to compare the continuous patient variables such as age, MoCA score, Cornell scores for depression, number of chronic conditions and number of prescription medications with average MPR rates.

Fischer-exact test was used to determine if there was an association between the non-feasibility of pill counts assessment and the causes of non-feasibility. As the cross-sectional study collected continuous adherence data, correlation analyses were carried out to examine the strength and nature of the relationship between the adherence scores measured by pill count and MPR. Using the dichotomous cutoff to determine the adherence status, the study analyzed the agreement between the assessment techniques using kappa statistics. The percent agreement between average medication adherence

estimates obtained by the pill count method and pharmacy refill data, and Cohen's Kappa coefficients were calculated. In absence of a gold standard, the Kappa coefficient is used to facilitate in describing the extent of agreement between these two different methods of assessing adherence.⁹⁵

Kappa coefficient is calculate using the following formula^{96,97} :

$$\text{Kappa} = \frac{(\% \text{Agreement observed}) - (\% \text{Agreement expected})}{100\% - (\% \text{Agreement expected})}$$

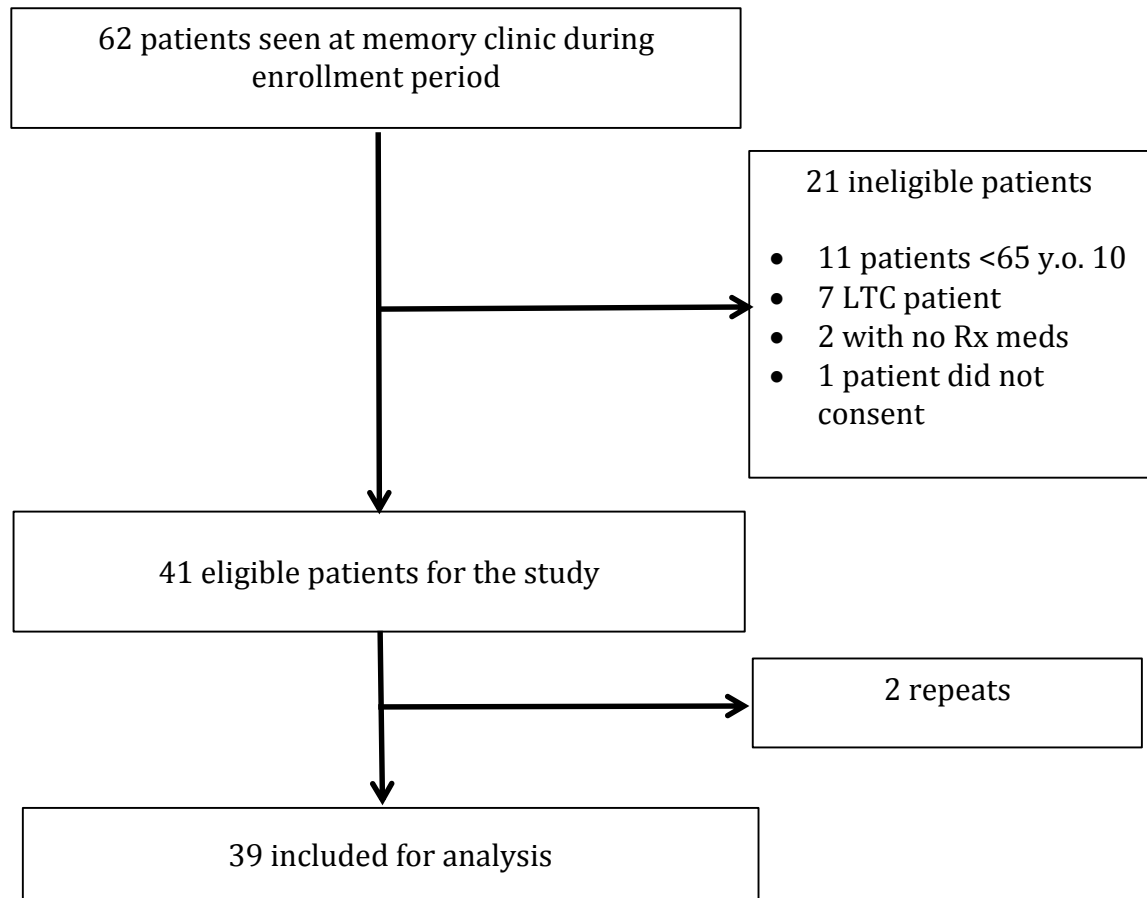
3.3. Results

3.3.1. Study participants

In total, 62 patients were approached to be included in the study during the memory clinic visits from September 2014 to June 2015. Of these, 39 met the inclusion criteria for analysis (Figure 5). The remaining 23 were excluded for the following reasons:

- 11 patients below age of 65;
- seven LTC patients;
- two patients with no prescription medications;
- two repeats and;
- one patient did not consent

Figure 6: Recruitment flow chart



Our sample consisted mostly of patients with an average age of 79 years and had a somewhat balanced gender ratio (Table 4). Subjects were taking an average of 5.74 prescription medications (Range 1-14) and were diagnosed with an average of 3.89 chronic conditions (range 1-8). As expected, there was a significant positive correlation between the number of chronic conditions and the number of prescription medications ($r = 0.521, p < 0.01$). Additionally, a caregiver accompanied most participants.

Tables 5 and 6 provide the list and frequency of co-morbidities presented in the patient sample. The mean MoCA score of the total sample was 19.22 (range 3-29). Less than half of the patients seen at the clinic had Mild Cognitive Impairment (16, 41%). The most common types of dementia seen in patients were mixed (18, 46.2%) and vascular (3, 7.7%). The most common co-morbid conditions among the patients were hypertension (25, 64.1%), depression (13, 33.3%), hyperlipidemia (13, 33.3%), and type II diabetes mellitus (9, 23.1%).

Table 4: Demographics of participants

Demographics	Results [n (%), where applicable]
Age, y	
Range	65–91
Mean (SD)	79.08 (6.83)
MoCA score	
Range	3–29
Mean (SD)	19.22
Chronic conditions	
Range	1–8
Mean	3.89
Prescription medications	
Range	1–14
Mean	5.74
Sex, no. (%)	
Male	22 (56.4%)
Female	17 (43.6%)
Race, no. (%)	
Caucasian	36 (92.3%)
South Asian	2 (5.1%)
Asian	1 (2.6%)
Marital Status, no. (%)	
Married	28 (71.8%)
Widowed	9 (23.1%)
Never married	1 (2.6%)
Divorced	1 (2.6%)
Living situation, no. (%)	
With spouse	22 (56.4%)
Alone	10 (25.6%)
With family	6 (15.4%)
Other	1 (2.6%)
Caregiver present at visit, no. (%)	
Yes	33 (84.6%)
No	6 (15.4%)
Caregiver type	
Spouse	18 (46.2%)
Offspring	8 (20.5%)
None	6 (15.4%)
Both	4 (10.3%)
Other	3 (7.7%)

Table 5: Percentages of cognitively impaired patients

Level of cognitive impairment	n (%)
No impairment	2 (5.1%)
MCI	16 (41%)
Mild	13 (33.3%)
Moderate	14 (35.9%)
Severe	10 (25.6%)
Type of dementia	n (%)
Mixed	18 (46.2%)
Vascular	3 (7.7%)
Alzheimer's disease	1 (2.6%)

Table 6: Diagnoses of participant

Co-morbid diagnoses	n (%)
Hypertension	25 (64.1%)
Depression	13 (33.3%)
Hyperlipidemia	13 (33.3%)
Diabetes Mellitus (Type 2)	9 (23.1%)
Osteoporosis	9 (23.1%)
Hypothyroidism	9 (23.1%)
Coronary artery disease	6 (15.4%)
GERD	6 (15.4%)
Atrial Fibrillation	4 (10.3%)
Anxiety	4 (10.3%)
Benign Prostrate Hyperplasia	4 (10.3%)
Congestive Heart Failure	2 (5.1%)
Asthma	2 (5.1%)
Gout	2 (5.1%)
Peripheral Vascular Disease	2 (5.1%)
Bipolar disorder	2 (5.1%)
Peptic Ulcer Disease	2 (5.1%)
Degenerative Disc Disease	1 (2.6%)
Parkinson's Disease	1 (2.6%)
Stroke	1 (2.6%)
Osteoarthritis	1 (2.6%)
Chronic Pain	1 (2.6%)
COPD	1 (2.6%)

3.3.2. Comparing categorical patient variables and MPR

There was no association between the MPR rates and patient gender, living situation, marital status, race or dementia type or level of impairment (Table 7).

Table 7: Correlations between categorical variables and MPR

Patient variables	Degrees of freedom	<i>F</i>-value	<i>p</i>-value
Gender	1	0.349	0.559
Living situation	3	0.534	0.662
Marital status	2	0.523	0.598
Race	2	2.625	0.087
Type of dementia	3	0.617	0.609

3.3.3. Comparing continuous patient variables and MPR

The MPR scores were not correlated with any patient variables, including age, MoCA score, Cornell scores, number of chronic conditions or number of prescription medications (Table 8).

Table 8: Correlations between continuous patient variables and MPR

Patient variables	Pearson's coefficients	<i>p</i>-values
Age	-0.204	0.226
MoCA scores	0.099	0.579
Cornell scores	-0.107	0.567
Number of chronic conditions	0.053	0.757
Number of prescription medications	-0.076	0.656

3.3.4. Feasibility of MPR vs. pill count

MPR using pharmacy refill history was more feasible than pill count. MPR was determined to be feasible in 38/39 (97.4%) patients while pill count was feasible in only 17/39 (43.6%) patients.

Over half of the time, the patient was provided with blister packs rendering pill count as infeasible because of the materials available for the review (see Discussion)[14/22 (63.63%), ($p < 0.001$)]. The second most common reason for non-feasibility was that the patients forgot to bring their pill bottles [8/22 (36.36%), ($p = 0.028$)] during their visit to the clinic.

The study examined the time taken to assess adherence using pill count and refill data. It took an average of 5:27min (SD 2:27min) to complete a pill count (from the beginning of counting the pills to the end calculation) versus 3:30min (SD 1:28min) to complete adherence assessment using MPR (time taken from the beginning of the call to the end calculation) [$p = 0.006$, 95% CI 0:40, 3:13].

Table 9: Descriptive of feasible assessment methods

Method of assessment	Results
Pill Count	
Feasible	17 (43.6%)
Not feasible	22 (56.4%)
Reason for non-feasibility	
Blister packs	14 (63.63%)
Forgot to bring pill bottles	8 (36.36%)
Medication Possession Ratio	
Feasible	38 (97.4%)
Not feasible	1 (2.6%)
Reason for non-feasibility	
Missing information	1 (2.6%)
Time taken	
Pill count	5:27 (SD 2:27)
MPR	3:30 (SD 1:28)

3.3.5. Comparison of assessment techniques

There was no correlation between the adherence scores measured by pill count and pharmacy refill data ($r=0.058$, $p=0.476$). Furthermore, there was no statistically significant association between the two scores ($r=0.241$ $p=0.476$).

An average of 81.6% ($n=31$) of patients were found to be adherent to their medications using MPR. On the other hand, only 60% ($n=9$) were adherent using pill count. The kappa coefficient showed no agreement between pill count and MPR ($\text{kappa}=0.045$, $p=0.825$).

Figure 7: Scatter plot between MPR and pill count

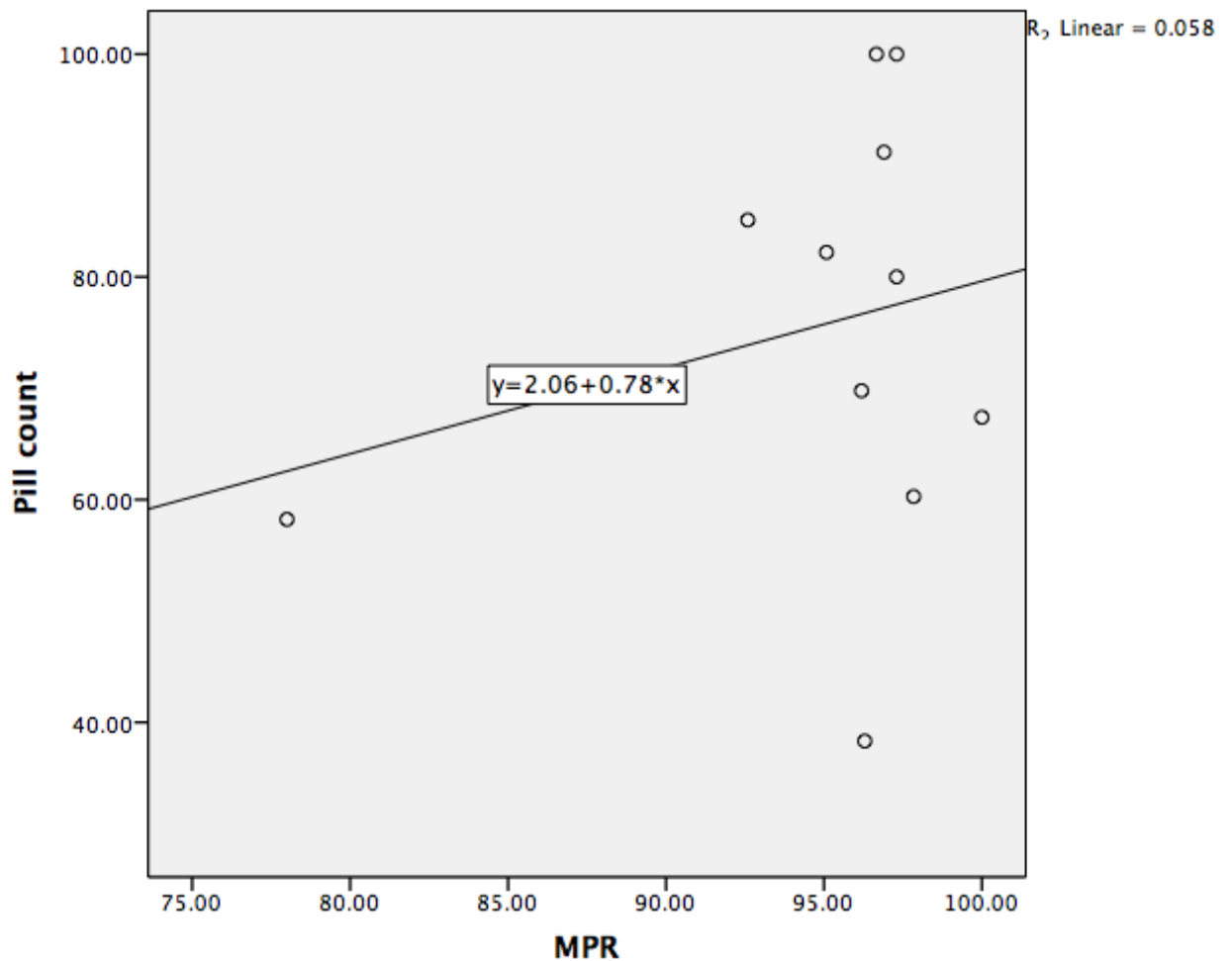


Table 10: Percentage agreement between pill count and MPR

Pill count (n= 14)				
% (N)				
	Adherent ≥ 80%	Non-adherent < 80%	Percent agreement	Kappa
MPR (n=14)				
Adherent (≥ 80%)	50 (7)	35.7 (5)		
Non-adherent (<80%)	7.14 (1)	7.14 (1)	57.4	0.046 (p=0.825)

3.3.6. Interventions used by caregivers

The interventions used as adherence aids as reported by the caregivers of patients/participants include blister packs, weekly pillboxes and miscellaneous interventions. Miscellaneous techniques involved the use of small circular pill boxes (n=1/3) intended for a once a time per day use (e.g., filled for lunch and supper), and placing pill bottles on a dining table to aid in remembering to take medications with meals (n=2/3). The most common adherence aid among the memory clinic population was the blister packs (14/38, 36.8%), followed by the weekly pillboxes (8/38, 22.1%).

Since the study also involved the use of a dichotomous cutoff of 80% to define adherence status, we explored if there was an association between adherence and intervention type (Table 11). All 8 patients using weekly pill boxes were found to be adherent according to overall MPR scores. Twelve out of fourteen (85.71%) patients were found to be adherent when they were on blister packs and two out of three (66.7%) when caregivers used miscellaneous interventions. Out of the thirteen caregivers who did not use any adherence interventions, only 4/13 (30.8%) were found to be non-adherent to their medications. Data was missing for one patient, as the information on this could not be obtained from the patients or the caregivers.

There was no difference in MPR rates between those who used interventions and those who did not (mean difference in adherence = 1.987%, 95% CI 5.10, 9.07, $p=0.573$). For the eight patients who used weekly pillboxes, the MPR rate was 6% higher than for those who did not (Mean difference in adherence = 5.66%, 95% CI 1.15, 10.17, $p=0.002$). There was no significant difference in MPR rates for the miscellaneous interventions, including those who used memory cues and small pillboxes.

Table 11: Interventions used by patients and caregivers

Intervention used	N (%)	Adherent	Non-adherent	Fisher-exact test
No intervention	13 (34.2%)	9 (69.2%)	4 (30.8%)	.164
Blister pack	14 (36.8%)	12(85.7%)	2 (14.3%)	.483
Weekly pill boxes	8 (21.1%)	8 (100%)	0	.161
Miscellaneous interventions	3 (7.9%)	2 (66.7%)	1 (33.3%)	.467

3.4. Discussion

3.4.1. Summary of results

The study revealed that the MPR method was more feasible than the pill count method. Pill count was infeasible mainly due to patients bringing unused blister packs or label of the blister pack during their visit to the clinic. The study also investigated the time taken to conduct these assessments and it was found that MPR took significantly less time than pill count. Further, there was no association between the adherence scores obtained using pill counts and using pharmacy refill data. The study also found that blister packs were the most commonly used adherence aids among caregivers, followed by weekly pillboxes and miscellaneous interventions. Correlation analysis did not find any difference in adherence rates amongst the different interventions used.

3.4.2. Correlations between different variables and adherence

Many interdisciplinary clinics that involve pharmacists on their team have a role to assess the medication regimen of the incoming patients. A memory clinic, in particular, sees older patients with memory concerns who are often burdened by a number of chronic conditions, which in turn results in a complex medication regimen. For these drugs to act optimally, adherence is required. Previous research indicates correlations between variables such as female gender, patients living alone, single marital status, and non-Caucasian race. For example, difference in female gender was associated with non-adherence in one study involving Korean patients with Alzheimer's disease.⁵³ Borah *et al.* have also shown that males are more likely to be adherent to their medication as compared to females (OR =1.175, p<0.05).⁶⁰ Other variables such as living situation, marital status, and race have also been shown to have an effect on adherence. A study

conducted in 11 countries demonstrated that living alone ($p < 0.001$) and being unmarried ($p < 0.001$) were negatively associated with adherence.⁴⁶ On further analysis, the results from logistic regression confirmed that being unmarried predicted non-adherence in older adults.⁴⁶ As pointed out by Poon *et al.*, non-Caucasians were more likely to be non-adherent to their medications, but the results from this study did not show any association of this sort.⁶¹ This study, however, was unable to demonstrate any significant correlations between all the categorical patient variables and adherence rates. This could be as a result of the smaller sample size as compared to previous studies that involved larger study population.

On examining correlations between MPR and continuous patient variables, no significant associations were observed. As shown by the study, there was no correlation between medication adherence and MoCA scores. These results conflict with literature because the literature points out that those patients with lower cognitive function were shown to have lower adherence rates.⁵² Moreover, many published studies and reviews have also confirmed that decreased cognition is a key factor leading to non-adherence.^{17,18,47,48,98} This study has also been unable to demonstrate any association between age, number of chronic diseases and number of prescription medications. These results are in line with those of a previous study that was conducted in 11 countries, where no association were seen between the given variables and medication adherence.⁴⁶

3.4.3. Feasibility of conducting pill counts versus MPR

In this study, the MPR method was found to be a more feasible method in comparison to pill count. The feasibility of MPR could be attributed to the readily available refill data from the pharmacies of the patients. The findings support the results

from previous studies, which have reported the ease of using refill data as an advantage of MPR in assessment of adherence.⁹⁰ Additionally, MPR was the only method available to assess adherence in patients who were either on blister packs or did not bring their medications during their appointment, further ascertaining the utility of easily available data to estimate patient adherence. Arguably, pill count could be conducted on patients who brought open blister packs, however, in the present study no participants had brought a used blister pack. Moreover, the findings from the study only found that MPR estimation took less time in comparison to pill count assessment on the clinic day. Currently, the evidence on the time taken to conduct MPR is not available in the literature and therefore, no comparison could be made.

On the other hand, pill count assessment could only be conducted for those patients who brought their medications. Previous studies have indicated that pill count could not be conducted for all their study participants, however, the reasons for unavailability were left unaccounted for.^{34,99} This study determined the reasons for non-availability. There is only one other study that has documented the reasons for non-availability of pill count in the community setting and they include missing information (labels, containers) (9.5%), prescription just filled and not yet started (9.1%), old prescription combined with new (5.9%), unclear information (2.0%), subject objected to pill count (1.0%) and dates not available (0.8%).⁹⁰ The results from this memory clinic study are consistent with data obtained from the previous study, where the researchers found missing information (including missing pill bottles) as the main reason for non-feasibility of pill count measure.⁹⁰

Although the study found that MPR was more feasible in comparison to pill counts, it cannot be assumed that both the methods measure the same medication taking behaviour. As noted earlier, MPR measures the patient's access to medications and not the actual consumption.

3.4.4. Comparison of scores assessed using pill count and MPR

As determining feasibility was the main objective of the study, it was also of importance to understand whether/if the scores obtained through these methods correlated. The results from the test did not show any correlation between the two tools.

For diagnostic studies, it is common to conduct sensitivity, specificity, Positive Predictive Value and Negative Predictive Value tests in the presence of a gold standard.⁹⁷ However, in this study these analyses could not be performed due to the lack of a gold standard adherence assessment tool. Instead, Kappa statistics was conducted on the tools, which revealed no agreement between the scores. The results from this study are in line with results of other studies, which have indicated a weak agreement between various indirect methods.⁵³ For instance, a study that involved a cohort of participants with probable and possible Alzheimer's disease were assessed for adherence using medication event monitoring system (MEMS), pill count and self-report measurement.⁵³ The study showed weak agreement between MEMS and other measures of adherence.⁵³ Another study conducted in a community setting also showed no agreement between self-reports and pill count.⁹⁰

A plausible explanation for no agreement between the adherence tools in this study could be that pill count and MPR measure different aspects of the patient's medication taking behaviour. In other words, pill count assesses the patient's ability to

follow the prescribed recommendations and/or dose, while MPR measures the ability of an individual to obtain medications on time or before they run out. Both of these methods do not assess the actual consumption, thus augmenting previous research by showing that adherence is a complex patient behaviour and this behaviour cannot be assessed using a single indirect measurement tool. Another reason that could explain the non-agreement between the tools is that there was a small observational sample in which both pill count and MPR were feasible (n=14).

3.4.5. Interventions used by the patient and/or caregiver

Patients and caregivers were found to use several adherence aids, for example, blister packs, weekly pillboxes, and other interventions such as small pillboxes meant for single dose and placing medications on the dining table. Among these interventions, the most popular adherence aid was blister packs. The reason for this could be that the patients, who were previously identified as non-adherent by the memory clinic team, were recommended to use blister packs to achieve an optimum adherence rate. However, this study does not confirm the given claim.

Most patients in the study were found to be using an intervention to maintain their medication adherence. This particular finding can be correlated to other studies where it has been found that patients who were cognizant of their memory concerns were more likely to use adherence aids. For example, in a study involving 51 older adults, depression and memory anxiety predicted the increased likelihood of using adherence aids.⁹¹ Furthermore, it was found that those who used adherence interventions were more adherent than those who did not but there was no statistically significant difference between adherent users and non-users. From the results, it was also shown that patients

using weekly pillboxes had significantly higher adherence rates as compared to any other intervention strategies. However, there was a huge difference between the number of weekly pillbox users in comparison to blister packs, or miscellaneous interventions. This can make the results unreliable and therefore this must be taken into account before generalizing from these results. Studies have also shown that weekly pillboxes may not be suitable for use in the cognitively impaired population. For example, the results from a study involving 27 older adults dwelling from the community showed that the participants with cognitive impaired would not benefit from organization boxes.⁶⁴ The difficulty of use can also be supported by another study which showed that multi-compartment pillboxes were difficult to use for participants with cognitive impairment.⁸³ Considering that memory clinic patients receive assistance from their caregivers to organize a weekly pillbox, these may still prove to be an effective strategy to improve adherence.

Blister pack users were also shown to have a large proportion of adherent patients. This study showed that almost 86% of patients using blister packs were adherent to their medications. This shows that the recommendation made by the memory clinic team to use blister packaging is an effective strategy when non-adherence is recognized. Further, results from this study corresponds to a study by Kakkad et al which showed Calendar blister packs users with cognitive impairment had 10% greater adherence rates than those who did not use blister packs.⁸² Caution should be taken in interpreting the results, as this was not a pre- / post-intervention study. A small proportion of participants used memory cues and other non-defined interventions to manage medications. The results

from this study on miscellaneous interventions are inconclusive, as the number of participants using these interventions was low.

3.4.6. Clinical implications on medication adherence assessment

Although the patient refill data was readily available in most cases, there were several limitations of using MPR in clinical settings that need to be addressed. For example, the study found that MPR calculation was not possible in case of one patient whose refill dates were missing as a result of a change in pharmacies. As MPR calculation requires two refill dates and the total days' supply for one drug, any one missing variable can lead to failure in calculating adherence scores. This can be true in this population, where a patient may move from independent living to a long-term care and consequently changing the pharmacy. Although, this particular patient had not moved into a longterm care facility, it provides an insight for other patients who may move into one in the future.

Another inherent limitation of MPR is that it does not necessarily measure a patient's medication use. The data from the pharmacy cannot infer whether the patient is or is not consuming the medications according to the given recommendations. There is a chance that the patients may be hoarding the pills or dumping them. Not only that, patients may also fill their prescriptions some time before needed, which can lead to overestimation of adherence. Furthermore, a number of memory clinic patients were on blister packs. Many pharmacies have a system by which the blisters are filled on a regular interval days. The problem with this automation is that, the pick up dates or the delivery dates are not recorded by the pharmacies, questioning the reliability of MPR assessment in blister pack patients. To the pharmacist's best estimate, it can be assumed that the

patient is taking the medications and not dumping them based on the clinical outcomes of the chronic disease. However, there can be patients who do not have a large number of chronic conditions or have conditions that cannot be monitored through a clinical outcome, making it difficult for the pharmacist to estimate the patient's medication taking behaviour. For example, adherence patterns can be estimated for chronic conditions such as hypertension where the blood pressure could be used as an end point as a measure of adherence. However, conditions such as dementia have no clinical outcome measures that can complement adherence measures.

Pill count is a simple method to administer in a clinical setting. The reason for this is that adherence calculation requires the refill date printed on the pill bottles, and the number of pills remaining in the pill bottle. Researchers have shown that pill count is one of the simplest methods to assess adherence, both in practice and research.^{27,41} Despite this, the pill count method largely relies on the patient's/caregiver's ability to recall and bring the pill bottles to the clinic. As noted, the clinic examines patients with declining memory and it should not be a surprise that many patients fail to bring their pill bottles during their appointment. Also, pill count could not be conducted in patients who were using blister packs. A plausible reason for this was that the blister packs are usually dispensed as two weeks' or four weeks' supply and on most occasions, patients did not bring all the blister packs. They either brought an unused blister pack or a list of medications they were taking. This made pill count assessment impossible to conduct. Another limitation of the pill count method is that the patient population seen at the memory clinic is diagnosed with an average of four chronic conditions for which they consume an average of six medications. Results from the study showed that conducting

pill counts on such a large number of medications can take significantly more time, which limits its practicality in a busy clinical setting. Furthermore, pill counts share the same limitation as MPR in that one cannot truly assess whether the patient is consuming the medication or not.

Although compromised by these disadvantages, pill counts may provide rich and useful information on patient's medication-taking behaviour at certain times. For example, the number of pills present in the bottle defines whether the patient consumes the right dose of medications. Several medications also require pill splitting in order to deliver the right dose and this can be verified using pill count. Pill counts also give an estimate of the current medication-taking behaviour of the patient rather than in retrospect as in case of MPR.

Previous studies have shown a lack of agreement between several indirect techniques. This was also the finding of the present study. As one would assume that there must be a strong agreement and a high correlation between pill count and MPR, however this study showed otherwise. It is clear from the literature that no one-assessment tool is successful in differentiating non-adherent from adherent patients. Therefore, it is suggested to triangulate two or more adherence assessment methods to ascertain patient adherence.

3.4.7. Strengths

This was the first of its kind study where pill count and pharmacy refill history were compared in a memory clinical setting. Previous studies have compared several indirect techniques in clinical and non-clinical areas, for example by Kim⁵³ and Vik et al⁹⁰, however these studies were carried out in a community setting rather than a primary

health care clinic. Not only does this study help in answering the question about which technique is most feasible in a primary care based memory clinic setting, but it also provides several outcomes that may be useful for future studies. For example, the standard deviation of the outcome measures (e.g. adherence rates, time taken, etc.) would help in estimating sample size. Moreover, this study also provides an insight into some of the issues related to participant recruitment and willingness of clinicians to recruit participants, for instance, irritable patients could not be recruited based on clinician's discretion.

3.4.8. Limitations

This study has several limitations that need to be considered before interpreting its results. The main limitation is the small sample size, which likely explains why most of the demographic variables were not correlated with adherence rates. For example, previous studies have found a correlation between patient variables such as gender, living situation, and race, and medication non-adherence. Such variables did not achieve a statistically significant correlation in our present study.

Secondly, the correlation between the adherence tools may be biased as a result of the absence of clear cutoff definition for adherence. Most adherence studies in the literature have agreed upon 80% as the cutoff to define adherent versus non-adherent.^{3,17,41} However, a previously published study has suggested that 90% adherence serves as a cutoff of 5 mg Donepezil.¹³ This cutoff was determined with the help of pharmacokinetic and pharmacodynamic study of Donepezil.¹³ Such considerations were not taken into account for the present study.

Thirdly, the validity of statistical tests is another limitation of the present study because it fails to provide statistically significant results. For example, statistical tests such kappa coefficient fail in a case when the value of one of the boxes in the 2x2 table drops below five.

Finally, the sample frame chosen in this cross-sectional study was small which questions the generalizability of the results to the entire memory clinic population. In this case, irritable patients along with some others could not be approached in the study. These patients may have unique characteristics that could have an effect on their adherence, which could not be determined. Despite of these limitations, the study design was useful in providing descriptive adherence data in an otherwise unexplored clinical setting.

3.5. Conclusion and future direction

Clinicians continue to face a dilemma of determining how well patients adhere to their medications. This study pointed out that MPR was more feasible than pill count, however, it cannot be concluded that one is better than the other. As several techniques are available to measure adherence, there is a lack of agreement between most indirect techniques. This study showed that there was no correlation or agreement between the scores measured by pill count and MPR. The reason for this could be that these techniques measure different aspects of adherence rather than just medication consumption. Perhaps the best approach for assessing medication adherence is to triangulate at least two adherence assessment methods. In absence of either MPR or pill count, one may consider the use of self-report measures on caregivers to ascertain

medication adherence. Future research could usefully explore the utility of the self-report measure in a memory clinic setting.

CHAPTER 4: OVERALL DISCUSSION AND CONCLUSION

As the population of Canada ages rapidly, it will face an increasing number of comorbidities, resulting in an increased number of personal medications. As shown in the results from the memory clinic study, the number of medications did indeed increase with the number of co-morbidities. With the ever-expanding aging population, the prevalence of dementia and Alzheimer's disease will continue to rise. At present, as there is no cure for these diseases, the current therapy relies on managing the condition and slowing down the progression of the disease using the non-curative drugs that are available. An important factor that will determine the success of slowing the progression of these diseases and their impact is optimum adherence to medication. However, factors such as memory impairment make it more difficult for older adults to manage their medications, setting up a vicious cycle of reducing adherence to necessary medication.

To help address these issues, the memory clinic model is well placed to address a number of interrelated issues of cognitive impairment including reduced medication adherence. Although memory clinics have already incorporated attention to adherence as part of their practice in dealing with cognitively-impaired older adults, clinicians still face the dilemma of choosing an accurate adherence method. It is the pharmacist in the memory clinic setting that is assigned to perform the adherence check on patients. He/she is well placed to consider this problem. This thesis has examined the issues around addressing the overall challenge through measurements that are part of the pharmacist's skillset.

Adherence is usually measured using pill count and/or pharmacy refill data. From the results of the memory clinic study, it was found that MPR was a more feasible method in

comparison to pill count. Pill count was infeasible as the patients that may have been seen previously were advised to use blister packs to improve adherence. This infeasibility of conducting pill count was attributed to patients either bringing a new blister pack instead of an unused pack or presenting with the blister pack label indicating the list of medications that were currently being blister packed. It was also infeasible as many patients forgot to bring their pill bottles to the clinic. In the study, we concluded that there is no correlation between adherence scores measured by pharmacy refill data and pill count which indicates that the best overall approach is to triangulate two or more adherence-assessing methods to measure medication adherence. Nevertheless, and although MPR was more feasible than pill count, it is advisable to still use both methods to ascertain medication adherence as MPR and pill count may assess different aspects of the medication-taking behaviour.

In cases where the pill count is not feasible, other indirect methods such as self-reports or semi-structured interviews may be used. For example, the Morisky scale is a simple to use and validated questionnaire intended to assess adherence by asking four questions. Use of self-reports may be questionable in the current setting as patients are presented with memory concerns, however the pharmacist may use this tool on caregivers instead. Literature reviews on this topic have again supported the suggestion of triangulation of data from another adherence assessment technique in addition to a self-report measure.^{27,28,41}

The ultimate prevalence of non-adherence in this population still remains unclear. The scoping review (Chapter 2) found that non-adherence had a wide range in the current population. This was also the finding in a meta-analysis that investigated older adults

regardless of any medical conditions.¹⁵ The memory clinic study (Chapter 3) also witnessed a disparity between the number of non-adherent patients identified using MPR and pill count. As addressed in Chapter 2, a commonly-cited reason for this wide range of prevalence of non-adherence has been due to a lack of a consistent ‘gold’ standard. Furthermore, it still remains unclear from the literature, as well as perspectives gained in the scoping review of Chapter 2 as well as the memory clinic study of Chapter 3 as to what proportion of adherence can be considered optimal.

For the purpose of defining adherence, this dissertation used a value of 80% as a cut-off to distinguish adherent patients from non-adherent. This seems justifiable, as most research on medication adherence across different older adult populations has regarded 80% as satisfactory compliance since the 1960s.^{7,12,27} However, a pilot study conducted in 2010 using pharmacokinetic and pharmacodynamic parameters determined that 90% adherence was necessary for the use of 5mg Donepezil in order to maintain a full therapeutic coverage of the drug.¹³ The quantitative assessment of adherence with the help of PK/PD model is referred to as ‘Pharmionics’.⁴¹ At this point, not many studies have investigated PK/PD parameters to establish a cutoff for adherence rates and the data remain sparse.

Absence of any gold standard along with an arbitrary adherence cut-off also hinders the ability to identify the predictors of non-adherence. From Chapter 2, it was seen that cognitive impairment along with increased caregiver stress were key barriers to adherence in cognitively impaired older adults. Although the approach taken in Chapter 3 (with the sample size that was feasible) was not successful in finding statistically

significant correlations between patient variables and non-adherence, the results did find a similar pattern as what has been accepted in the literature.

The memory clinic study described in Chapter 3 showed that caregivers used adherence aids such as blister packs, weekly pillboxes and miscellaneous techniques. Although the study could not find significant differences between adherence rates according to different adherence interventions, it was still interesting to know what kind of interventions are being used in the memory clinic population. In the literature reviewed in Chapter 2, it was found that interventions such as transdermal patches and once-daily higher doses received significant caregiver satisfaction. These interventions, however, were not found to be in use in the current practice. Several reasons could explain this, for example, transdermal alternatives are not available for many of the oral chronic medications that a patient might be on within the study population. Further, once-daily higher dose cannot be implemented for all drug classes. Nevertheless, adherence aids such as blister packs and weekly pillboxes have been studied and have been implemented in practice with great success. One particular disadvantage that could hamper the use of weekly pillbox is that it may be difficult to use for patients with cognitive impairment. However, it was found that all the patients in the memory clinic who used this intervention were adherent. This adherence pattern could possibly be due to caregiver support.

In conclusion, this thesis explored different aspects of medication adherence in an otherwise uncharted area. The work presented in this thesis showed that knowing the most feasible instrument does not guarantee an accurate assessment of non-adherence and that this area of research still remains of significant importance.

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APPENDICES

Appendix 1: Search strategies for literature review

DATABASE: PUBMED
SEARCH DATE: 1966 – December 3, 2014
KEYWORDS →("medication adherence" OR "Medication Adherence"[Mesh] OR "Medication Non-Adherence" OR "Medication Non Adherence" OR "Medication Nonadherence" OR "Medication Compliance" OR "Medication Non-Compliance" OR "Medication Non Compliance" OR "Medication Noncompliance" OR "Medication Persistence" OR "drug adherence") AND (dementia OR Alzheimer OR alzheimer's disease OR "lewy body" OR "lewy bodies" OR "cognitive impairment") AND (assess* OR measur* OR evaluat*)
RESULTS: 90 articles
FILTERS: No filters activated
COMMENTS: Dr. Fernandez and I went through titles/abstracts and agreed on articles that looked like they had potential for the scoping review. Collectively agreed on 45 (2 Spanish and 1 Japanese) articles that were relevant to the project and it decided to include these in the literature review.

DATABASE: EMBASE
SEARCH DATE: 1974 to January 24, 2015
KEYWORDS →(medication adherence OR medication non-adherence OR medication non Adherence OR medication nonadherence OR medication compliance OR medication non-compliance OR medication non compliance OR medication noncompliance OR medication persistence OR drug adherence) AND (dementia OR Alzheimer OR alzheimer disease OR lewy body OR lewy bodies OR cognitive impairment) AND (assess* OR measur* OR evaluat*)
RESULTS: 174 articles
FILTERS: No filters activated
COMMENTS: 45 (1 Spanish) relevant articles were identified out of which, 23 articles were previously identified in PUBMED search.

DATABASE: CINAHL
SEARCH DATE: 1996- January 24, 2015
KEYWORDS →(medication adherence OR medication non-adherence OR medication non Adherence OR medication nonadherence OR medication compliance OR medication non-compliance OR medication non compliance OR medication noncompliance OR medication persistence OR drug adherence) AND (dementia OR Alzheimer OR alzheimer disease OR lewy body OR lewy bodies OR cognitive impairment) AND (assess* OR measur* OR evaluat*)
RESULTS: 65 articles
FILTERS: No filters activated.
COMMENT: 18 articles were found relevant to the research question, out of which 9 articles were previously identified in PUBMED and EMBASE databases.

DATABASE: PSYCINFO
SEARCH DATE: January 24, 2015
KEYWORDS →medication adherence OR medication compliance OR medication persistence OR medication nonadherence OR medication noncompliance OR medication non-persistence OR drug adherence OR drug compliance OR drug persistence OR patient compliance OR patient adherence AND (dementia OR Alzheimer OR alzheimer disease OR cognitive impairment)
RESULTS: 4 Articles
COMMENT: 3 articles were identified as relevant. 2 articles were previously identified in the previous databases.

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Title: An Interdisciplinary Memory Clinic: A Novel Practice Setting for Pharmacists in Primary Care

Logged in as:
Zain Hudani

Author: Carlos H. Rojas-Fernandez, Tejal Patel, Linda Lee

LOGOUT

Publication: The Annals of Pharmacotherapy

Publisher: SAGE Publications

Date: 06/01/2014

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Appendix 3: Office of Research Ethics clearance

UNIVERSITY OF WATERLOO

<http://iris.uwaterloo.ca/ethics/form101/ad/reports/certificateB1.asp?i...>

UNIVERSITY OF WATERLOO

OFFICE OF RESEARCH ETHICS

Notification of Ethics Clearance of Application to Conduct Research with Human Participants

Faculty Supervisor: Carlos Rojas-Fernandez

Department: Pharmacy

Student Investigator: Zain Hudani

Department: Pharmacy

ORE File #: 19939

Project Title: Assessing medication adherence in patients with memory concerns

This certificate provides confirmation the above project has been reviewed in accordance with the University of Waterloo's Guidelines for Research with Human Participants and the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans. This project has received ethics clearance through a University of Waterloo Research Ethics Committee.

Note 1: *This ethics clearance is valid for one year from the date shown on the certificate and is renewable annually. Renewal is through completion and ethics clearance of the Annual Progress Report for Continuing Research (ORE Form 105).*

Note 2: *This project must be conducted according to the application description and revised materials for which ethics clearance has been granted. All subsequent modifications to the project also must receive prior ethics clearance (i.e., Request for Ethics Clearance of a Modification, ORE Form 104) through a University of Waterloo Research Ethics Committee and must not begin until notification has been received by the investigators.*

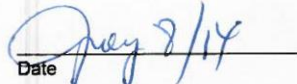
Note 3: *Researchers must submit a Progress Report on Continuing Human Research Projects (ORE Form 105) annually for all ongoing research projects or on the completion of the project. The Office of Research Ethics sends the ORE Form 105 for a project to the Principal Investigator or Faculty Supervisor for completion. If ethics clearance of an ongoing project is not renewed and consequently expires, the Office of Research Ethics may be obliged to notify Research Finance for their action in accordance with university and funding agency regulations.*

Note 4: *Any unanticipated event involving a participant that adversely affected the participant(s) must be reported immediately (i.e., within 1 business day of becoming aware of the event) to the ORE using ORE Form 106. Any unanticipated or unintentional changes which may impact the research protocol must be reported within seven days of the deviation to the ORE using ORE form 107.*


Maureen Nummelin, PhD
Chief Ethics Officer

OR
Julie Joza, MPH
Senior Manager, Research Ethics

OR
Sacha Geer, PhD
Manager, Research Ethics


Date

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Appendix 4: Clinical report form

University of Waterloo, School of Pharmacy	Subject Identification Number: (e.g. MMYYYNo.)

Patient demographics	
• Age	
• Sex	<input type="radio"/> Male <input type="radio"/> Female
• Ethnicity	<input type="checkbox"/> Caucasian <input type="checkbox"/> Black <input type="checkbox"/> Asian <input type="checkbox"/> South-Asian <input type="checkbox"/> Aboriginal; Other:
• Marital status	<input type="radio"/> Married <input type="radio"/> Never married <input type="radio"/> Widowed <input type="radio"/> Divorced
• Living situation	<input type="radio"/> Alone <input type="radio"/> With spouse <input type="radio"/> With family
• Caregiver present	<input type="radio"/> Yes <input type="radio"/> No
• Type of accompanying caregiver	<input type="checkbox"/> Spouse <input type="checkbox"/> Off-spring; Other:

Basic diagnostics details	
• Co-morbidities present	<input type="radio"/> Yes <input type="radio"/> No
• Number of co-morbidities	
• MOCA test score	
• Level of cognitive impairment	<input type="radio"/> Mild <input type="radio"/> Severe <input type="radio"/> Probable ADRD
• Type of dementia	<input type="radio"/> Vascular <input type="radio"/> Lewy bodies <input type="radio"/> Mixed

Date of printing: YYYY-MM-DD

Page 1

University of Waterloo, School of Pharmacy	Subject Identification Number: (e.g. MMYYYNo.)

Medication details	
• No. of Over-the-counter medications	
• No. of prescription drugs	
• Pill count feasible	<input type="radio"/> Yes <input type="radio"/> No
• If no, reason for non-availability	<input type="checkbox"/> Forgot to bring pill boxes/containers <input type="checkbox"/> Missing information (labels, original containers) <input type="checkbox"/> Prescription just filled, not yet started <input type="checkbox"/> Old prescription combined with new <input type="checkbox"/> Unclear information <input type="checkbox"/> Subject objecting to pill count <input type="checkbox"/> Regimen altered by physician <input type="checkbox"/> Subject using old prescription <input type="checkbox"/> Tablets differ from the label <input type="checkbox"/> Other reason:
• Pharmacy refill data available	<input type="radio"/> Yes <input type="radio"/> No
• If no, reason for non-availability	<input type="checkbox"/> Missing information <input type="checkbox"/> Switched pharmacy <input type="checkbox"/> Unclear information <input type="checkbox"/> Pharmacist objecting to refill history data <input type="checkbox"/> Other reason:

University of Waterloo, School of Pharmacy	Subject Identification Number: (e.g. MMYYYNo.)

--	--

Pill count data					
Sr. no.	Drug name	Drug class	No. of pills dispensed	No. of pills present in pill box/container	No. of pills expected to be taken according to the instructions

Adherence enhancing strategy used by caregiver	
Adherence enhancing strategy used by caregiver	<input type="checkbox"/> Weekly pill-box <input type="checkbox"/> Blister packs <input type="checkbox"/> Medication reminder devices <input type="checkbox"/> Other:

University of Waterloo, School of Pharmacy	Subject Identification Number: (e.g. MMYYYNo.)

Result					
Adherence assessment using pill count data:					
Sr. no.	Name of drug	Drug class	No. of pills dispensed – No. of pills present in pill container /No. of pills expected to be taken according to the instructions	Adherence status (Y/N)	Comment
Adherence assessment using pharmacy refill data					
Sr. no.	Name of drug	Drug class	MPR	Adherence status (Y/N)	Comment

Date of printing: YYYY-MM-DD

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Appendix 5: Information letter and consent form (Participants)

**WATERLOO
PHARMACY**

SCHOOL OF PHARMACY | UNIVERSITY OF WATERLOO
Health Sciences Campus, 10 Victoria Street South, Kitchener, ON, Canada N2G 1C5
MAILING ADDRESS: 200 University Avenue West, Waterloo, ON, Canada N2L 3G1
519-888-4499 | fax 519-883-7580 | pharmacy.uwaterloo.ca

Project: Assessing medication adherence in patients with memory concerns.

Organizers: Zain Hudani (Student), Carlos Rojas-Fernandez (Supervisor)

INFORMATION LETTER & CONSENT (Participant)

Date:

Dear Potential Participant:

This letter is an invitation to participate in a study being led by Mr. Zain Hudani at the Centre for Family Medicine Family Health Team's memory clinic, Kitchener, ON to fulfill my academic requirements. We are asking you to participate in a study where we will explore your medication adherence behaviours.

Study objectives

Older people commonly take multiple medications. Managing multiple medications is a challenge to patients due to multiple doses required in a day. Memory problems, and specifically dementia are common concerns as people age, and these concerns increase in frequency as we age. The ability to take medications properly (i.e., medication adherence) may be lower among those with memory problems and/or dementia. In practice there are no widely accepted and feasible methods for clinicians to assess medication adherence in this population.

The aim of this project is to compare two common methods to assess adherence, and determine which might be best suited for use in this population.

Study overview

As a participant in this study, you will be asked to present your pill boxes/containers and your prescription details from the container's label (for example the date of dispensing, drug name, etc.) along with the number of pills present in the container will be recorded on a data collection form. In addition, your pharmacy will be contacted to obtain your prescription history (dates of refill) and these data will be used to calculate medication adherence. Also, your caregiver will be asked about the adherence enhancing methods that they use for your medications. With your agreement, your basic diagnostic data will also be accessed from the clinic for further analysis of the adherence data.

Your participation is voluntary

Participation in this study is voluntary. You may decline access any of the information/data we ask for, if you so wish. Further, you may decide to withdraw from this study at any time without any negative consequences by advising the researcher.

Risks

We do not anticipate any risks to you due to participating in this study.

Eligibility Requirements for Participation

Patients presenting to the clinic with memory concerns.

Confidentiality and Data Retention

All information you provide will be considered confidential and will remain anonymous. A unique study identifier (e.g., 06201401) will be assigned in addition to your name initials on data collection forms.

The data collection forms will be stored in a locked cabinet in the Principal Investigator's office. The resulting electronic dataset will be kept on a research computer that is password protected and is kept in a locked, secure office (of the PI). The findings will be summarised as aggregate data, thus you, as an individual will not be identified. When the research report is prepared and published, only the research team will have access to your data from the evaluations.

Remuneration

We will not be providing any payment to you for participating in this study.

Questions and Contact

If you have any questions about participation, or would like additional information to assist you in reaching a decision about participation, please contact me: Zain Hudani, at (519) 888-4567, X 21392 (Office), (647) 879-2765 (cell) or via email at zhudani@uwaterloo.ca.

Ethics Review and Clearance

I would like to assure you that this study has been reviewed by, and received ethics clearance through, the Office of Research Ethics at the University of Waterloo. However, the final decision about participation is yours. In the event you have any comments or concerns resulting from your participation in this study, please contact Dr. Maureen Nummelin, the Director, Office of Research Ethics, at 1-519-888-4567, Ext. 36005 or maureen.nummelin@uwaterloo.ca.

We hope that the results of our study will be of benefit to those organizations directly involved in the study, other voluntary recreation organizations not directly involved in the study, as well as to the broader research community.

Yours sincerely,

Zain Hudani, B.Pharm
Graduate Student
School of Pharmacy
University of Waterloo
10 Victoria St S, Room 7004
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CONSENT FORM – AGREEMENT TO PARTICIPATE

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

I have read the information presented in the information letter about a study being conducted by Zain Hudani of the School of Pharmacy at the University of Waterloo. I have had the opportunity to ask any questions related to this study, to receive satisfactory answers to my questions, and any additional details I wanted.

This project has been reviewed by, and received ethics clearance through, the Office of Research Ethics at the University of Waterloo. I was informed that if I have any comments or concerns resulting from my participation in this study, I may contact Dr. Maureen Nummelin, the Director, Office of Research Ethics, at 1-519-888-4567, Ext. 36005 or maureen.nummelin@uwaterloo.ca.

With full knowledge of all foregoing, I agree, of my own free will, to participate in this study.

YES NO

Participant Name: _____ (Please print)

Participant Signature: _____

Date: _____

Appendix 6: Information letter and consent form (Caregivers)

**WATERLOO
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SCHOOL OF PHARMACY | UNIVERSITY OF WATERLOO
Health Sciences Campus, 10 Victoria Street South, Kitchener, ON, Canada N2G 1C5
MAILING ADDRESS: 200 University Avenue West, Waterloo, ON, Canada N2L 3G1
519-888-4499 | fax 519-883-7580 | pharmacy.uwaterloo.ca

Project: Assessing medication adherence in patients with memory concerns.

Organizers: Zain Hudani (Student), Carlos Rojas-Fernandez (Supervisor)

INFORMATION LETTER & CONSENT

Date:

Dear Potential Participant's caregiver:

This letter is an invitation to participate in a study being led by Mr. Zain Hudani at the Centre for Family Medicine Family Health Team's memory clinic, Kitchener, ON to fulfill my academic requirements. We are asking you and your spouse/parent to participate in a study where we will explore his/her medication adherence behaviours.

Study objectives

Older people commonly take multiple medications. Managing multiple medications is a challenge to patients due to multiple doses required in a day. Memory problems, and specifically dementia are common concerns as people age, and these concerns increase in frequency as we age. The ability to take medications properly (i.e., medication adherence) may be lower among those with memory problems and/or dementia. In practice there are no widely accepted and feasible methods for clinicians to assess medication adherence in this population.

The aim of this project is to compare two common methods to assess adherence, and determine which might be best suited for use in this population.

Study overview

As a participant in this study, your spouse/parent will be asked to present his/her pill boxes/containers and his/her prescription details from the container's label (for example the date of dispensing, drug name, etc.) along with the number of pills present in the container will be recorded on a data collection form. In addition, his/her pharmacy will be contacted to obtain his/her prescription history (last refill date) and these data will be used to calculate medication adherence. Also, you, as a caregiver will be asked about the adherence enhancing methods that you use for your spouse's/parent's medications. With your agreement, your spouse's/parent's basic diagnostic data will also be accessed from the clinic for further analysis of the adherence data.

Your and your spouse's/parent's participation is voluntary

Participation in this study is voluntary. You or your spouse/parent or you may decline access any of the information/data we ask if you so wish. Further, you may decide to withdraw from this study at any time, on his/her behalf without any negative consequences by advising the researcher.

Risks

We do not anticipate any risks to you or your spouse/parent due to participating in this study.

Eligibility Requirements for Participation

Patients presenting to the clinic with memory concerns.

Confidentiality and Data Retention

All information you provide will be considered confidential and will remain anonymous. A unique study identifier (e.g., ABC-123) will be assigned in addition to your spouse's/parent's name initials on data collection forms.

The data collection forms will be stored in a locked cabinet in the Principal Investigator's office. The resulting electronic dataset will be kept on a research computer that is password protected and is kept in a locked, secure office (of the PI). The findings will be summarised as aggregate data, thus your spouse/parent, as an individual will not be identified. When the research report is prepared and published, only the research team will have access to your spouse's/parent's data from the evaluations.

Remuneration

We will not be providing any payment to your parent/spouse for participating in this study.

Questions and Contact

If you have any questions about participation, or would like additional information to assist you in reaching a decision about participation, please contact me: Zain Hudani, at (519) 888-4567, X 21392 (Office), (647) 879-2765 (cell) or via email at zhudani@uwaterloo.ca.

Ethics Review and Clearance

I would like to assure you that this study has been reviewed by, and received ethics clearance through, the Office of Research Ethics at the University of Waterloo. However, the final decision about participation is yours. In the event you have any comments or concerns resulting from your participation in this study, please contact Dr. Maureen Nummelin, the Director, Office of Research Ethics, at 1-519-888-4567, Ext. 36005 or maureen.nummelin@uwaterloo.ca.

We hope that the results of our study will be of benefit to those organizations directly involved in the study, other voluntary recreation organizations not directly involved in the study, as well as to the broader research community.

Yours sincerely,

Zain Hudani, B.Pharm
Graduate Student
School of Pharmacy
University of Waterloo
10 Victoria St S, Room 7004
Kitchener, ON, N2G 1C5

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crojas-f@uwaterloo.ca
www.the-ria.ca

CONSENT FORM – AGREEMENT TO PARTICIPATE

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

On behalf of my parent/spouse and myself, I have read the information presented in the information letter about a study being conducted by Zain Hudani of the School of Pharmacy at the University of Waterloo. I have had the opportunity to ask any questions related to this study, to receive satisfactory answers to my questions, and any additional details I wanted.

This project has been reviewed by, and received ethics clearance through, the Office of Research Ethics at the University of Waterloo. I was informed that if I have any comments or concerns resulting from my participation in this study, I may contact Dr. Maureen Nummelin, the Director, Office of Research Ethics, at 1-519-888-4567, Ext. 36005 or maureen.nummelin@uwaterloo.ca.

With full knowledge of all foregoing, I agree, on behalf of my parent's/spouse's and my will, to participate in this study.

YES NO

Caregiver's Name: _____ (Please print)

Relationship with the participant
(wife/husband/son/daughter): _____

Caregiver's Signature: _____

Date: _____

Appendix 7: Information letter and consent form (Severely impaired participants)

**WATERLOO
PHARMACY**

SCHOOL OF PHARMACY | UNIVERSITY OF WATERLOO
Health Sciences Campus, 10 Victoria Street South, Kitchener, ON, Canada N2G 1C5
MAILING ADDRESS: 200 University Avenue West, Waterloo, ON, Canada N2L 3G1
519-888-4499 | fax 519-883-7580 | pharmacy.uwaterloo.ca

Project: Assessing medication adherence in patients with memory concerns.
Organizers: Zain Hudani (Student), Carlos Rojas-Fernandez (Supervisor)

INFORMATION LETTER & CONSENT (Participant with severe impairment)

Date:

Dear Potential Study Participant's family member/caregiver:

This letter is an invitation for your family member to participate in a study being conducted by Mr. Zain Hudani at the Centre for Family Medicine Family Health Team's memory clinic, Kitchener, ON to fulfill Mr. Hudani's academic requirements as a graduate student, at School of Pharmacy, University of Waterloo. As a part of normal practice at this clinic, the pharmacist (Dr. Rojas-Fernandez) assesses how patients are taking their medications either visual examination of prescription medication vials and/or calling the patient's pharmacy to obtain a detailed refill history. We are asking you, as the legal guardian of the patient, to consent on behalf of the patient to participate in a study where we intend to use this data to explore medication adherence of people with memory concerns.

Study objectives

Older people commonly take multiple medications. Managing multiple medications is a challenge to patients due to multiple doses that may be required in a day. Memory problems are common as people age, and increase in frequency as we age. The ability to take medications properly (i.e., medication adherence) may be lower among those with memory problems. In practice there are no widely accepted and feasible methods for clinicians to assess medication adherence in patients with memory problems.

The aim of this project is to determine the most feasible adherence assessment method that is best suited for use in a population with memory concerns who come to this clinic.

Study overview

As a part of routine clinic practice, a pill count is conducted and labelled information/instructions from the medication container(s) are recorded to assess medication adherence. In addition, the patient's pharmacy is also contacted to obtain his/her prescription history (last refill date) and this data is used as a second method to assess medication adherence. The pharmacist (CF) also asks the caregiver about medication management of the patient. This includes asking the methods by which they ensure the patient is taking his/her medications to suggest perhaps better medication management interventions. Your responses are recorded as part of practice and we intend to use these for research. With your agreement, your responses and the patient's/family member's information such as, age, gender, and medication history along with his/her

medication adherence data will be accessed from the clinic for the purpose of this study. No additional data will be sought from the pharmacy or the clinic without your permission.

Your and your family member/caregiver's participation is voluntary

Participation in this study is voluntary. On behalf of the patient, you may decline access any of the information/data we ask if you so wish. Further, you may decide to withdraw from this study at any time, without any negative consequences by advising the researcher.

Risks

We do not anticipate any risks to you or the patient due to participating in this study.

Eligibility Requirements for Participation

Patients presenting to the clinic with memory concerns and their family members/caregivers.

Confidentiality and Data Retention

All information gathered will be considered confidential. A unique study identifier (e.g., ABC-123) will be assigned on data collection forms. The data collection forms will be stored in a locked cabinet in the Principal Investigator's office. The resulting electronic dataset will be kept on a research computer that is password protected and will be kept in a locked, secure office (of the Principal Investigator) for a period of 7 years. This data will then be destroyed by confidential shredding and by erasing electronic data from the research computer. The findings will be summarised as aggregate data, thus you and your caregiver/family member, as an individual will not be identified. When the research report is prepared and published, only the research team will have access to your data from the evaluations.

Remuneration

We will not be providing any payment to you or your family members/caregiver for participating in this study.

Questions and Contact

If you have any questions about participation, or would like additional information to assist you in reaching a decision about participation, please contact me: Zain Hudani, at (519) 888-4567, X 21392 (Office), (647) 879-2765 (cell) or via email at zhudani@uwaterloo.ca.

Ethics Review and Clearance

We would like to assure you that this study has been reviewed by, and received ethics clearance through a University of Waterloo Research Ethics Committee. However, the final decision about participation is yours. In the event you have any comments or concerns resulting from your participation in this study, please contact Dr. Maureen Nummelin, the Director, Office of Research Ethics, at 1-519-888-4567, Ext. 36005 or maureen.nummelin@uwaterloo.ca.

We hope that the results of our study will be of benefit to those organizations directly involved in the study, as well as to the broader research community.

Yours sincerely,

Zain Hudani, B.Pharm
Graduate Student
School of Pharmacy
University of Waterloo
10 Victoria St S, Room 7004
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CONSENT FORM – AGREEMENT TO PARTICIPATE

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

On behalf of the patient, I have read the information presented in the information letter about a study being conducted by Mr. Zain Hudani of the School of Pharmacy at the University of Waterloo. I have had the opportunity to ask any questions related to this study, to receive satisfactory answers to my questions, and any additional details I wanted.

This project has been reviewed by, and received ethics clearance through a University of Waterloo's Research Ethics Committee. I was informed that if I have any comments or concerns resulting from my participation in this study, I may contact Dr. Maureen Nummelin, the Director, Office of Research Ethics, at 1-519-888-4567, Ext. 36005 or maureen.nummelin@uwaterloo.ca.

With full knowledge of all foregoing, On behalf of the patient, I agree to participate in this study.

YES NO

Name: _____ (Please print)

Signature: _____

Date: _____

Researcher:

Name: _____ (Please print)

Signature: _____

Date: _____

Appendix 8: Feedback Letter

**WATERLOO
PHARMACY**

SCHOOL OF PHARMACY | UNIVERSITY OF WATERLOO
Health Sciences Campus, 10 Victoria Street South, Kitchener, ON, Canada N2G 1C5
MAILING ADDRESS: 200 University Avenue West, Waterloo, ON, Canada N2L 3G1
519-888-4499 | fax 519-883-7580 | pharmacy.uwaterloo.ca

Date

Dear *(Insert Name of Participant)*,

I would like to thank you for your participation in the study entitled “**Assessing medication adherence in patients with memory concerns**”. As a reminder, the purpose of this study was to determine the most feasible method to assess medication taking behaviour that is best suited for use in population with memory concerns.

The data collected during this study will contribute to a better understanding of the appropriate medication adherence assessment tool in a clinical setting. This, in turn, will help clinicians identify the medication adherence behaviours of the visiting patients.

Please remember that any data pertaining to you as an individual participant will be kept confidential. Once all the data are collected and analyzed for this project, I plan on sharing this information with the research community through seminars, conferences, presentations, and journal articles. If you are interested in receiving more information regarding the results of this study, or would like a summary of the results, please provide your email address, and when the study is completed, anticipated by January, 2015, I will send you the information. In the meantime, if you have any questions about the study, please do not hesitate to contact me by email or telephone as noted below. As with all University of Waterloo projects involving human participants, this project was reviewed by, and received ethics clearance through a University of Waterloo Research Ethics Committee. Should you have any comments or concerns resulting from your participation in this study, please contact Dr. Maureen Nummelin, the Director, Office of Research Ethics, at 1-519-888-4567, Ext. 36005 or maureen.nummelin@uwaterloo.ca.

Zain Hudani, B.Pharm.

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