A Mixed Methods Systematic Review of the Barriers and Facilitators of Medication Regimen Adherence in Primary Care Patients with Alzheimer's Dementia and Related Disorders

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ABSTRACT

Background: The prevalence of Alzheimer's disease and related disorders (ADR) is increasing worldwide due to population aging. It is estimated that one in five baby boomers will be affected. These patients, often treated in primary care, frequently have numerous co-morbidities which require complex medication regimens. Adherence to medications in these patients is poor with important effects on disease outcomes. The adherence to medications is influenced by multiple factors and has been synthesized in frameworks of adherence, but these are either not dementia specific, or not comprehensive enough, or lack information about the impact of identified factors on adherence. **Objectives:** To develop a comprehensive and dementia specific framework on adherence to any prescription medications and to synthesize the influence of factors on adherence to medications.

Methods: We did mixed methods systematic review of qualitative, quantitative and mixed methods studies published in MEDLINE, PsycINFO, EMBASE, and CINAHL up to October 2013. In the first phase, qualitative evidence was synthesized through an inductive-deductive thematic analysis; a comprehensive and dementia specific framework was thus proposed. In the second phase, based on the new framework, a narrative synthesis of the influence of identified factors was provided. In the third phase, through integrating the output of the first and second phases, a synthesis of the direction of influence of factors of adherence to any prescription medications was provided. **Results**: From 4560 references, we retained 34 articles of the following designs: 26 quantitative, 6 qualitative and 2 mixed methods studies. Factors of medication adherence to any prescription medications can be categorized in five categories: patient factors, caregiver factors, patient and caregiver factors, prescriber and other healthcare professional (such as nurses and pharmacists) factors (labeled as prescriber for the rest of the thesis) and healthcare system factors. Two sub-categories of factors have major importance for patients, caregivers and prescribers: "behavioral" and "treatment and support". For each sub-category, a list of specific factors was provided. The influence of specific factors on adherence was organized as: possible barriers, possible facilitators, factors with no impact, factors for which contradictory evidence exists and factors for which the impact on adherence has not been measured yet. **Conclusions:** The comprehensive and dementia specific framework and the direction of influence of specific factors on adherence can inform efficient interventions for

increasing adherence to medications. Based on the influence on adherence, suggestions for clinical practice and for future studies are provided.

RÉSUMÉ

Contexte : La prévalence de la maladie d'Alzheimer et des maladies apparentées (MA/MA) augmente partout dans le monde du fait du vieillissement de la population. On estime ainsi qu'un baby-boomer sur 5 sera atteint. Ces patients, pris en charge la plupart du temps au sein des services de soin de santé primaire, sont souvent atteints de comorbidités multiples qui nécessitent des associations médicamenteuses complexes. Ils ont une observance thérapeutique sous-optimale ce qui a un retentissement important sur leurs résultats thérapeutiques. L'observance est influencée par de nombreux facteurs, qui ont été conceptualisés dans des modèles théoriques. Cependant, aucun modèle ne concerne spécifiquement les démences et aucun modèle ne prend en compte l'ensemble des dimensions et des facteurs identifiés dans la littérature. **Objectifs:** développer un modèle théorique de l'observance thérapeutique aux médicaments en général multidimensionnel et spécifique des démences. Réaliser une synthèse des connaissances sur les facteurs influençant l'observance thérapeutique. **Méthodes:** Il s'agissait d'une revue systématique, réalisée selon des méthodes mixtes, des études qualitatives, quantitatives, et mixtes publiées dans MEDLINE, PsycINFO, EMBASE, et CINAHL jusqu'à Octobre 2013. Dans un premier temps, une analyse inductive-déductive réalisée sur les études qualitatives a permis de proposer un modèle théorique de l'observance thérapeutique multidimensionnel et spécifique des démences. Dans un second temps, une synthèse narrative de l'influence des différents facteurs identifiés a été proposée, en se basant sur notre modèle théorique. Dans un troisième temps, en tenant compte des résultats des deux premières phases, une synthèse des types d'influence des différents facteurs identifiés a été proposée. **Résultats**: De 4560 références 34 articles ont été retenus : 26 études quantitatives, 6 études qualitatives, et 2 études mixtes. Les facteurs associés à l'observance thérapeutique aux médicaments en général se répartissaient en cinq catégories : facteurs associés au patient, à l'aidant, ou au duo patient/aidant, au prescripteur ou au système de santé. Deux sous catégories de facteurs avaient une importance primordiale pour les patients, les aidants et les prescripteurs : « comportemental » et « traitement et soutien ». L'influence des facteurs sur l'observance était décrite ainsi : barrière possible, facilitateur possible, absence d'impact, existence de données contradictoires, aucune donnée d'impact disponible à ce jour.

Conclusions: Ce modèle théorique de l'observance thérapeutique aux médicaments multidimensionnel et spécifique des démences et l'identification du type d'influence qu'ont les différents facteurs sur l'observance thérapeutique peuvent aider à la construction d'interventions efficientes pour augmenter l'observance thérapeutique. A partir de nos résultats sur les facteurs influençant l'observance, des suggestions pour la pratique clinique et les recherches futures sont proposées.

INTRODUCTION

According to the World Health Organization, Alzheimer's disease and related disorders (ADR) is "perhaps the 21st century's most serious health challenge" and it "urges countries to view dementia as a critical public health priority"[1]. Due to increased life expectancy, the prevalence of Alzheimer's disease will explode in the next decades; close to 20% of Canadian baby boomers are expected to develop ADR in their lifetime[2].Over 60% of persons with cognitive impairment are diagnosed with Alzheimer's dementia[3] which is a chronic disease characterized by a progressive functional and cognitive deterioration leading to death[4], [5]. Alzheimer's disease is one of the main causes of disability in older people[6]. Worldwide, ADR contributes to 11.2% years of life lived with disability, which is greater than cerebral vascular accident (9.5%), heart disease (5%) and cancer (2.4%)[7]. Moreover, patients with Alzheimer's disease have a mean of 2.4±1.4 co-morbidities[8], making caring for those persons much more complex. It requires coordination across multiple sectors of care, including caregivers' involvement[2], [9] and important financial expenditures as the disease progresses [10]. We witness a shifting trend from long-term care towards home and community based care and from specialists visits towards an increased role of family physicians in diagnosing and managing these patients[10]. Primary care physicians and professionals are best positioned for treating patients with ADR in line with the patient-centered concept of care; three Canadian consensus conferences on ADR recommend that treatment of those patients should be primarily the responsibility of primary care healthcare professionals[11].

Pharmaceutical treatment of patients with ADR is of paramount importance, not only for co-existing morbidities but also for the treatment of dementia per se. Alzheimer's dementia specific medications are generally efficient on the disease evolution by ameliorating cognitive performance, improving global functional status, alleviating behavioral disturbances and decreasing caregiver burden[12]. Dementia specific medications, while not curing the disease, can delay the progression of the disease and nursing home placement[13].

Poor adherence to any prescription medications is associated with increased incidence of complications, increased frequency of institutionalization, disability and premature death[14]. Adherence is defined by the WHO as "The extent to which a person's behavior-taking medication, following a diet, and/or executing lifestyle changes- corresponds with agreed

recommendations from a health care provider."[15]. Persons receiving medications for chronic conditions have lower adherence compared to those treated for acute conditions[16]. The adherence to cholinesterase inhibitors (dementia specific medications) is sub-optimal, as reflected by 40-60% persistence at 12 months after initiation of treatment[12], [17] or 0.627 (± 0.124) probability of continuing the treatment with Donepezil (a cholinesterase inhibitor) at 6 months[18].

A multitude of factors have been described so far as having an impact on medication adherence, both in patients with dementia and patients without cognitive disorders. These factors are organized in frameworks which in turn inform interventions with the ultimate goal of increasing adherence to medications. Examples of factors with impact on adherence include but are not limited to: patients' motivation and health related beliefs, education, number of chronic conditions, disease severity, number of medications, dosing and administration, economic factors such as cost of treatment, quality of relationship with healthcare providers and adequate follow up, expectations of treatment benefits, and demographic factors[17], [19], [20]. Some frameworks of adherence to treatment are based on reviewing only qualitative[17] or quantitative[19] data on adherence, some frameworks are dementia specific[17] while others are not dementia specific[19], [20]. While existing frameworks offer a good theoretical basis, they offer very limited guidance pertaining to the influence of the factors on adherence to medications[17], [19], [20] and cannot be used as is to inform the development of innovative clinical interventions.

As shown in a Cochrane review, multiple complex interventions targeted to improve adherence to medication have been implemented so far but even the most effective interventions were not able to contribute to important improvement in adherence[21]. A possible explanation is represented by interventions informed by theoretical frameworks of adherence not comprehensive enough or by using in the same intervention multiple theoretical models without knowing which is better, because there is a paucity of studies comparing theoretical models of adherence and their components[22].

Consequently, it is important to organize the factors of adherence to any prescription medications in patients with ADR in a comprehensive framework based on a systematic review of the literature by including qualitative, quantitative and mixed methods studies on adherence.

Moreover, assessing the influence on adherence of identified factors represents a prerequisite for generating more efficient interventions for improving adherence to medications. Therefore, in this review I have addressed the following research questions: "What are the factors that influence adherence to medicines in patients with Alzheimer's dementia and related disorders treated in primary care?" and "What is the influence of these factors on the adherence to medicines in patients suffering from dementia?"

LITERATURE REVIEW

I. Prevalence and physiopathology of dementia

According to DSM-5, dementia belongs to Neurocognitive Disorders (NCD)[23]. Based on etiology, in DSM-5 dementia is sub-classified in following entities: Alzheimer's disease, frontotemporal lobar degeneration, Lewy body disease, vascular disease, traumatic brain injury, substance/medication use, HIV infection, prion disease, Parkinson's disease, Huntington's disease, another medical condition, multiple etiologies, and unspecified[23]. Among them, Alzheimer's disease and vascular dementia are the most frequently diagnosed[10]. Alzheimer disease (AD) alone represents 63% of all dementia patients[10].

The global prevalence of AD is estimated at 44 million and is predicted to double every 20 years until 2040[10].The WHO has characterized the worldwide increase of the prevalence of dementia by calling it a "dementia epidemic"[10]. By 2038, the percentage of Canadians with dementia is projected to increase from 1.5% (in 2008) to 2.8%,representing 1,125,200 Canadians[10]. Due to this trend, the burden on all those involved in the care of these patients, doctors, nurses and caregivers, is expected to increase tremendously, along with the annual economic burden which is expected to increase from $15 billion in 2008 to $153 billion in 2038[10]. The prevalence of dementia in nursing homes is estimated at 50%[24]. We witness a shifting trend from long-term care beds towards home respectively community based care (where informal caregivers play a paramount role), and from specialists visits towards an increased role of family physicians (primary care) in diagnosing and managing these patients[10].

AD is a progressive, neurodegenerative and fatal brain disease characterized by a progressive deterioration of cognitive function –including language, judgment, orientation, decision making, learning and memory- as a consequence of progressive and irreversible loss of

neurons, especially in the cortex and hippocampus [10][17][25]. The mechanisms of neuronal degeneration have not been clearly elucidated but strong neurochemical evidence suggests that AD is the result of impaired cholinergic neurotransmission caused by loss of cholinergic neurons[25]. A broadly accepted mechanism is represented by the decreased level of choline acetyltransferase – the enzyme responsible for synthesizing the neurotransmitter acetylcholine- in the cortex and hippocampus; additionally, evidence suggests that the level of depletion is correlated with cognitive impairment[25]. Dementia can be the result of multiple cerebral infarcts, can be categorized as dementia with Lewy bodies, can accompany chronic HIV infection[26]or Parkinson's disease[27], and has been described also in rare genetic diseases such as Huntington chorea.

Parkinson disease (PD), besides typical extrapiramidal motor manifestations, is frequently associated with dementia and depression[27]. The association of cognitive spectrum manifestations with depression in PD is especially troublesome, creating diagnostic difficulties and negatively impacting the management of the disease, because of the correlation between psychiatric symptoms, cognitive impairment and impaired adherence to treatment[27][16].

In HIV infected individuals, the associated neurocognitive disorders can range from asymptomatic neurocognitive impairment to mild neurocognitive disorder or even dementia[26]. In this category of patients, three main mechanisms are believed to be responsible for the cognitive impairment: 1) the HIV neurotropism 2) the adverse effects of the antiretroviral treatment and 3) the result of substance abuse before the HIV infection[26]. Cognitive deficits associated with HIV infection are similar to those seen in other subcortical-frontal disorders, as for example in Alzheimer's disease, and include impairment of concentration and attention, lower psychomotor speed, delayed information processing, and negative effects on executive functioning and verbal memory[26]. In line with advances in HIV treatment, the plethora of cognitive manifestations has changed; fatal subcortical dementia has been replaced by a chronic inflammatory disease which is addressed by long term medical treatment[26].Therefore, we witness an increased prevalence of minor cognitive problems in HIV infected individuals which now occur in patients with controlled viral loads and high CD4 counts; this suggests that HAART (highly active antiretroviral therapy) does not have the capacity of totally eliminating cognitive degeneration[28].

II. Management of patients with dementia

A. Pharmacological treatment of patients with Alzheimer's disease

It is more complicated to address medical problems in patients with dementia than in non-demented patients. This is largely explained by their decreased decisional capacity, decreased ability to adhere to treatment plans and to signal adverse effects of medication[25].

Worldwide, the medication management of AD relies on two classes of medications: cholinesterase inhibitors (tacrine, donepezil, rivastigmine, galantamine) and the NMDA (N-methyl-D-aspartate) receptor antagonist memantine[25]. Cholinesterase inhibitors contribute to preserving neuronal signal transmission by decreasing the degradation of acetylcholine in the synaptic cleft. The first agent approved was tacrine but it rarely used because of its known hepatotoxicity[25]. Donepezil and galantamine are known for reversibly inhibiting acetylcholinesterase while rivastigmine inhibits both acetyl and butyrilcholinesterase[12]. Additionally, they prevent the degradation of acetylcholine and possess an anti-inflammatory effect[12]. Donepezil, galantamine and rivastigmine have largely the same clinical benefits and are prescribed in various proportions based on individual tolerability, physician experience and cost.[25]. The second class, represented by memantine, is effective by inhibiting the excitatory effects of glutamate which has been involved in the physiopathology of neurodegenerative diseases such as AD. Memantine is a noncompetitive NMDA receptor antagonist and has a remarkable safety and tolerability profile due to its strong voltage dependency and rapid blocking/unblocking kinetics[25]. Acetylcholinesterase inhibitors (AChEI's) are approved in Europe for the treatment of mild to moderate AD while in the USA Donepezil has been approved by the FDA for all stages of the disease. Memantine, on the other hand, is indicated in moderate to severe AD either alone or in combination with other AChEI's [12].

The prescription of these medications is reinforced by international guidelines based on randomized controlled trials which have proven favorable clinical effects of these medications, not only on cognition but also on behavior- due to the fact that behavioral and psychological manifestations have been frequently signaled-, function, global status and caregiver burden[12]. Other long term benefits have been described, as for example lowering the risk of nursing home placement by 47% after one year- compared to untreated patients- and a 40% decrease of the

risk of nursing home placement after 18 months of treatment[13]. Examples of international bodies who jointly recommend the prescription of AChEI's are the American Academy of Neurologists (AAN), the National Institute of Clinical Excellence (NICE) in England and Wales, and the European Federation of Neurological Societies (EFNS)[12].

In Canada, the most prescribed medicine class in the management of Alzheimer's disease is represented by acetylcholinesterase inhibitors which are viewed as first line medicines[29]. Optimal management of medicines in dementia includes achieving and keeping for a significant period of time the recommended acetylcholinesterase inhibitor dose[30].

B. Challenges of care in dementia patients

The management of patients with dementia is complex and includes involvement of multiple layers of healthcare providers. It is estimated that more than 70% of AD patients live at home and that caregivers are mostly informal, represented by family (most frequently spouse or children) or a friend[31]. Frequently, spousal caregivers are also older persons and display coping difficulties[31]. On the other hand, younger caregivers have additional responsibilities related to their professional, social and family life, and have to permanently find solutions for managing the task of care-giving, which becomes more and more time consuming and emotionally and physically stressful as the diseases progresses[31]. Therefore, it has been shown that AD significantly impacts the quality of life (QoL) of the patient-caregiver dyad[17]. Due to the short life expectancy (3-8 years) of these patients, stabilizing symptoms and delaying the progression of the disease represents realistic goals which positively impact the QoL of both the patients and their caregivers[17]. Sustained medication use permits delaying the decline of cognitive symptoms but complying with the medication regimen represents a significant challenge for both caregivers and patients[13]. Approximately 73% of AD patients require assistance in managing their medications[25].

Older adults take more medications and many of them have polymedication due to multiple chronic diseases. Canadian and U.S. studies have shown that prescription medicine utilization increases dramatically with age, especially among women[32]. Older adults have greater sensitivity to medications, more frequently develop adverse effects and suffer from multiple chronic conditions which are treated with multiple medicines[32]. Pharmacodynamics and pharmacokinetics of medicines are influenced by physiological changes -considered normal

in older adults -such as: decreased renal function, slower liver metabolism, reduced body water and fat, and changes in the number of receptors for medicines[33]. These particular characteristics encountered in older adult patients and specific barriers to medication –which are exhaustively described later on- impact medication utilization by making older adults vulnerable to incorrect medication management [32].The response to medications of older adults does not follow a predictable pattern and requires lower doses for minimizing toxicity and adverse effects while maintaining therapeutic goals [32].

Given that patients with AD are prescribed many medications due to other chronic conditions, maintaining an optimal level of adherence is challenging.

III. Adherence to medication regimens in patients with Alzheimer's dementia and related disorders

A. Definitions

Adherence is defined by the WHO as "The extent to which a person's behavior-taking medication, following a diet, and/or executing lifestyle changes- corresponds with agreed recommendations from a health care provider."[15]. Adherence, often used in medical research interchangeably with compliance has been described by Becker and Maiman as: "the best documented but least understood health behavior"[19]. It usually includes three key aspects: initiation, persistence-which represents taking the medicine for the recommended time interval- and compliance, which implies respecting the recommended timing, dosage and frequency[34]–[36].

In the past, "medication compliance" was the preferred term but the trend has changed, with researchers nowadays using more and more the term adherence[32]. This can be explained by the fact that "compliance" is suggestive of a unidirectional relationship between the healthcare provider and the patient -where the patient is supposed to follow instructions without being given the chance to provide a feedback based on personal opinions- thus placing the whole responsibility of adequate medication related behavior on the patient[32].Feedback from patients is a valuable aspect, especially when complicated or expensive medication regimens are prescribed; by being open to patients' opinions, healthcare providers show that they are considerate of the lifestyle, habits and socioeconomic status of the patients[32].Consequently,

adherence can be better defined as an "active, voluntary, collaborative involvement of the patient and provider to produce a desired preventive or therapeutic result" [37]. Basically, the new concept acknowledges that the patients should have the last word in deciding their own therapy[37]. In line with the bi-directional concept of adherence, prescribers have the opportunity to evaluate the patient's position vis-à-vis adherence and recommend the most appropriate intervention[32].

B. Prevalence of non-adherence

Due to unprecedented population aging in developed countries, (on the American continent referred to as "the graying of America" [32]) many research projects have targeted adherence to any prescription medications among older adults, especially because of age associated multiple morbidity[32]. In persons over 60 years, non-adherence to medication regimens varies between 40 and 75%[32].Individuals suffering from chronic conditions have lower adherence rates as compared to those having acute diseases [16]and the adherence decreases significantly after 6 months of treatment; therefore, only 40-60% of patients with chronic diseases are adherent to treatment[32][13]. In a trial of assessing the use of donepezil in AD patients, authors concluded that only 52.5% of new patients were still taking the medication after six months of treatment[18]. Because this study exclusively used pharmacy claims, the authors could not conclude what the reason for discontinuation was[18]. Non-adherence can occur because of under- or over –utilization of medicines or by incorrect dose scheduling; under-utilization is the most frequently encountered form of non-adherence[32][13].Non-adherence in the US population is considered a major public health issue with negative consequences on health; it is also associated with increased healthcare costs[14]. Pertaining to its influence on health, poor adherence is associated with increased incidence of complications, increased frequency of institutionalization, disability and premature death[14]. As a result, researchers are constantly trying to find solutions for measuring and improving medication adherence in older adults.

C. Measurement of adherence to medication

Measuring adherence to any prescription medications remains a challenging task in older adults, partly because of cognitive impairment, multimorbidity, polypharmacy and altered

pharmacokinetic and pharmacodynamics response to medicines as previously mentioned[14]. Despite the importance of properly assessing medication adherence, no particular method (direct or indirect) has proven its reliability even in the hands of pharmacists; this is valid for measuring adherence in both young and old individuals[32].

Evaluation of adherence in studies using automated (claim) databases include medication possession rate (MPR) and discontinuation rate (often named "persistence")[38]. MPR is a measure of medication availability (also referred to as proportion of days covered PDC) and is defined most frequently in the following ways: a) "(number of days supply obtained during observation period/number of days in observation period) X 100" or b)" (number of days supply obtained (excluding last refill)/number of days between first and last dispense date) X 100"[38]. Adherence measured by MPR (or PDC) is dichotomized into adherent and non-adherent based on the MPR value; most authors consider patients adherent if MPR>80%[38]. Medication discontinuation on the other hand focuses on termination of medication re-fills; frequently, a patient is considered to have discontinued a specific therapy if no refill occurs within 60 days of depletion of the prescription (gaps of 30 and 90 days are sometimes used for defining discontinuation)[38]. Another measure of adherence in studies using automated (claim) databases is represented by switching therapies[38]. However, in this review, switching was not considered an outcome of interest because dementia therapy is a prescription therapy and I consider that when switching occurs, it is the result of a doctor's decision; therefore, the patient remains compliant with the prescribers' recommendation while receiving another dementia-specific medication.

Frequently used indirect methods for evaluating adherence include prescription refill records or pill counts; both are considered to be potentially biased because of failing to prove that a patient is actually taking the medication; sometimes patients or caregivers discard the medicines and return empty containers[16][32]. Medication (re) fill measurement method is considered safe, correlates well with plasma levels of medicines, physiological markers and self-reported adherence, while offering real-life information pertaining to medication use[14], but it requires that all prescriptions be delivered through the same administrative source[39]. Electronic monitoring of administration implies recording the dosage of the medication on a microprocessor, allowing researchers to count the number of doses administered, and the interval between doses[16]. On the other hand, reports from patients or caregivers are considered

highly unreliable, along with estimations from physicians[32].Patient interview and doctor's evaluation (e.g. clinical control vs. no control) can rapidly detect noncompliance but only in 50% of cases[39]. An example of a validated tool for assessing adherence is the Morisky-Green test (MGT), which can be administered to the patient or caregiver and consists of four questions[16]. In a study evaluating adherence to medications of Parkinson disease patients, neurologists perceptions revealed 93.6% adherence while the MGT test found only 60.5% of patients adherent to treatment[16].

Objective measurement such as biomarkers (direct method) is often difficult because of: logistic reasons (transportation issues), difficult interpretation caused by age related changes in metabolism and unavailability of testing methods for some medicines[14][39].

Some authors consider that the most practical method of evaluating adherence in older adults is to gather information related to medication administration from caregivers as part of an open and compassionate relationship[32]. Others consider medication (re)fill a very appropriate method assuming that patients filling a prescription also take it[14]. Other researchers consider electronic monitoring the most reliable way to evaluate adherence even though it is an expensive method which is cumbersome to use in clinical routine[16].

Consequently, because of potential biases linked to any evaluation method mentioned, it is recommended to use a combination of methods whenever medication regimen adherence is assessed[32].

Many studies that evaluated medication adherence and persistence are based on retrospective analyses of administrative healthcare databases or pharmacy claims taking into account dispensation of medicines and not the real-life intake of the medicines by the patients[17]. Persistence with AD medicines at 12 months after treatment initiation is considered by most authors to be in the range 40-60%[12], [17]. Two Canadian studies in which the use of oral AChEI's was evaluated concluded that the persistence at 12 months after starting the treatment was 40-54%[17]. Generally, persistence with AD medicines is low and it is accepted that older adults are at risk of early discontinuation of medication, especially when displaying cognitive impairment[12].

Most available studies pertaining to adherence were restricted to oral medicines without considering over the counter medications (OTC's)[32]. A study focused on administration of

OTC's (including herbal products) in older adults found that well educated seniors living in the community were using on average 5.9 prescription medications, 3.5 OTC's and 0.4 herbal products daily. Self-medication is an important aspect in the medication management of older adults because this class (OTC's and herbals) can interfere with prescription medicines and physicians are often not aware or are not specifically inquiring about additional medication use by their patients [32][39].

D. Factors that negatively impact adherence (Barriers)

Factors influencing adherence to treatment have been extensively described in the literature. Consequently, in the following pages I have synthesized current evidence pertaining to adherence in people with cognitive impairment and dementia.

a. Patient related

Cognitive disorders and co-morbidities

In older adults, one should be highly suspicious of cognitive impairment. It is known that with the process of aging, the prevalence of chronic diseases increases[13]. Therefore, this population group should be holistically regarded from the point of view of factors which influence medication adherence.

The following chronic diseases are predictors of medication non-adherence: chronic obstructive pulmonary disease, breast cancer, hypertension, congestive heart failure and glaucoma[32]. As highlighted by a study evaluating factors impacting adherence to medication in Parkinson disease patients, participants with cognitive impairment were 2.1 times (CI 95%; 1.24, 3.61) more likely to display poor adherence to treatment[16]. Generally, cognitive impairment (MMSE score less than 24) and decreased visual memory skills are considered an important barrier to medication adherence and these barriers become more and more important as the disease progresses[17][16][32].In HIV infected individuals, deficits in memory, decision making and problem-focused strategizing are linked to poor adherence to antiretroviral medication[28]. Multiple studies have clearly recommended the need to avoid medications that can impact cognition in patients with coexisting cognitive impairment; this recommendation is difficult to follow especially in complex patients with multiple chronic diseases accompanying

their cognitive decline[40]. Among psychiatric pathologies, depression has been signaled to be a barrier to medication adherence[16][32][41].

In HIV infected individuals -who often have cognitive impairment- a plethora of barriers to treatment have been described: younger age, low socioeconomic status, female gender, ethnic minority groups especially when English is not the mother tongue, medication regimen complexity, co-morbidities (depression) and active recreational drug use[28].

Health literacy and beliefs

Health literacy, defined as the ability to read and understand medication instructions for patients and act accordingly is also considered a barrier to medication adherence [32].Furthermore, there is evidence that in older adults poor health literacy is associated with increased mortality[42]. Poor understanding of instructions on how to administer medication has also been identified as being a barrier to medication adherence in HIV infected patients[26]. Poor understanding of medical instructions can also be caused by language barriers[42].Evidence exists that in Parkinson disease patients, adherence is related to their education level[16].

Patient knowledge, understanding and beliefs about their disease appear to play an important role in medication adherence, as better adherence was found in those who understand their disease and the consequences of not following the recommended treatment[32][43]. In patients with cognitive impairment, two specific barriers of adherence are: 1) difficulties in understanding how to administer new medications and 2) not being knowledgeable of the treatment plan[44]. Qualitative research studies highlight following important aspects linked to medication non-adherence in older adults: low faith in their physician in diagnosing a disease and recommending the proper treatment, the effectiveness of prescribed medication and the beliefs about the disease itself[17]. Besides the understanding and awareness of illness, specific personality traits such as a high level of independence and high self confidence have been reported to have a negative influence on adherence[41]. In a study which evaluated discrepancies between self-reported adherence and evaluation of adherence by caregivers, it was found that there were important differences between the reports, especially in patients who relied on themselves to take medications[41]. In a study conducted by Monane et al, the authors found that medication adherence was significantly better in patients who had eight or more recent

physicians visits[19]. This suggests once again that highly independent patients not accepting external help are at risk for low adherence to medications.

In patients with dementia and their caregivers, disappointment with treatment results when using prescription medicines –especially because it has been signaled that stabilization of the disease is not highly valued-can be followed by intentional non-adherence and increasing interest for alternative medicines[17][13][32]. In these situations it is important that the physician agrees with the patient and caregiver upon realistic treatment goals[13]. Unrealistic expectations from the treatment especially affect treatment with AChEI's, because as mentioned before, these medicines do not stop the evolution of the disease but are effective in treating symptoms. Some authors signaled that intentional medication non-adherence can be as high as 71%, the most frequent reasons being the feeling that the medication is not needed (52%) or causes adverse events (15%)[32] Another term used for intentional non-adherence is "intelligent non-compliance" which implies that older adults who reside in the community -thus preserving a high level of independence- decrease the recommended dose, mainly because of adverse effects with the hope that the treatment remains effective[24].

Cultural beliefs are another barrier of treatment adherence as in some cultures (Hispanic and Chinese patients) it is believed that AD is part of the normal aging process; in these situations help is only requested later in the evolution of the disease[17].

Decline of physiological processes

Another recognized barrier is related to decreasing visual acuity, swallowing and feeding difficulties and manual dexterity; consequently older adults are rendered, to various degrees, unable to differentiate pills based on their color and shape, to open medicine bottles and to swallow the medicines[17][32][40][43][41]. In HIV infected individuals, motor control impairment caused by peripheral neuropathy has the potential to prevent patients from properly taking medications[28].

In the incipient stages of the disease, AD patients are often involved in managing their own medication but as time passes their physical abilities diminish even though many patients remain unaware of their grade of impairment and continue to trust their capacity of self managing the medications[17][32]. Under these circumstances, additional medicines required for

treating superimposed chronic conditions in these patients only complicate the medication management process[17].

Behavioral manifestations of dementia

A somehow distinct category of barrier is represented by behavioral symptoms characteristic of the clinical picture of the patients with Alzheimer's disease; these symptoms are represented by wandering, socially inappropriate behavior, active resistance to care and verbal or physical abuse[40]. It is noteworthy to mention that some medicines, besides affecting cognition may trigger behavioral symptoms, thus complicating the medication management[40].

b. Caregivers

Caregivers play a paramount role in the management of patients with Alzheimer's disease and related dementia from early onset of disease; sometimes adherence in AD patients is "caregiver driven"[17][13]. The caregiver strain is another recognized barrier of adherence to medication in AD patients; strain is a "normal" outcome of their long term care-giving commitment[13]. Old caregivers themselves are prone to risk factors linked to poor adherence because of multiple co-morbidities often encountered in older adults, decline in cognitive function- a study highlighted that 12% of caregivers were suffering from dementia as well- , psychiatric pathologies (especially depression), physical abilities, etc. Therefore, caregivers may face difficulties in assisting patients with the medication management, including scheduling and safety issues[17][44]. On the other hand, their involvement in assisting patients with medication may vary because of the overestimation of the patient's ability to take medications or because of their expectations from the treatment or specific preferences for route of administration and dosing schedule[17]. When caregivers are not able to recognize medication adherence issues, the situation becomes even more complicated -patients often deny their condition or minimize their symptoms in front of the physicians- because physicians lose their only reliable source for assessing the adherence level: the caregiver[13].Unsatisfactory patient-caregiver relationship has been also linked to poor medication adherence[44].

Factors of medication non adherence in elders suspected of being abused or neglected were analyzed in a study which revealed that the three most important factors involved in non-

adherence were caregiver neglect (37%), dementia (24%), mental illness and lack of family and social support (15%)[45].

c. Healthcare provider

Not only do patients' beliefs appear to be important but also physicians' beliefs which can impact both treatment adherence and persistence; if physicians are not satisfied with treatment results they may stop the treatment altogether[17]. A particular situation is represented by poor clinical results due to treatment non-adherence; in this circumstances, physicians may incorrectly discontinue treatment (e.g. donepezil) assuming that the prescribed medicine is not efficient[13][18].

Another typical case where poor adherence to medications complicates the medication management process is represented by patients with Parkinson's dementia. In these patients, non adherence can be misinterpreted as poor efficacy of the recommended medicines leading to changes in doses and administration schedules –already complicated especially in advanced stages-which in turn can generate adverse effects further responsible for decreasing adherence[16].

Physicians' position related to the treatment can be viewed as a barrier to adherence especially when physicians do not comply with treatment guidelines- e.g. when physicians do not see any clinical benefit of the treatment- or when the poor relationship quality between physician and the patient-caregiver dyad precludes frequent contact and open communication[17][13].

Even though initially documented in nursing home residents, community patients may as well display "enforced compliance" which is the result of receiving medication for a long period of time without dose adjustments and/or revisions; this aspect becomes even more important when healthcare providers (nurses and physicians) or caregivers are not aware of the adverse effects of medication[24]. The result of such a situation can be prescribing of new medicines - because the adverse effects are wrongly interpreted as new symptoms- giving rise to the so called "prescribing cascade" which eventually leads to polypharmacy[24].

It has been proved –as one would expect- that caregivers and physicians do not share the same opinions pertaining to aspects related to care such as: disease etiology, adherence, dosage

of medicines, etc, drawing authors to the conclusion that improving communication between healthcare providers and AD patients and their caregivers may help in addressing divergent opinions about the disease management[17]

d. Medication therapy

Adverse events

Patients' tolerability of any prescribed medicine is an important barrier to adherence as a relationship between adverse effect of medications and poor adherence has been proven[17][44]. Special attention is needed when prescribing some specific medicines to older adults because these have been associated with high incidence of adverse events such as: warfarin, hypoglicemics and digoxin[43]

The most frequent adverse events of AChEI's are gastrointestinal (nausea, vomiting, diarrhea) while administration of memantine is mostly linked to headache and dizziness. These effects are prominent at the initiation of the treatment or when attempts are made to maximize the dose but they gradually wear off as the treatment continues[12]. A difference in adverse effects related to the administration of AChEI's has been noticed between patients suffering from AD as compared to those with moderate cognitive impairment (MCI)[46]. Thus, AD patients treated with AChEI's more often experienced depression, dizziness, headache and nausea/vomiting than their counterparts[46].

Polymedicine, polypharmacy and frequency of administration

Adverse reactions to medicines are important barriers to adherence in the context of polymedicine and polypharmacy which are frequently encountered in older adults. It is important to make the distinction between the two terms: polymedicine refers to the administration of multiple medications in patients with multiple chronic conditions while polypharmacy represent an unwanted but yet frequently encountered situation characterized by "duplicative" medications, drug-drug interactions and insufficient attention to pharmacokinetics and pharmacodynamics in older adults[39]. Concurrent use of zero to four medicines is not considered polypharmacy while use of five to nine medicines is considered polypharmacy and more than 10 medicines excessive polypharmacy[40]. In a study, 73% of adverse reactions in

older adults were attributed to unnecessary medicines, drug-drug interactions or contraindicated medications[39].

Older adults residing in the community often have at least one unnecessary medication,- meaning medicines with no identifiable indication or medicines with probably little benefit at the time of prescription- especially if the patients have multiple prescribers or have been recently hospitalized[43]. A study performed in Quebec demonstrated that the use of multiple physician prescribers was the most important determinant of polypharmacy (drug-drug interactions) in persons 70 years and older[39].

It is important to mention that adverse events can cause cognitive impairment per se (especially in older adults) which in turn acts as a barrier to medication adherence; in a study, it was found that the risk of adverse reactions expressed as cognitive impairment was augmented at least nine times in patients receiving more than four medicines[39]. Guided by the estimated life expectancy of these patients and the time needed for a specific treatment to be followed by clinical benefits, excessive polypharmacy could be avoided in this specific segment of patients[40].

Older adults are frequently treated with multiple medicines as showed by a US survey which concluded that half of community-dwelling patients over 65 years use more than five prescription medications and OTC's per week[42]. Even though multiple medicines are prescribed to these patients, opinions about the influence on adherence by the number of medicines are divided; some authors believe that an increased number of medications (more than four daily) represents a barrier to adherence[16][13][44] while others argue that seriously ill patients may actually be more aware of the risk of complications/need of treatment if they do not comply with the treatment[24][19].

Evidence shows that patients taking multiple medications for the same disease were as adherent as patients treated with only one medicine; conversely, those who took different medications for different conditions displayed lower adherence[19]. Therefore, the frequency of administration appears to be a more important determinant of adherence; this opinion is reinforced by systematic reviews which proved that interventions targeted at simplifying dosing may be effective[24]. Once and twice daily regimens have no significant impact but in the case of three times daily administration the adherence can decrease to 52% and with four times daily

to 42%[32].Medicines administered once a day may not represent a solution for improving adherence because if the patient forgets to take the pill on a specific day he becomes automatically 100% non-adherent on that day. It is believed that in time -because administration errors can be repetitive- the initial advantage brought by the convenient once daily administration can become insignificant[41].

e. Demographics

Socio-economic status

Another important barrier to adherence is represented by the socio-economic status of the patient[19] and quality of life[16]. High cost of medications is therefore considered a barrier to adherence[41][44]. When asked about the cost of medications, older adults who believed that medicines were expensive displayed a lower adherence to medication than those who believed the contrary or expressed no opinion[19]. A possible solution to this is prescribing lower cost generic alternatives (where available); reducing medication cost has positive influence on the patient's financial well being in general[43].

Age and gender

Age per se appears not to be a predictor of non-adherence[19], especially because it has been proven that generally older adults are aware of the purpose of 88 % of their medications[43]. Studies of adherence have shown that age can be associated either with improved or decreased adherence[41]. A study among patients diagnosed with AD in the US found better adherence in patients 86 years old compared to those aged 75(OR=1.4, 95%CI:1.13-1.74, p=0.001)[44]. The same study found that male patients with AD have a better adherence than females; generally gender is not considered associated with adherence problems[19]. In line with previous results, Monane et al found in a study based on health administration data that adherence in participants aged over 85 was higher or equal to 80% (which is considered a good adherence level)[19].

Ethnicity

Ethnicity represents a barrier to medication regimen adherence: authors of a retrospective cohort study concluded that adherence in whites was significantly higher than in blacks (OR=0.55 for blacks, 95%CI, 0.44-0.68)[19].

In a US study designed to determine whether AChEI's are used less often in minority groups compared with white patients with AD, the authors found that minority patients have lower rates of AChEI's use than their white counterparts even after adjusting for covariates such as demographics, health insurance status, severity of disease or co-morbid diseases[45]. In the same study, minority ethnicity was associated with 40% lower odds of AChEI's use (OR 0.6; 95% CI: 0.5 to 0.7). A smaller proportion of minority participants (25% African American, 26% Asian, 26% Latino)reported current use compared with white patients (37%) at $p<0.001$[45]. Another study using the Veterans Health Administration database of more than 56,000 patients showed that minorities (African Americans and Hispanics) were less adherent to Alzheimer's medications than Caucasians[44]. Same results were obtained in another study from a state Medicaid program which concluded that persistence to AD medication was higher in Caucasian patients compared to non-Caucasians (74% vs. 52%, $p<0.001$)[44].

E. Facilitators of adherence

a. Administration of medicines

Simplifying medication regimens, as for example recommending once-daily administration, acts as a facilitator to improving medication adherence[25][13][41]. The following medications are suitable for once-daily administration: donepezil, memantine and galantamine (all three oral form) and rivastigmine (patch)[25]. Whenever once-daily administration is possible, evidence exist in favor of morning administration for improving adherence[41]. In a study of persistence with AD medications using a national healthcare administrative database in Ireland, the authors concluded that patients were more adherent to once-daily formulations (patients treated with donepezil and galantamine) compared to multiple daily doses of rivastigmine; in this study the rivastigmine patch was not available[12]. The same study showed that a combination of AD medications (in this case memantine and donepezil) almost doubled the time to non-persistence[12].

Covert administration refers to concealing medications in foods or drinks; this practice is mostly adopted as a measure to manage AD medications in nursing homes rather than in ambulatory patients; a study conducted in Norway highlighted that 17% of nursing home dementia patients were administered medications in a concealed form[24]. The main reason for

administering medicines covertly in nursing homes is non-compliance of patients, especially when refusing to take the medicines or spiting them out[47]. Dementia represents one of the factors that triggers covert administration of medicines in nursing homes, especially antiepileptics, antipsychotics, and anxiolytics[47].

b. Patient and caregiver level

Another facilitator of adherence is represented by empowering patients to participate in their own care. Empowerment is associated with increased self-efficacy, better clinical outcomes and increased quality of life[24]. Empowering patients increases adherence to medicines most probably by decreasing voluntary non-adherence. A way to empower caregivers in the medication management process is to recommend delivery modes which allow better control of administration such as skin patches[13][48]. Besides being simple to use and delivering constant therapeutic levels of the active ingredient –thus reducing adverse effects[31]-, patches (e.g. rivastigmine patch) also represent a visual reminder that the medicine has been administered and offers the possibility of rapid removal if adverse effects become a threat because of accidental overdose[13].Respecting caregivers preferences pertaining to administration of medicines can act as a facilitator of adherence because studies have demonstrated higher preference of caregivers towards patches as compared to oral medications for Alzheimer's disease[31][41]. The main reasons evoked by caregivers in preferring the patch over oral AD medications, in decreasing order of importance, are: ease of use, the patient can self-administer, easier to integrate with the schedule of other concomitantly administered medicines and fewer adverse effects[31].

Cultural and ethnicity determinants influence the attitude towards physicians' recommendations; a positive attitude -as shown in a study involving Japanese participants- was associated with better adherence levels while suspicious attitudes vis-à-vis the doctor's competency and reasons for prescribing certain medications – as shown in another study involving members of the African-American ethnic group- was associated with lower adherence[41].

Pertaining to adherence to antiparkinsonian therapy in patients with Parkinson dementia, facilitators of adherence are represented by higher knowledge of the disease (62.8% vs. 51.02%; $p=0.04$), good control of disease symptoms (63.6% vs. 46.25%; $p<0.001$), being married versus other marital status (63.4% vs. 51.5%; $p=0.037$) and higher income[16]. Parkinson disease

patients displaying a higher awareness of their symptoms and good knowledge of the disease were more frequently categorized by their physicians as adherent to medications compared to their counterparts[16].

In HIV infected patients with cognitive impairment -because of complicated dosage schedule and increased number of medication- it has been suggested that creating and maintaining a daily routine of various activities can act as an important facilitator of maintaining high levels of adherence to medicines[28].Daily rituals have been proven to be efficient in AD patients as well and doctors are advised to recommend cues to their patients for improving medication adherence[25].

c. Healthcare provider

A good relationship with the physician is considered a facilitator through increasing the number of routine visits. A one year retrospective study of persistence to treatment with rivastigmine or donepezil proved that patients who visited their physician's office six or more times were less likely to discontinue or switch AD medicines than patients who had less encounters with their doctor[13]. A few decades ago (1957), Balint underlined the role of transference in the patient-physician relationship which has positive influence on the medication management[41].

Taking into account difficulties of cognitively impaired patients to follow medication schedule recommendations, a facilitator of adherence is to constantly review the complete list of medications[25] because of frequently encountered discrepancies between healthcare recommendations and patients' understanding related to the treatment scheme[43]. Maintaining a detailed log of medication utilization – which could include symptom evolution, adverse effects, perceived barriers of medication administration- can help the medication management process and provide useful information to the physician[27].

Where available, social workers can play an important role in facilitating adherence by encouraging the patients to constantly fill out the medication log[27]. General recommendations for improving medication handling refer to encouraging the use of pill organizers, blister packs, and electronic dispensing devices[43].

Involvement of the pharmacist in medication management is viewed as a facilitator to adherence; among other advice, pharmacists utilize prescription-refill reminders and specific packaging designed to facilitate adherence[19]. Maximizing visual recognition through implementing distinct shape and color of medication and packaging is considered to positively impact adherence to medications in cognitively impaired patients[13].

By negotiating realistic treatment goals with the patients and their families and/or caregivers, unrealistic expectations are avoided; thus, voluntary non-adherence is minimized[43]. The caregiver's role in medication adherence in patients with dementia has been insufficiently described[41] despite the fact that as patients lose autonomy in the course of the disease, motivating the caregiver to actively participate in the medication management probably has a facilitating influence on adherence[41]. Ensuring a good patient-caregiver relationship is considered a prerequisite of good adherence, especially in patients concerned about their memory problems, because concerned patients are considered more likely to use external strategies for remembering to take their medicines[41]. Skilled social workers, by mobilizing family and environmental supports, can facilitate a good treatment adherence level[27].

A facilitator of adherence is represented by the availability to doctors of specific medication lists, containing medicines which are not recommended/should be avoided if possible for/in older adults. Taking into consideration these recommendations by the physicians can improve adherence[43]. On the other hand-depending on the socio-economic status of the patients-prescribing lower tier (cheaper) medications for AD has been associated with improved adherence[44].

Due to encountered difficulties of patients with cognitive impairment in understanding treatment instructions, it is advisable to make additional efforts in explaining the treatment; this approach should include writing additional notes pertaining to the dosing schedule, asking the patient and/or the caregiver to describe in their own words the treatment plan and possible adverse effects[43].In clinical practice, on the other hand, awareness of poor adherence as a consequence of cognitive decline is low; therefore, education of healthcare providers is considered a facilitator for improving adherence levels[41].

Implementing a healthcare advocate for each patient, in charge with coordinating the patient's overall care is a proposed facilitator of adherence which acts primarily by reducing

polypharmacy[42]. Other facilitators would be improving communication with healthcare providers and asking patients or caregivers to bring all medications (including OTC's) with them to each visit; this would permit the physician to permanently evaluate the need of each medicine and eliminate those considered inappropriate[42]. Additionally, research has suggested that involvement of a geriatrician in the care chain of AD patients can act as a facilitator of medication adherence primarily by reducing the number of prescribed medicines[40].

d. Pharmacogenomics

An aspect under development which can bring spectacular advancement in the treatment of various diseases, including Alzheimer's disease, is represented by pharmacogenomics. The potential of pharmacogenomics lies in the fact that the efficacy and safety of medications vary from one individual to another, sometimes significantly[49]. This can be explained by genotypic variants of different enzymes and proteins that influence the efficacy and safety of a medicine[49]. By mapping these genetic differences, particular medicine administration can become personalized with the goal of increasing efficacy, minimizing adverse effects and increasing adherence[49]. These effects will in turn produce better therapeutic effects and disease management overall, including unnecessary costs as a result of unnecessary health service use[49]. This field is in the early stages of development as reflected by the results of an online survey conducted in 2011 with 284 pharmacists in Quebec which concluded that: a) the majority of pharmacists (95.6%) would recommend pharmacogenomics testing if this could help predict efficacy or safety/adverse effects of medicines and b) less than 8% of pharmacists feel properly trained for advising patients on how to take medicines based on pharmacogenomic test results[50]. According to my knowledge, no study has been published yet in regards to personalized treatment of dementia patients.

F. Interventions to increase adherence

There is a continuous debate on what is more appropriate: to implement individual or complex interventions for increasing medication adherence. Randomized controlled trials of interventions designed with the goal to increase adherence have mixed results and are often complex, containing multiple interventions applied simultaneously[43]. According to Haynes et al (2008), even the most effective complex interventions implemented failed to contribute to

significant improvement in adherence and therapeutic outcomes[21]. Complex interventions are implemented in the hope that individual interventions have cumulative effect; unfortunately, in trials containing complex interventions, it is difficult to evaluate the efficacy of each intervention taken individually[43]. Another rationale behind testing of complex interventions is when evidence exists that individual interventions are not effective. For example, Steinman et al (2010) suggested that education in oral or written form is efficient but not as solo interventions; they also suggest that getting feedback from patients or their caregivers on their understanding on how to use medications after receiving the recommendation can positively contribute to adherence[43].

Using pillboxes and home delivery services increases medication adherence as reported by Blais and Kergoat in a Canadian study evaluating adherence to AD medicines using administrative databases with no comparison group[51]. The authors found an exceptionally high adherence (measured using MPR) to acetylcholinesterase inhibitors as a class of 93.5% (95% CI =93.1–93.8%) in these patients which can only be explained by the use of pillboxes[51], considering that adherence in this category of patients is usually reported at 40-60%[12], [17].

In HIV patients the most efficient interventions to improve adherence, based on a review of the literature conducted by Uldall et al in 2004, were complex and involved information, counseling, medication reminders, involvement of external support such as family and supervision of medication administration[37].

In the management of AD disease, many strategies for improving medication adherence have focused on drug delivery alternatives. Examples include extended-release tablets (galantamine), rivastigmine skin patch and once-daily administration of donepezil[17].

The utilization of a computer telephone system (CTS) intervention in a randomized controlled trial (Leirer et al 1991) that involved 16 patients living in community with a mean age of 70.9 showed that the voice mail system for reminding patients to take medications has been followed by an improved adherence ($P<0.05$)[52]. Analyzing the satisfaction of caregivers with CTS revealed that caregivers in the intervention group were more satisfied with human interaction[52].

In a study conducted by Kripalani, using both postcard refill reminders and illustrated medication schedule interventions were successful in improving adherence (37% versus 31% in usual care) but no benefit in the subgroup with cognitive impairment was obtained[44]

Interventions which maintain a high frequency of contact with patients and/or caregivers might represent a good approach in improving adherence to medication. Another effective approach towards improving adherence would be to implement interventions that promote human communication rather than automated services(e.g mail)[44].

IV. Key points of adherence

i. The increasing prevalence of dementia worldwide represents a major public health issue which has mobilized important human and financial resources in the process of finding solutions for managing this health problem.

ii. Older adults affected by dementia are often affected by multiple chronic conditions that require treatment with multiple medicines. Due to age related particularities, multiple co-morbidities and inappropriate adherence to any prescription medications, the management of this category of patients is complicated.

iii. Multiple methods of measuring adherence to any prescription medications are currently used with variable effectiveness. Therefore, it is important to pay attention to the method(s) used to measure the adherence to medication regimens.

iv. A vast number of barriers to medication adherence in older adults have been identified but there is a paucity of studies pertaining to adherence to medication in dementia patients.

V. Existing frameworks of factors impacting medication adherence

Barriers and facilitators of adherence have been systematized in a number of frameworks in the last three decades. Balkrishnan (1998) proposed a framework of factors that influence adherence to all types of medication in older adults, based on a review that included only quantitative studies[19]. Factors predicting medication non-adherence were structured in the following categories 1) Demographics: age, race, gender, socioeconomic status, support, 2)

Medical variables: self reported health status, number of chronic conditions, disease severity, 3) Medication related factors: medication class, number of medications, dosing and administration, packaging and reminders, 4) Economic factors: reimbursement, monthly cost, perceptions of patients related to costs, 5) Physician-patient interaction: number of visits to doctors, communication of medication instructions, 6) Patients' health related beliefs and knowledge: motivation, required length of treatment[19]. In this study, the process of identifying factors relies only on quantitative data, does not provide a ranking of importance of identified factors, and includes information pertaining to all kind of medications, not only those directed towards treating AD.

Murray et al (2004) developed a conceptual model of medication adherence adapted for older adults with chronic heart failure, independent of their cognitive status[20]. They identified three major categories: environmental, health care system related and patient related[20]. The authors defined as external environment the patient's home and community characteristics, including: relationship with family members and community, economic development status, level of stress and violence; weather conditions were included because extreme temperatures can impede the ability of older adults to continue treatment[20].Health care system related factors include: "the policies, resources, organization, and financial arrangements influencing the accessibility, availability, and acceptability of medical care services (e.g., physician supply)."[20]. Insurance status, availability and cost of transportation to healthcare facilities were also considered important factors. Patient characteristics were divided in "Predisposing characteristics" such as: knowledge, attitudes, beliefs and expectations, cognitive status, health literacy, age, etc, "Enabling resources" including: income, distance to health service, transportation, insurance, relationship with healthcare providers, level of support and "Need" which comprises perception of illness including its severity and reaction to prescription medication[20]. Again, the framework does not evaluate the importance of identified categories in achieving a good level of adherence and is not tailored for patients with dementia.

Driven by the importance of a good adherence to cholinesterase inhibitors in the treatment of patients with AD, Brady et al (2013) proposed a framework based on a non-systematic review[17]. Determinants of non-adherence were categorized as intentional (patient and prescriber beliefs) or unintentional (patient, caregiver and prescriber factors)[17]. Examples of intentional factors include: 1) patient related: beliefs related to AD disease, unrealistic

expectations, low confidence in physicians, 2) physician related: unrealistic expectations of treatment benefits, quality of relationship with patients and caregivers and 3) caregiver related: unrealistic expectations of treatment benefits[17]. Examples of unintentional factors include a) at the patient level: age related sensorial and motor limitations, co-morbid illnesses, medications' adverse effects, b) at the physician level: resistance in switching treatments, lack of knowledge of patients' beliefs and c) at the caregiver level: overestimation of the patient's ability to administer medication, caregiver health status, preference for medication delivery mode[17]. This framework derives from a narrative description of qualitative studies and does not provide data on the importance of identified factors in determining the level of adherence. It does not include system related factors as for example treatment cost, demographic factors, etc. and is restricted to adherence to acetylcholinesterase inhibitors.

The proposed frameworks offer a good overview of the various factors that have to be accounted for when designing interventions for improving adherence but none is fully comprehensive. Unfortunately, these guidelines -derived from other frameworks (Murray et al 2004), from analyzing quantitative evidence only (Balkrishnan 1998) or qualitative data only (Brady et al 2013) - do not provide a comparative assessment of the importance of different factors in maintaining an optimal level of medication regimen adherence. Moreover, these frameworks (with the exception of Brady's framework) are either not specific for dementia patients or too specific by highlighting only factors that affect adherence to cholinesterase inhibitors (Brady et al 2013).

In a review of 38 systematic reviews on effectiveness of interventions to improve adherence to medications in general (patient with various pathologies and medication regimens), authors highlighted that theoretical approaches (e.g. technical, behavioral, educational, social support) only partially explain the effectiveness of adherence interventions[22]. According to a Cochrane review, less than half of medication adherence interventions are successful for long term treatments and the majority of these are complex interventions which contain components from different theoretical approaches[21]. Interventions informed by multiple theories (complex interventions) make the task of deciding which theoretical approach is best even more difficult[22].

In conclusion, it is important to provide a comprehensive list of factors that influence adherence to medication regimens specific to dementia patients, to organize the factors in a systematic way and to assess their direction of influence on adherence (e.g. facilitators, barriers, no influence) The created knowledge will better inform the development of more effective interventions for increasing long term adherence to medicines in older adults with dementia spectrum diseases.

RESEARCH QUESTIONS AND OBJECTIVES

The aim of the study was to deliver a comprehensive portrait of factors influencing adherence to medicines in patients with Alzheimer's dementia and related disorders in primary care, in order to provide guidelines for clinical practice and facilitate the development of interventions for improving adherence to medications in this category of patients.

The following research questions were addressed:

i. What are the factors that influence adherence to any prescription medicines in patients with Alzheimer's dementia and related disorders treated in primary care?

ii. What is the influence of these factors on the adherence to medicines in patients suffering from dementia?

The general objectives were to develop a comprehensive and dementia specific framework on adherence and to synthesize the influence of factors on adherence to medications while the specific objectives were:

i. To propose a preliminary framework based on existing reviews on adherence.

ii. To synthesize current literature on factors of adherence to any prescription medications in patients with Alzheimer's disease and related disorders in order to develop a comprehensive and specific framework.

iii. To summarize existing quantitative evidence on factors that influence adherence in dementia patients.

iv. To assess the direction of influence (barrier, facilitator, no impact) of the identified factors on adherence by using the comprehensive and dementia specific framework and a synthesis of the quantitative evidence.

METHODS

I. Background and methods overview

In order to answer the two research questions, the review included both a qualitative and a quantitative component. Generally, it is accepted that the philosophy behind qualitative and quantitative studies is significantly different even though in practice researchers frequently apply both methodologies, making the reality less dichotomized[53]. While qualitative studies mostly fall in the constructivism ideal type –which include idealism, relativism and subjective arguments-, quantitative studies are the opposite, being guided by post positivism- which include materialism, realism and objective arguments[53]. It is accepted that logical empiricism is related to the nineteenth century positivism and includes the post-positivistic philosophy of the twentieth century[53]. My general position pertaining to this research was post-positivistic due to the fact that I assumed that multiple factors impacting adherence had been already identified and that the review contains a quantitative synthesis phase necessary for providing an answer to the quantitative question.

The qualitative question (first research question) emerged from the assumption that there were factors which had not been highlighted yet and that newly identified and already identified factors could be re-grouped and explained in a way which reflects more accurately the management of patients suffering from Alzheimer's disease and related disorders.

Moreover, by answering the quantitative question (second research question), the study provides an accurate synthesis of the impact of factors on adherence to medications (narrative synthesis) and a synthesis of the direction of influence of these factors through integrating qualitative and quantitative evidence.

When combining in a review studies with diverse design –e.g. qualitative, quantitative and/or mixed methods- the review can be best defined as a mixed studies review[53]. This

approach in synthesizing data from studies with diverse designs represents an emerging form of literature review and has gained momentum especially in public health with the purpose of designing and evaluating interventions and programs[53]. By including both qualitative and quantitative studies in a review the researcher joins the power of both approaches in generating rich explanations with a value beyond of data which could be generated by separately reviewing quantitative or qualitative studies [54]. In mixed studies reviews, researchers engage in a preplanned fashion two different methods based on their goals: in this review, the motivation was to answer both a qualitative and a quantitative question[53][54].

The most relevant mixed studies review designs are: a) sequential, which comprise two distinct entities: sequential exploratory and sequential explanatory and b) convergent, which can be convergent qualitative or convergent quantitative[55]. Convergent synthesis designs consist of addressing either a quantitative (convergent quantitative) or qualitative (convergent qualitative) question while sequential synthesis designs address both a qualitative and a quantitative question[55]. In sequential explanatory design studies, the quantitative question is answered first and informs the second phase of the study (qualitative) which has the goal to explain (hence the term explanatory) the results of the first phase, while in sequential exploratory design studies the qualitative question is answered first and the results inform the quantitative phase which follows[55].

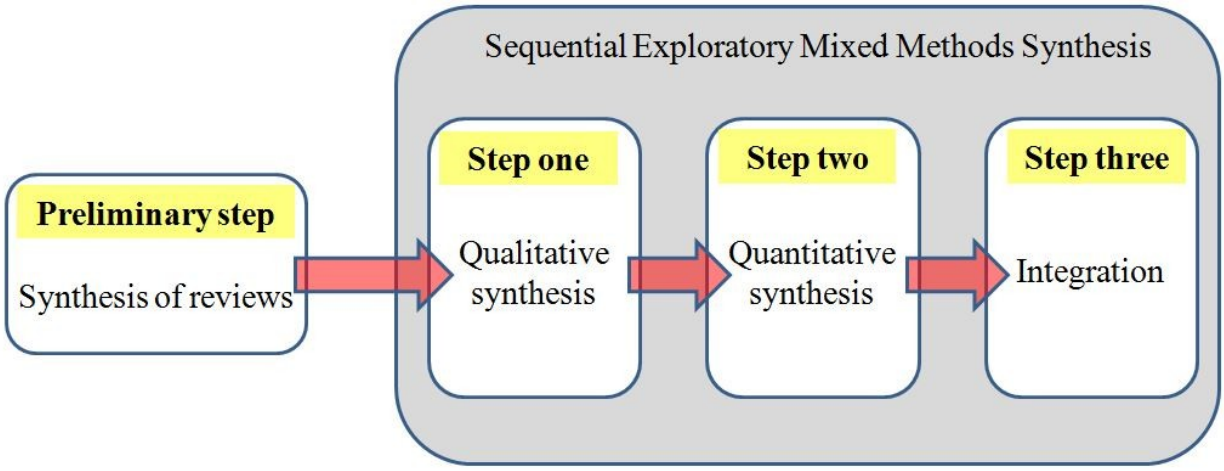
The goals of this review were to answer first a qualitative question ("what are the factors…?") and then a quantitative question ("what is the influence of the identified factors…?"). Addressing the quantitative question was informed by the answer of the qualitative question. Consequently, I decided to structure the review based on the sequential exploratory synthesis design. As mentioned before, the sequential exploratory synthesis (review) begins with a qualitative (Qual) phase which informs the next phase, the quantitative (Quan) synthesis[53][55]. In the Qual phase, the researcher analyses all studies retained for the review and generates a qualitative output by applying qualitative data analysis methods[53][55]. In the subsequent phase (Quan) the outcomes of interest –as suggested by the qualitative phase- are extracted and synthesized (pooled). Consequently, the researcher proceeds to integrate the results by comparing the results of the qualitative phase with the extracted quantitative evidence[53][55]. In summary, the most important features of the sequential design are: 1) the two methods (phases) are linked meaning that the researcher proceeds to the Quan phase based

on the results of the Qual phase and 2) results of the two phases are integrated (compared) in the final analysis step[53][56].

In summary, as depicted in Figure 1, the preliminary step of the synthesis was to develop a "preliminary framework" by integrating factors of adherence described in the reviews by Brady, Balkrishnan and Murray[17], [19], [20]. The preliminary step was based on data from reviews and not on the final set of included studies and had the role of informing the first step of the sequential exploratory mixed methods synthesis: qualitative synthesis. In the qualitative synthesis step, we identified factors of medication adherence in patients with Alzheimer's disease and related disorders. The preliminary framework was adapted and the output of the qualitative synthesis was a comprehensive and specific framework of factors influencing adherence (called "final framework" for the rest of the document). During the second synthesis step, we conducted a quantitative synthesis in order to summarize available quantitative evidence of factors influencing adherence in dementia patients. In the last step (integration), we provided a synthesis of the direction of influence of the factors described in the final framework on adherence to medications in patients with dementia and related disorders.

Both the methods and reporting of this systematic review were informed by the PRISMA statement for reporting items for systematic reviews and meta-analyses[57]

Figure 1- Summary of methods



II. Review phases according to PRISMA

A. Information sources and search strategy

The following electronic databases were searched by a Solidage Research Group librarian (MG): Medline, PsycINFO, EMBASE, and CINAHL. All searches have been performed in 2013, the last date of search was September 24th for Medline, October 3rd for PsycINFO , October 6th for EMBASE, and October 17th for CINAHL. The search strategy was developed jointly together with my supervisor (IV), co-supervisor (EK) and the librarian (MG). The search strategy for Medline provided in Appendix 1 was adapted by the librarian for the other databases.

B. Identification of relevant studies

After retrieving relevant records from the four databases based on the search strategy, only journal articles were retained, resulting in exclusion of conference articles, theses, books, book sections, dissertations etc. The following information was extracted from the four databases and exported to MS Excel: author, publication date, name of journal and abstract. The selection process unfolded in two phases based on inclusion and exclusion criteria mentioned below. In the initial phase, articles were selected based on information available in titles and abstracts. In the subsequent phase, retained articles were read in full and the final set of articles was identified based on pre-defined inclusion criteria. The selection process in both phases was performed by myself and an additional reviewer, (MB), Research Assistant at "Solidage" McGill University - Université de Montréal Research Group on Frailty and Aging. For articles in German, my co-supervisor (EK) was consulted. Full agreement was reached at the end of the first phase while disagreements in the second phase were mediated by my supervisor (IV). Three articles qualified for mediation and two were retained for the final review.

In the first phase, the following inclusion criteria were applied: 1) Qualitative studies of any methodology (e.g. phenomenology, grounded theory or qualitative descriptive studies, etc) OR 2) Quantitative studies: surveys, observational studies or intervention studies, OR 3) Mixed methods studies of all designs, AND 4) Description of factors (barriers and facilitators) of medication adherence, AND 5) Population: patients with dementia (and related disorders) receiving medicines (any medicine) or physicians or pharmacists or nurses or caregivers AND 6)

Setting: primary care, AND 7) Outcome measure: medication adherence, AND 8) Languages: English or French or German.

Exclusion criteria of articles based on titles and abstracts were: commentaries or letters or recommendation only, reviews, no dementia in patients, only therapeutic effects assessed, study of safety or efficacy only with no adherence data, data on developing of screening tools only, information on physiopathology of dementia only, information on etiology of AD (or related disorders) only, information restricted to diagnostic or screening procedures, study protocols, only pharmacokinetics, setting not in primary care (e.g. hospitals or nursing homes or long term facilities, etc).

C. Selection of references

In the second phase (based on full text articles), the inclusion criteria described for the first phase remained in place and two additional exclusion criteria were applied: a) dementia in less than 50% of participants recruited in the study as we wanted to develop a specific framework for patients with dementia and b) unimportant functional limitations resulting from cognitive impairment. When the article included a combination of different populations and did not provide the percentage of patients suffering from dementia, we looked at the percentage of patients with functional limitations. If the proportion of participants with important functional limitations – assessed by Instrumental Activity of Daily Living (IADL) or Activities of Daily Living (ADL) scores- in a study was <50%, the study was excluded.

Examples of validated tools used by authors of studies under review to assess dementia were: Mini Mental State Examination (MMSE), Clinical Dementia Rating (CDR) Scale, Alzheimer's disease Assessment Scale-cognitive subscale (ADAS-COG), etc.

D. Data collection

General data extracted include: a) basic study characteristics (author, year, country, and design), b) characteristics of study participants (sample size and description of participants), c) study objective(s) and d) how adherence data were collected and measured (outcome). The mentioned information is reported separately for qualitative and quantitative studies (see Appendix 2) and the appraisal score for each study has been appended to the table.

I consider it important to mention that qualitative data collection was done separately from the quantitative data collection despite the common pool of studies under consideration. By doing so, I was able to increase the accuracy of the process of collecting data by focusing on each methodological approach (qualitative or quantitative) individually.

Qualitative data collection consisted of extracting qualitative raw data without any interpretation or analysis and storing it separately for each study in a Microsoft Office Excel table. Qualitative studies –in which data were collected by authors from interview and focus group responses-, provided rich experiences and insights from patients, informal and formal caregivers, physicians, pharmacists, etc. For example, one of the patients explained his motivation for taking medications, "I'm taking my medication...Is it the medication that will keep me...as sane as I am now? If I keep on with my medication, is that the answer?"[58]. On the other hand, in quantitative studies different variables hypothesized as having influence on adherence were explored. Each piece of information (from qualitative or quantitative studies) was stored individually as a separate entry in an Excel table while marking it with a number corresponding to the study it was extracted from. Examples of qualitative data (factors or variables) extracted from quantitative studies include: “age”, more than 4 medications”, “adverse effects”, “health literacy”, “oral medications”, “dysphagia status”, “functional status”, “depression” “out of pocket cost” etc. For studies which provided both qualitative and quantitative information (mixed method studies), the data extraction followed the same rationale and as the raw data were stored for further analysis. The result of the data collection process was a list (sum of lines in Excel) of statements and variables/factors all related to medication adherence in dementia patients living in the community.

Quantitative data collection was done, as previously mentioned in a separate phase from the qualitative one. It comprised extracting quantitative evidence (e.g. proportions, means, odds ratios, and hazard ratios) for each factor hypothesized as having influence on the outcome (adherence). Collected data were saved in Excel one by one for each included study. The data were organized in a systematic way –meaning it corresponded to the already decided themes- to facilitate further analyses by sorting according to desired criteria.

E. Appraisal of included studies

Appraising the quality of included studies represents a prerequisite for delivering highly valid results and conclusions. There are multiple appraisal tools available to researchers, some of them designed for appraising only qualitative studies, as for example the CASP (Critical Appraisal Skills Program) tool for appraising Qual studies, while other tools are for appraising only quantitative studies, as for example the CASP tool for Quan studies (additional information is available at http://www.casp-uk.net)[53]. I have decided to use a tool which allows assessing studies of various designs (Qual, Quan or mixed methods). The mixed Methods Appraisal Tool (MMAT) is a validated and reliability tested tool developed at McGill University which comprises of a total of 19 methodological quality criteria for appraising quantitative (randomized controlled trials 4 criteria, non-randomized studies 4 criteria and quantitative descriptive studies 4 criteria), qualitative (4 criteria) and mixed methods studies (3 criteria) which are scored on a nominal scale (Yes/No/Can't tell). Thus, for quantitative and qualitative design studies the maximum score is 4 out of 4, while for mixed methods studies the maximum score is 11 and is calculated by adding the score of the qualitative component with the score of the quantitative component (depending on the design of the quantitative component) and with the score for mixed methods studies based on 3 criteria as mentioned before. A full description of the MMAT tool is available at: http://toolkit4mixedstudiesreviews.pbworks.com[53]. In line with the systematic review methods guidelines, the appraisal was done independently by me and a PhD student in the Family Medicine department (QNH); all disagreements were successfully mediated between the two reviewers. For the two articles in German I have translated the articles and QNH appraised them independently. Currently, there is a conflicting view about including in the final review of articles based on their quality; some authors recommend including only high quality articles, others recommend including both categories[59]. Due to the lack of consensus, I have decided to include in the final analysis all articles independent of their quality. The appraisal score is reported separately for qualitative and quantitative studies along with the general data extracted (Appendix 2); additionally, the appraisal score of quantitative studies is also provided in Appendix 4.

F. Synthesis

a. Preliminary step: developing a preliminary framework of adherence

As previously stated, none of the proposed frameworks represent an ideal description of the factors impacting medication adherence in patients with dementia. Therefore, I have developed a preliminary framework with the goal of improving the synthesis process. The adapted framework -based on the work of Brady R (2013), Murray M. (2003) and Balkrishnan R (1998) - was developed guided by the objective of making it more comprehensive in terms of categories, subcategories and factors.

b. Step one: qualitative synthesis

The qualitative input has both a "discovery-oriented" and a "development-oriented" motivation [60]. The discovery-oriented goal pertains to revealing new factors which influence adherence to medicines while the development-oriented motivation permits a better understanding and re-grouping of the new identified topics with those already included in various frameworks[60]. In other words, the development-oriented qualitative work- which means reorganizing factors- complements the discovery-oriented approach – which means discovering new factors-, permitting a "fine tuning" and improvement of existing frameworks. A better understanding can be achieved by looking at factors impacting medication adherence across a variety of studies and settings and by combining them into meaningful categories. The new set of created categories (themes) can ensure that these are relevant to a broad spectrum of individuals by involving a broad experience of respondents and can be equally useful in testing the accuracy of existing theoretical models[61]. Various qualitative data collection methods used by authors of included qualitative articles are relevant for my discovery and development goals. These include for example focus groups, and unstructured or semi-structured individual interviews[62]. Obviously, some of the original qualitative data collection methods can be discovery or development oriented per se, being for example discovery oriented focus groups or development oriented interviews [63]. The initial purpose of the data collection in included qualitative articles was less important for my work; of importance was the richness of the data provided –including quotes of participants' experiences-which further permitted an adequate analysis. From quantitative studies, qualitative data was collected by looking at how

independent variables were coded (e.g. age, visits to doctors, religion, etc); then, their meaning was analyzed together with "pure" qualitative data from qualitative studies.

A meaningful qualitative data analysis method employed in published sequential synthesis design studies is represented by thematic analysis[53], [64]–[66]. We analyzed the entirety of the result section of each qualitative article. As usual in thematic analysis, themes are identified through an iterative process which includes reading the studies multiple times; it represents a step by step process in which initially subcategories are created, then by merging subcategories the analysis produces categories which eventually are merged into themes. Therefore, themes are essentially the result of a "comparative process which allows investigators to describe, organize and interpret study results"[53]. Thematic analysis can be conducted in three major ways: inductively, deductively or inductive-deductively[53]. Inductive thematic analysis, also called theory building approach implies moving from data to theory; in other words, themes and eventually theories are created based only on the qualitative data analyzed[53]. As opposed to the inductive approach, when qualitative data is analyzed (e.g. coded) based on pre-existing theories, the approach is called deductive[53]. In my study, I applied a "hybrid" analysis method, involving both the deductive approach (when organizing qualitative data based on existing frameworks) and the inductive approach in which new factors impacting adherence were identified. Deductively, I coded the material based on categories extracted from my preliminary framework while in the inductive process I remained open to new codes. The coding process relied on a coding scheme which was developed iteratively during the process. Rigor in analysis of qualitative data can be obtained by a) "going back and forth from textual data to themes" and b) involving an additional researcher in analyzing the meaning of developed subcategories, categories and themes[53]. The themes were developed by me and their accuracy was confirmed independently by my primary supervisor (IV) and one of the members of the thesis committee (CT). The theme development process was reported in a transparent way by giving selected quotes extracted from qualitative studies and examples of qualitative data from quantitative studies in order to illustrate the analysis process. This approach enables the reader to easily understand how the final framework (comprehensive and dementia specific) of factors impacting medication adherence was developed from the preliminary framework during the qualitative analysis phase.

Qualitative data analysis started with assigning information to one of the five major categories identified in the preliminary framework displayed in Figure 3. Each piece of data was assigned a number from one to five in line with one of the five categories: "Patient factors", "Caregiver factors", "Prescriber/physician factors", "Healthcare system related factors" and "Economic factors". During the process, based on the observation that some information was common for both patients and caregivers, a new category was created called "Patient and Caregiver Factors" along with a corresponding code. Additionally, I have decided to merge the categories "Healthcare system related factors" and "Economic factors" into a single category called "Healthcare system" based on the fact that factors related to cost of medication and insurance are covered by the generic category "Healthcare system". For example, in Canada the public insurance system ensures a quite homogeneous coverage of costs associated with medications and medical care across provinces, even though differences in coverage and healthcare related services exists from one province to another. For countries with a less developed public healthcare coverage, in my opinion, the insurance status and final cost of medications are still a consequence of the organization of the healthcare system. Therefore, the initial step of assigning qualitative information to categories was largely a deductive process based on the categories proposed in the preliminary framework. It also had an inductive component where a new category was formed and two initial categories were merged into a single component.

In the next phase, I grouped the already coded qualitative data into the categories mentioned before and I started the inductive-deductive analysis process in a successive order for each category. The first step was deductive and consisted of grouping the raw qualitative data from my table around the proposed themes found in the preliminary framework. The process was supplemented by an inductive process during which new themes emerged; this was the case when qualitative data could not be matched with the themes obtained after the deductive analysis.

Finally, all themes were listed according to the sub-categories they belonged to (medical, medications, behavioral and socio-demographic) and a new sub-category was created in an inductive way, called "Treatment and support". This new sub-category replaced the preliminary framework "Other" category for caregivers and prescribers and proved to be adequate in

organizing themes in the "Patient factors" category and in the newly created "Patient and caregivers" category.

Reporting the output of the first (Qual) phase was inspired by the work of Pluye, Mills and Keating who propose a cross-tabulation of the themes (and subthemes) with the individual qualitative and quantitative studies which contributed to the development of individual themes[64]–[66]. By doing so, the reader quickly comprehends the composition of themes and how these are spread across the analyzed studies of various designs (the whole pool of included articles)- see Appendix 3.

Reporting the output of this phase concluded with providing a comprehensive and dementia specific framework (final framework) of factors that influence adherence to medications in patients with dementia and related disorders.

c. Step two: quantitative synthesis

The quantitative (Quan) part, as previously mentioned, followed and was informed by the qualitative (Qual) phase. As opposed to "classical" mixed methods studies of Qual -> Quan design where the Quan phase has the role of generalizing the qualitative findings- as for example in the process of developing surveys or experiments based on results of previous qualitative research[67]-, in my synthesis the Quan phase served a different goal. The goal was to assess the influence of different factors on the level of adherence to medicines in patients with dementia. Therefore, the fundamental logic of the Quan phase was to bring added value to the qualitative phase and to be able to answer the quantitative question.

As mentioned before, data pertaining to adherence was extracted from all included quantitative studies based on the variables assessed in each study and saved in the MS Excel sheet which already contained the output of the qualitative synthesis: themes, sub-categories and categories. Two more columns were added. One with the purpose of organizing the studies into the following categories: database, observational and interventional. The other, with the purpose of organizing the results based on their statistical significance. Quantitative data was excluded from the analysis if no statistical significance test was reported in the respective study. As an example, if results were reported in percentages but no statistical test was performed to highlight significant differences between groups, then the quantitative evidence was excluded from the

final analysis. Based on this strategy, results of individual studies were either partially excluded from the quantitative synthesis (e.g. some of the results were tested for significance and others not) or fully excluded (meaning no statistical test was done at all).

A common way of reporting data from quantitative studies is by narrative review (synthesis)[59]. In narrative reviews (synthesis), the researcher reports the number of statistically significant and statistically non-significant results separately for each included study. The results are accompanied by commentaries pertaining to the relevance of the individual results to the overarching goal of the review[59]. Examples of this approach include the work of Pluye et al[64] and Keating et al[66]. The authors organized the results of the quantitative synthesis by themes -which were identified in the preceding qualitative synthesis step- and reported the results in percentages (range) or/and odds ratios with confidence intervals. In this review, results of quantitative synthesis -organized by categories and factors (themes) in line with the final framework of factors impacting medication adherence-, were reported separately for observational, claim data-base studies and interventional studies. It was not possible to conduct a meta-analysis because of the heterogeneity in the measurement of independent variables (factors) and different measurement techniques for adherence.

d. Step three: integration

Firstly, for enabling an overview of the influence (barrier, facilitator or no impact) of different factors on adherence, evidence was displayed by using an integration matrix (Appendix 4). The rows represent the factors of adherence (as displayed in the final framework) and the columns the reference numbers of the quantitative studies analyzed. In the intersecting cells, the influence of individual factors (barrier, facilitator or no impact) on medication adherence is displayed. For each factor (qualitative evidence), the impact based on quantitative evidence was abbreviated as follows: a) F for Facilitator, b) B for barrier, c) NI for no impact, meaning that the statistical test(s) revealed no statistically significant influence and d) NM meaning not measured which comprise factors not measured at all or factors for which the measurement does not include a statistical test. The analysis and filtering process was done in Excel and the results were transcribed in the integration matrix. Thus, the tables (Appendix 4) contain the following annotations: F for facilitator, B for barrier, NI for no impact. Eventually cells were left blank for factors that fulfilled the "not measured" criterion.

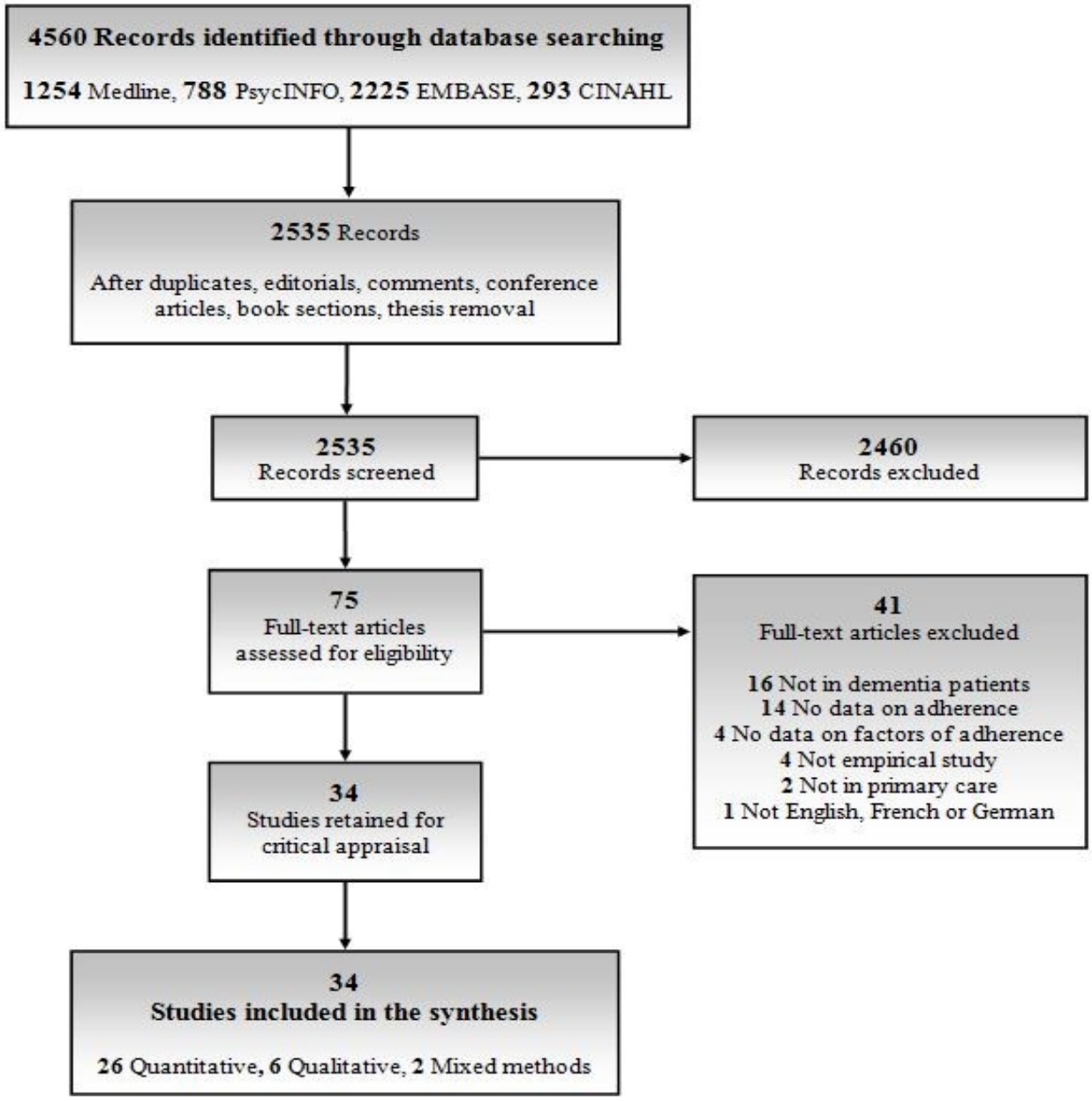
Secondly, the direction of influence was synthesized (Table 1), based on the results displayed in the integration matrix (Appendix 4). The evaluation of the direction of influence was based on following criteria: a) possible barrier, meaning a mix of evidence of 'barrier (B)" and "no impact" with at least one "barrier" in the analyzed studies b) possible facilitator meaning a mix of evidence of 'facilitator (F)" and "no impact" with at least one "facilitator" in the analyzed studies, c) exclusive evidence of no impact (NI), meaning in all studies evidence for "no impact" was found, d) contradictory evidence meaning all three possibilities (B, F, NI) were found for the same factor and e) not measured. No impact (NI) was considered when statistical test(s) revealed no statistically significant influence while not measured (NM) comprised factors not measured at all or factors for which the measurement did not include statistical test(s). In the integration stage, evidence from all quantitative method studies was included, independent of the quality appraisal score. The number of studies endorsing the impact of a factor was variable. If evidence of "barrier", "facilitator" or "no impact" for a specific factor was present in at least one study, than the information was used for assessing the direction of influence on adherence of that specific factor, and displayed in Table 1.

RESULTS

I. Included studies and flowchart

Out of a total of 4560 references, we retained 34 articles for the analysis. Based on the reported study design, the final pool of studies consisted of 6 qualitative, 2 mixed methods and 26 quantitative studies - see flowchart provided below.

Figure 2- Flowchart of studies



II. Quality appraisal

The maximum quality appraisal score possible (based on the MMAT tool) depends on the study design: for qualitative and quantitative studies the maximum score is 4 while for mixed method studies the maximum is 11. Results show that 5 out of 6 qualitative studies and 20 out of 26 quantitative studies received a score of 3 or higher while the 2 mixed method studies received one 6 and one 8.

Referring to qualitative studies, 4 out of 6 studies lost points because no details were provided related to the influence of the researchers' positions and experiences on study results and no consideration was given to reflexivity[68]–[71]. In two included randomized controlled trials[72], [73], no description of randomization or concealment was provided. Pertaining to quantitative non-randomized studies, most frequently, points were lost due to not providing information on the number of patients lost during follow-up[74] or not reporting results for at least 75% of the factors impacting adherence in at least 80% of the study population[75]–[77]. The most often encountered inaccuracy in quantitative descriptive studies was the lack of a flowchart or description of missing data[78]–[81]. Both included mixed method studies lost points because of a lack of consideration to context, setting and reflexivity[82], [83].

III. Preliminary step: a new framework of adherence: "Preliminary framework"

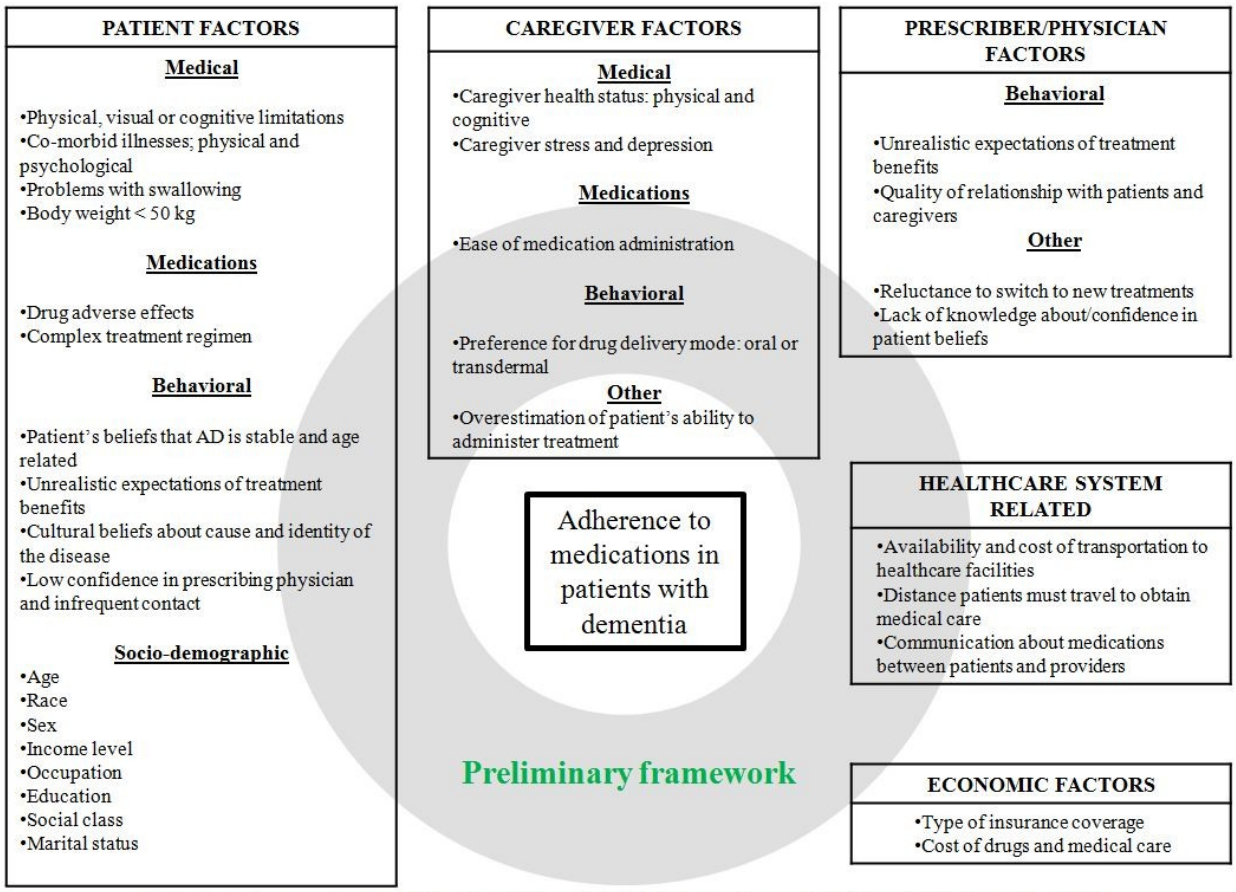
In this phase, I synthesized evidence pertaining to medication adherence based on three reviews: Brady, Balkrishnan and Murray[17], [19], [20]. These reviews were either selected during the "Identification of relevant studies" phase (Brady) or were recommended by experts in the adherence field (Murray and Balkrishnan). These three reviews were exclusively analyzed during the preliminary step and were not retained in the pool of studies analyzed during step one to three of the synthesis.

A common feature of both Brady's and Murray's work is the organization of factors in three major categories: patient, caregiver (environmental factors which include the family and caregivers as per Murray) and prescriber; in addition, Murray proposes a healthcare system category. Balkrishnan has a different approach, by structuring factors involved in adherence as: 1) medical factors (severity and duration of illness, number of co-morbid conditions, frequency

of use of medical services, patient satisfaction with the healthcare provider and quality of care), 2) medication related factors (type of medication, drug delivery system, therapeutic regimen, adverse effects), 3) behavioral variables (patient-physician interaction, patients knowledge about their medical condition, self-reported compliance, attitudes and beliefs about health), 4) economic factors (type of insurance, cost of drugs and medical care) and 5) socio-demographic (age, race, sex, income level, occupation, education, social class, marital status). Interestingly, while not mentioning it as a major category, Murray emphasizes as well the importance of behavioral-cognitive factors as predictors of adherence.

The framework development process therefore emphasizes the structure and factors proposed by Brady. By looking closer at the categories proposed by Balkrishnan, I observed that the medical, medication and behavioral categories can be used to further categorize the factors proposed by Brady while concomitantly eliminating Brady's "intentional" and "unintentional" dichotomization. These three last categories were a good match for explaining almost all factors provided by Brady under the "patient", "caregiver" and "prescriber" headings. A couple of factors in the caregiver and prescriber categories could not be re-grouped and were organized under the definition "other". I decided on three additions to Brady's framework: 1) the addition of a socio-demographic section as a sub-category under the "Patient factors" category (derived from Balkrishnan's work and comprising all factors proposed by him) 2) the addition of a distinct category "Healthcare system" based on Murray's work (which contains factors provided in the corresponding article) and 3) a stand-alone "Economic factors" category as suggested by Balkrishnan.

Figure 3- Preliminary framework



Preliminary framework adapted from Brady R. et al (2013), Murray M. et al (2003) and Balkrishnan R. (1998)

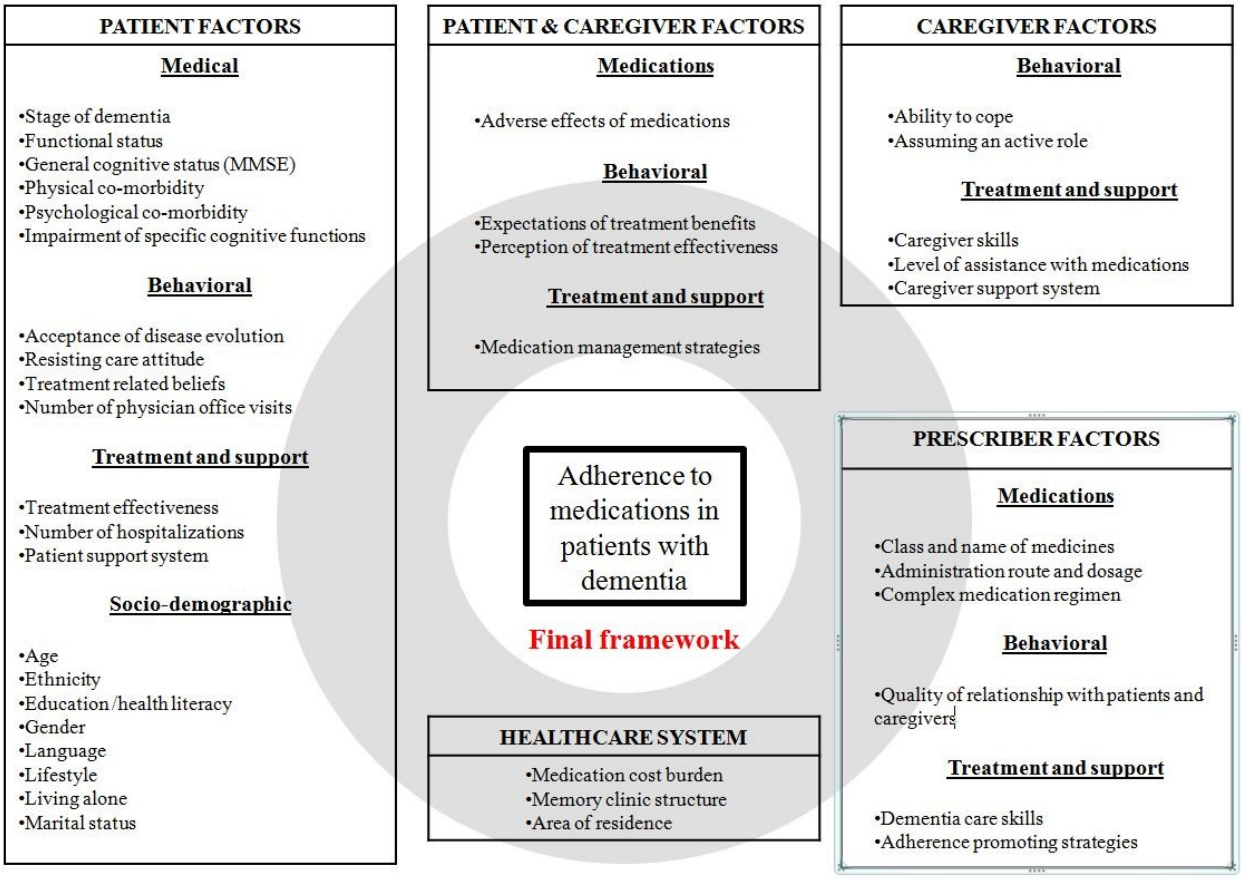
IV. Step one: qualitative synthesis and comprehensive and specific framework (final framework)

A. Comprehensive and specific framework (final framework)

In the qualitative phase of the synthesis, all 34 retained studies were analyzed.

The output of the qualitative analysis is represented by factors which influence adherence to medication in patients with dementia, grouped in categories and sub-categories and called "Final framework" (Figure 4).

Figure 4- Comprehensive and specific framework (final framework)



Comprehensive and specific framework (final framework) - Factors of adherence to medications in patients with dementia

In the following paragraphs, details are provided on how themes emerged during the qualitative deductive/inductive analysis process for each category separately. By "initial factor", it is meant the factor proposed in the preliminary framework, while the "final" factor represents the factor/theme mentioned in the final framework. The terms factors and themes are sometimes used interchangeably as factors mentioned in the final framework are actually themes derived from the qualitative analysis.

For better comprehending the development of the "final framework" the reader should look for each category (e.g. Patient) and sub-category (e.g. Medical) first at the factors proposed in the "preliminary framework". Details are provided on how new factors emerged during the deductive-inductive analysis process.

B- Patient Factors

a. Medical

The initial factor “Co-morbid illnesses; physical and psychological” was split into 2 separate final themes: “Physical co-morbidity” and “Psychological co-morbidity”. The physical co-morbidity theme was suggested by the following qualitative data: “Other coexisting diseases (cardiovascular, stroke, diabetes mellitus, hypertension, cancer)”[84], “Chronic disease score”[85], “weight loss (>=4%)”[86], “dysphagia status”[87], “fractures, falls”[77] etc. The theme “Psychological co-morbidity ” was suggested by following data: “apathy score on NPI scale”[86], “feels more ill than others in the same age segment”[72], nurse statement:"As time goes on, people become a little more paranoid and suspicious about why you're giving them medication..."[88], loss of insight as reflected by the following affirmation from a caregiver “So it's hard when the whole family is shaking their head behind them saying, 'They're so much better'. And they're saying, ‘No, I'm no different’"[88], “depression”[75], [86], [89]–[91], etc. As can be seen, the original factors “Problems with swallowing” and “Body weight<50 kg” are comprised by the theme “physical co-morbidity” together with the physical and visual limitations mentioned in the first initial theme in the “Medical” sub-category.

The following themes have been added to the preliminary framework: “Stage of dementia”, “Functional status”, “General cognitive status (MMSE)” and “Impairment of specific cognitive functions”. These new themes bring added value to the initial factor “cognitive limitations” which represents a broad concept.

The factor “Stage of dementia” is based on the data extracted from the work of Kaasalainen S. (2011) who suggested that strategies to improve adherence to medications in patients with dementia living in the community should be adapted to the stage of the dementia; the author highlighted particularities of medication management in early dementia in contrast to late dementia [88]. The theme “Functional status” was developed based on the mentioning of “activities of daily living”, “instrumental activities of daily living” in a couple of studies[75], [85], [86], [90]. The final theme “General cognitive status (MMSE)” reflects a global limitation of cognitive abilities and comprises: evaluation based on the MMSE score[75], [78], [85], [86], [89], [91]–[93] as well as “difficulties in remembering discussions about treatment and information received” as mentioned by a patient [68], “misinterpretation of instructions” and

"forgetfulness"[74], [77]. While general cognitive impairment is frequently assessed by MMSE in clinical practice –values and evolution over time of MMSE scores are even used by some health authorities for granting/continuing reimbursement of acetylcholinesterase inhibitors[85] - qualitative data suggested that sub-components of cognitive function may be important in predicting adherence to medications. The following data were captured and suggested the development of the final theme "Impairment of specific cognitive functions" : " long term verbal memory"[73], "executive functioning"[73], [90], [94], "memory awareness"[91], "inferential judgment"[76], "ability to form or abstract associations", "ability to begin, switch and end an action with ease"[90], "Level of awareness of medication management deficit"[92] etc.

b. Behavioral

The initial theme "Unrealistic expectations of treatment benefits" was used to develop the theme "Expectations of treatment benefits". As this is a common theme for both patients and caregivers, I have placed it in the "Patient and Caregiver Factors" category (see that category).

The initial theme "Low confidence in prescribing physician and infrequent contact" was kept form the initial framework. The final theme "Number of physician office visits" was produced in essence based on the variable found in a couple of quantitative studies "Number of physician office visits"[84], [85], [95].There was no explanation on the underlying process that lead to an office visit; in particular, this was not related to a lack of accessibility to primary care physicians. In addition, while low confidence in the prescribing physician is an explanation for infrequent contact, I have found no qualitative data in concordance with this statement. This is why we put the number of physician office visit in category of patients' factors. On the other hand, low confidence might be the result of a superficial relationship with the physician and is reflected by the final theme "Quality of relationship with patients" mentioned in the "Prescriber Factors" category.

By moving from data to theory, I created the final theme called "Resisting care attitude". Suggestive examples of data include: (patient) "being dependent on the tablets"[68], (caregiver and patients) "They were unwilling or unable to consider hypothetical future scenarios involving worsening health"[69], "treatment refusal"[74] or "refusal of antidementia treatment"[96]. In my opinion, the two initial themes "Patient's beliefs that AD is stable and age related" and "Cultural beliefs about cause and identity of the disease" are somehow related to the resisting care attitude

because those beliefs would prevent them to seek medical assistance; this opinion could not be further documented as I have not found data related to it.

A new theme “Treatment related beliefs” was generated as studies suggest that patients sometimes perceive that medications are not needed[74], that “Most medicines are addictive"[94], others are concerned about the effects of medications "I sometimes worry about the long term effects of my medication"[94] or the number of prescribed medications "Doctors use too many medications"[94] while other patients have a more positive view "My life would be impossible without medications"[94].

Another new generated theme is represented by “Acceptance of disease evolution” which represents the concept of anticipated necessity to stop the medication at some point in time; this is a concept which varies from person to person. The following participants’ thoughts were grouped around this final theme: "...she wants to stay, you know, living. By no means does she want to die. But she doesn't want to be a burden, you know, that way, and she doesn't want to not know what's going on or what she's doing"[69] ,"Well, we discussed this a little bit in the car today, and I think that he would still want to take medicine as long as he thought that there was any possibility of it helping him any. If he gets to the point, you know, where you can't walk and it's the tube feeding and all that stuff, you know that's, that's a no-no"[69] and "I don't deal with what tomorrow brings. I live to the day to the fullest...But I'm not a negative thinker...I'm not afraid of dying but I'm not looking forward to it. So, each day has its own merits. And I get the most that I can from those merits"[69].

c. Treatment and support

In this newly created sub-category, the “treatment’ component is reinforced by the themes ‘Treatment effectiveness” and “Number of hospitalizations” synthesized based on the following evidence:” decline under medication”[96], “Ineffectiveness of treatment”[75], “baseline ER visit count and baseline inpatient visit count”[95], hospitalizations AD or non AD related[86]. It is important to highlight the fact that poor adherence can trigger treatment ineffectiveness or an increased number of hospitalizations due to adverse effects. The number of hospitalizations or ER visits could be grouped under the category “Healthcare system” because it could reflect low availability of primary care physicians; still I preferred grouping them under the “Patient factors” category because besides being influenced by the adherence level, it can

also reflect patients (and sometimes) caregivers preferences for healthcare assistance. The patient support component came up in one study under the form of "availability of social support"[90]. Information around the support concept is pertinent for all categories (patient, caregiver and prescriber) and appears to be linked together with the concept of treatment; support can be beneficial for the patient, caregiver (for example respite care) or prescriber (in case of patients who refuse to follow treatment advices).

d. Socio-demographic factors

Most of the factors suggested in the preliminary framework were retained in the final framework with the exception of "Income level", "Occupation" and "Social class". The income level factor was put in the "Medication cost burden" theme listed under the "Healthcare system' category as it is a blend between the price of the medication and the financial power of the patient. The factor occupation was not found in the studies, probably because the prevalence of dementia is higher among persons over 65 who are retired in the majority of the cases. Social class might represent a determinant factor of adherence and merits further investigation. Additional factors in the final framework are represented by "Language", "Lifestyle" and "Living alone". The latter is of special importance as it can reflect the preference of the patient, can increase the rate of adverse effects and hospitalizations or can trigger gaps in medication supply (forget to re-fill)[88].

The sub-category "Medication" was placed under the theme "drug adverse effects" in the new created category "Patient and Caregiver Factors". The theme "Complex treatment regimen" was moved under category "Prescriber Factors" as the complexity of medication regimens can be the responsibility of the prescriber(s).

B. Patient and caregiver factors

As stated before, this category of factors represents an addition to the preliminary framework and was created based on the observation that some determinants of medication adherence are common to patients and caregivers. Thus, it highlights the strong interrelation between dementia patients and caregivers in the process of medication management.

a. Medications

Adverse effects emerge as a theme, being mentioned as a separate cause for therapy discontinuation or together with treatment ineffectiveness[75]. Adverse effects of medications are viewed as a challenge of the AD therapy[83]. When receiving a treatment, patients and caregivers are aware of a trade-off between adverse effects and benefits of the treatment: "...if I could stand it. I mean, you know, if it's something that I could get through with-without a large amount of nausea or something, why then, I would say, you know, I'd probably try to stay on it as long as I could"[69].

b. Behavioral

Two themes were integrated in this sub-category: "Expectations of treatment benefits" and "Perception of treatment effectiveness". The first theme was listed in the preliminary framework as a patient factor but I have re-categorized it as a common patient-caregiver factor. It was deductively developed and has its roots exclusively in data provided by qualitative method studies (interviews and focus groups). "Expectations of treatment benefits" is intertwined with the feeling of hope and desire to hold back time which represents a motivation to take dementia medications (AChEI's) as stated by participants: "I was hoping that the medication would stabilize me. That's a lot. Keep me at the stage where I was"[69], "I'm hoping it continues to work for many more years. You know, like the others have said, one day at a time, but you know, I'm just hoping for a real gradual decline, not, you know, the other shoe falling or something like that"[69]. In addition to patients, caregivers display as well unrealistic expectations: "Howard would continue to take the medication. That's because there is always a certain amount of hope that it will have an impact that's positive"[69], caregivers want a regimen that "cure" or "freeze" the progression of AD[83]. Sometimes, these expectations are fuelled by media reports:" I think the drug companies as well when they release this information you know you get big splashes in the Chronicle [local evening newspaper] and this lady couldn't make a cup of tea a year ago and now is running the household. And then your phone lines are buzzing you know 'Where do you get this drug?' 'How do you get this drug?'[71].

The other theme "Perception of treatment effectiveness" was also newly developed. The opinions about the benefits of the acetylcholinesterase inhibitors (AChEI's) in treating dementia

lie on a continuum, between worsening of symptoms under treatment to improving as a result of taking medication. Some do not perceive medications as having any influence on the natural course of the disease "It's not making any progress at all, I mean if there's a weed in the garden you pull it out but these weeds stay"[68], "I don't know whether, if it's doing any good, I don't know"[68]. Other participants value the disease stabilization effect of medications which represents a driver to continue the treatment: "He would never regain what he's lost, but it could stabilize...and that's what we sort of virtually, what it seems to be doing. So whatever John had lost at that stage he would never regain"[70]. In a concise way, they would characterize the stabilization effect by saying: "no better, no worse"[70]. The most satisfied dementia patients are those who improved under treatment with acetylcholinesterase inhibitors: "The medication...enhances...my mental...attitude and I can comprehend things much better..."[58], "The medication gave me an opportunity and if I didn't take advantage of it...I wouldn't be where I am today...I have actually improved. It has been a Godsend"[58].

c. Treatment and support

The theme "Medication management strategies" emerged by summarizing the following data. While some patients rely on themselves for remembering to take medications[89], others deliberately use adjuvant strategies: "I'm a very visual person so I have to have them [medications] where I can visually see them to remind me and, and so it took a little while to find a location that worked for me"[88]. Other general strategies employed by patients and caregivers are: notes, reminders, compliance packs, telephone calls, etc[68], [88]. Sometimes, utilization of medication reminders for example can be hindered by patients and caregivers unwillingness to adopt new technologies or by a malfunctioning device[77].

C. Caregiver factors

a. Behavioral

The initial theme "Preference for drug delivery mode: oral or transdermal" was merged with the new developed theme "Ability to cope". The task of care-giving for persons with dementia has been associated with stress[81], [88], caregiver burden[74], [77] which can be determined by: a) difficulties in administration of medicines and level of satisfaction with the route of administration[97], b) negative impact of medicine administration schedule ("too many

pills", "too many times a day"[83]) on caregivers' time which in turn results in restricting his/her activities[68], c) frustration determined by the resisting of care attitude of the patient " Frustrations when they don't understand, when they refuse because they think you're trying to poison them..."[88] and d) caregiver status and living arrangements[86]. All these factors have the capacity to influence the adherence to medications, pointing to the theme "Ability to cope".

The level of assistance with medication is determined by the level of involvement (or in other words) dedication of the caregiver in the care-giving process: "It was reassuring to know that twice a day somebody would actually see her and check on her"[82] or "It gave me peace of mind knowing that she was taking her pills"[82]. Certainly, a pro-active role as stated by one caregiver "trying anything, grasping any straws"[68] represents a goal the care-giving process should achieve: "I heard on the news one night. Now you see if I hadn't gone and asked the doctor about it I don't suppose he would have put him on them... (medications)"[68]. A pro-active role is reflected also by the interest of the caregiver in obtaining and maintaining the therapeutic effect of the medication, as for example in keeping blood pressure under control [77]. A high level of involvement is especially important for maintaining dementia patients in the community for as long as possible: "First of all, trying to respect their independence. So not trying to hand that over to somebody else too quickly, or too soon."[88]. All these concepts contributed to developing the theme "Assuming an active role".

b. Treatment and support

Another new developed theme was generated: "Caregiver skills". This theme includes the preliminary framework theme "Overestimation of patient's ability to administer treatment" and emerged based on following information. The lack of awareness of the importance of treating associated pathologies in dementia patients (e. g. hypertension, diabetes) was one of the factors related to adherence mentioned by caregivers[81]. Limited discussions with the prescriber about the treatment –suggesting insufficient information about the medication management- impacts the adherence[68] as well as an inappropriate match between the caregiver's strategy of properly administering the medications and the level of cognitive decline of the patient[92].

The developed theme "Level of assistance with medications" includes both the involvement of the caregiver with medication administration when a caregiver exists and the general level of assistance to the patient with medications. Indeed, while assisting with the

treatment, caregivers can provide any level of assistance with medications on a scale varying from no assistance to complete assistance which implies dispensing each dose of the regimen[92]. Intermediate scenarios include: very occasional reminders and/or occasional check of pill box, frequent pill box check, utilization of reminders but leaving the final responsibility for taking the medications on the patients[92]. When a permanent caregiver does not exist, external assistance is sometimes available.

A newly generated theme “Caregiver support system” includes the following information. The support system involves multidisciplinary collaboration as stated by a nurse: "I need the support of the family physician, the pharmacist, my physician here and homecare. And the reason why I mention all of those, I may need just one person to help, two persons to help or all five, depending on the degree of dementia and caregiver availability"[88]. Unfortunately, the support system is not equally distributed as mentioned by one caregiver: "Yes, yes. If you've got a strong voice and you get into that service then there are additional supports. I mean we have quite a good support service. And if you get into that service, you do have more support and there is closer monitoring of medication and things like that but the access for that service is very unequal"[71]. As care-giving represents a long term commitment, support is an integrative part of the disease management process: "It is crucial that you get support-not just pills from the doctor and send you home…"[88]. Thus, availability of support facilitates patient centered-care: "It is very important to have consistency among the people who are administering the meds, and that there is not a lot of switching because that's extremely confusing for my mother"[82], “It really helped her with the medicine...It helped her to get the accurate amount of medicine and the right time of the day”[82].

I consider important to highlight that the “Medical” subcategory from the preliminary framework- including the factors “Caregiver health status: physical and cognitive (and depression)” - could not be reinforced in the final framework based on qualitative data under scrutiny. As mentioned by Brady, the health status of the caregivers is an important factor to consider, especially when they manifest impairment of cognitive functions. Consequently, a categorization based on physical and psychological impairment (similar to that suggested for patients) would be appropriate.

D. Prescriber and other healthcare professionals factors

a. Medications

This sub-category represents an addition to the preliminary framework and represents a group of factors which should be considered when focusing on medication adherence in patients with dementia. Prescribers decide what medication to initiate, the administration route and dosage, and how to combine effectively other medications in line with existing co-morbidities with the final goal of avoiding deleterious effects of polypharmacy.

In this sub-category, the following themes emerged: "Class and name of medicines", "Administration route and dosage" and "Complex medication regimen". Pertaining to the "Class and name of medicines", the pool of studies analyzed provided information on medications to treat dementia (acetylcholinesterase inhibitors and Memantine)[78], [79], [84], [96], antihypertensives (including sub-classes)[79], [98], antipsychotics[84], [86], [98], anticholinergics[86] and other medicines such as: anticoagulant and antiplatelet agents, antidiabetic agents, hypolipemic agents, antiasthmatic drugs and NSAIDs[98]. The theme "Administration route and dosage" included oral (tablets, capsules and solution) and transdermal (patches) respectively the prescribed dose; in all cases, the information was related to the administration of dementia medications[74], [82], [84], [86], [88], [97]. Both the daily pill burden and the frequency of administration contributed to the development of the theme "Complex medication regimen". Indeed, the number of daily medications[74], [87], [89], [90], [94], [95], [98], [99], in addition to the number of daily intakes (e.g. once, twice or three times daily)[72], [100] are determinants of medication adherence.

b. Behavioral

Another theme "Quality of relationship with patients and caregivers" was newly developed. This theme includes the theme "Lack of knowledge about/confidence in patient beliefs" from the preliminary framework which was described by Brady as being the result of the frequency and quality of contact between prescriber and patient/caregiver. The newly developed theme ("Quality of relationship with patients and caregivers") is reinforced by the information mentioned below. Achieving treatment goals implies patience[88] and good person-centered approach of health care personnel when dealing with dementia patients[80]. An effective

communication process between prescribers, patients and their caregivers is of utmost importance: (caregiver) “I still think there should be more monitoring done to see what effects the tablets are having. It's no good asking us, I don't think we really know. We see changes every day of the week, but somebody in authority, a doctor or whatever it is should have some, I don't know history of what's happening. And we should be made aware of it"[71]. The basics of good communication require understanding the partner’s priorities: (physician) "Certainly when I am reviewing the medication, the MMSE I never do it. What is the functioning that is what the carers want to know and what the patients want to know is are they just coping in the community regardless of what their mental state is like, if the carers can cope"[71]. Proper medication management can be achieved by assuring a proper level of collaboration between the involved parts: (physician) "The only strategy that will work with patients with dementia is to actually see them in the office and ensure that their caregivers are informed and the pharmacist is involved. That's the best strategy at the moment that we know"[88].

c. Treatment and support

The prescriber’s general approach of medication treatment in patients with dementia – negative perceptions of treatment up to therapeutic nihilism[71] - represents an integrative part of the knowledge required for treating this category of patients: (patient) "...even though I've only seen him twice, the knowledge that he had and the fears I had that he relieved for me was just, it was awesome"[88]. A prerequisite in addressing compliance issues is to be aware of possible compliance issues in general[80] and of historical compliance of the patient under treatment[90]; often times physicians can not accurately assess compliance, partly because of relying on responses from patients and/or caregivers[72]. Clearly, specific knowledge is required for treating dementia patients, as for example awareness of swallowing difficulties[80] or awareness of specific contraindications of medications[96]. Being knowledgeable in dementia care depends also on the specialty of the prescriber[98]. Consequently, prescribers must possess special skills when treating patients with dementia, including being aware of and addressing medication adherence issues. For this reason, I have proposed the theme “Dementia care skills” with the purpose to summarize the preparedness of the prescribers; this theme also includes the preliminary framework theme “Reluctance to switch to new treatments” which was listed under “Other” in “Prescriber/Physician Factors”.

The preliminary framework theme “Unrealistic expectations of treatment benefits” was not retained in the final framework. It has been explained by Brady as the reluctance of physicians to persist with AD treatments because they do not consider disease stabilization as an important benefit. Brady mentioned as a remedy, physician education on the importance of temporary disease stabilization for both patients and caregivers. Therefore, I consider this negative perception which can be ameliorated through education a feature which can be included under the ‘Dementia care skills theme”.

The newly created theme “Adherence promoting strategies” emerged from the data mentioned below and represents the concept of unveiling proactive solutions for addressing adherence issues. Because the treatment of dementia patients represent a multidisciplinary approach, the level of awareness of prescribers related to the role of the caregiver (informal or formal) is paramount[80]. Adjusting the treatment of associated diseases in patients with dementia or modification of dementia specific treatment has been suggested to play a role in improving adherence to medications[74]. Referring to the latter, it has been suggested that switching from one acetylcholinesterase inhibitor to another or from oral forms to patches can impact adherence[74], [87], [100]. Another proposed strategy is adapting (reducing) the number of doses[88], usage of compliance aids such as automatic pill dispenser and/or medication reminder devices[77], [80] or simply being creative/adaptable which corresponds to what a pharmacist suggested: " Just to try and create a pattern that they can easily remember"[88]. Providing tailored information –adapted to the level of health literacy, language proficiency and cognitive status- represents another alternative[73]. Avoiding providing too much information and providing medication information in an easily understandable form (drug labels are preferred over medication charts) are other ways to handle medication adherence issues in dementia patients[76]. Other approaches suggested for addressing low levels of compliance resulting from memory impairment are the usage of automated phone calls -with the purpose of reminding patients to take their medications[73] - or the implementation of video or phone monitoring techniques, which allows maintaining regular contact with the dementia patients[82]. As the decline process of dementia patients can be lengthy, motivational support[74] and providing specific information about the disease in order to help patients and caregivers better understand and manage the illness[74] are proposed ways for addressing adherence issues in this category of patients.

E. Healthcare system

The theme "Medication cost burden" includes several aspects outlined below. One of the most stringent issues intertwined with medication adherence is represented by the affordability of the medications. The "out of pocket cost of medications"[85], [87] depends on the patients' type of insurance[69], [99] and on the reimbursement policies as these can trigger termination of permission from the insurer[78], [85]. The level of reimbursement of medications is very important as the co-payment for some medications varies depending on the level of reimbursement (patients pay less for Tier 2 than for Tier 3 medications)[95], [99]. Therefore, the cost of medication[69] can render the medicines "too expensive"[81], facilitating treatment discontinuation. The healthcare system influences not only the final cost of medication but also the cost of medical care[99]; a low reimbursement level for health-related services increases the financial strain of the patient. The household income[86] and the social assistance recipient status[85] are also determinants of medication affordability; even if not related to the healthcare system (being patient driven), these are also important economic factors.

A newly developed theme is represented by "Area of residence". Rural or urban residence[85], as well as the geographical area of residence (West or South of the Unites States)[95], [99] have been suggested as factors of medication adherence. This theme includes the following themes mentioned in the preliminary framework: "Availability and cost of transportation to healthcare facilities" and "Distance patients must travel to obtain medical care", themes for which no evidence was found in the qualitative data.

The preliminary framework theme "Communication about medications between patients and providers", is comprised in the final framework under "Quality of relationship with patients and caregivers" listed in the 'Prescriber Factors" category.

The newly added theme "Memory clinic structure" summarizes the university or non-university affiliation of health-related services for patients with cognitive impairment[96]. Thus, memory clinics –a pivotal structure in managing patients with dementia- can have different functional characteristics (e.g. diagnostic procedures, specialty of attending physicians, prescription procedures, etc) depending on their aforementioned affiliation status[96].

In conclusion, the output of the qualitative synthesis phase represents a comprehensive and dementia specific framework of factors that influence medication adherence in patients with dementia who live in the community. The qualitative synthesis phase provided a response to the first research question leaving the door open for the quantitative phase which comes to assess the importance of the identified factors with the goal to provide answers to the second research question.

V. Step two: quantitative synthesis

Step two is based on the analysis of 22 quantitative studies. Indeed, 5 quantitative studies were completely excluded from the quantitative analysis phase because none of the provided results were tested for statistical significance[76], [77], [80], [81], [100]. One mixed methods study[83] was used only in the qualitative synthesis part of this review, because in the quantitative part of the cited study the psychometric properties of a questionnaire were tested, which was not the objective of this review.

The 22 quantitative studies used various designs: 9 observational[75], [86], [89]–[92], [94], [96], [97], 8 claim database studies[78], [79], [84], [85], [87], [95], [98], [99] and 5 interventional studies[72]–[74], [82], [93]. In the next section, the synthesis of quantitative evidence is organized by: a) study design and b) category of factors (e.g. patient, caregiver, etc.) as presented in the "final framework".

A. Observational studies

a. Patient factors

Medical

In the medical sub-category, relevant data were found pertaining to the following factors: functional status, general cognitive status, physical co-morbidity, psychological co-morbidity and impairment of specific cognitive functions.

Functional status was not found to be a statistically significant factor neither for discontinuation of specific dementia medications-acetylcholinesterase inhibitors (AChEI's)[75], [86] nor for adherence to medications in general[90].

Two of the quantitative studies under scrutiny proved that the general cognitive status – which is mostly assessed clinically with MMSE- has no impact on discontinuation of the treatment with acetylcholinesterase inhibitors[75], [86]. The general cognitive status had no statistically significant influence on medication management decision making[91]. MMSE values are indirectly related to the level of adherence due to a positive correlation between the MMSE score with the reliance on oneself to take medications[89] and a negative correlation between the reliance on oneself to take medication and the level of adherence[89]. Therefore, low MMSE scores seem to contribute to increasing adherence.

In the majority of quantitative evidence, physical co-morbidity was not significantly related to medication adherence. Other studies imply that co-existing diseases have no impact on discontinuation of AChEI's at six months[75] or on adherence to medications in general[90]. The plasma viral (HIV) load was not significantly associated with medication accuracy (OR=1.0, CI: 0.7-1.4) or consistency (OR=0.7, CI:0.5-1.2)[94]; medication accuracy reflects patients' ability to transfer pills from prescription bottles to a medication organizer, while medication consistency reflects the ability of the patient to take the medications at the same time of the day each day[94]. However, one study suggested that physical co-morbidity (weight loss greater or equal to 4%) increases the risk of discontinuation of AD treatment (HR 3.77, CI:1.15-12.33, p=0.028) [86].

Pertaining to psychological co-morbidity, the evidence globally suggest no link with adherence. Indeed, being diagnosed with depression has no impact on adherence to the wide range of medications administered to patients with dementia[89], [90] or to dementia specific medications[75], [86]. Depression has no influence on the decision making component of the medication management[91]. In line with previous results, patients' apathy score[86], stress, concerns related to various aspects of their life and behavioral changes have no impact on discontinuation of AChEI's[75]. However, in one study, having sleep disturbances (assessed with the Neuropsychiatric Inventory Score tool) almost reached statistical significance in suggesting increased risk of discontinuation of AChEI's (HR 2.55, CI:0.99-6.56, p=0.053)[86].

Impairment of specific cognitive functions refers to selective deficits such as: memory awareness, executive functioning, psychomotor performance, ability to form abstract associations, verbal fluency and visuospatial skills, etc. Firstly, memory awareness implies the ability to evaluate: a) personal difficulties in medication management – such as identifying the

medicines, specifying the number of pills per day and specifying the correct time of the day the pill must be taken- and b) advantages and disadvantages of receiving help with administering medications such as assistive devices (pillbox) or external assistance in taking the medications[91], [92]. Decreased memory awareness resulted in over-predicting the ability to time ($t=2.86$, $p=0.09$) and dose ($t(26)=2.45$, $p=0.02$) medications correctly as evaluated by the DRUGS test[92]. In the context of very mild to mild AD, the medication management capacity is determined mostly not by the state of global cognition (routine MMSE evaluation) but by the self-awareness of cognitive impairment; memory awareness is clearly associated ($p=0.007$) with performance on the aptitude to realize personal difficulties in administering medications and balancing the advantages and disadvantages of implementing medication adherence enhancing strategies such as: assistive devices, help from caregivers, etc.[91]. Secondly, the ability to recall information after a brief delay and the ability to recognize previously presented information (assessed by the memory subscale of the Dementia Rating scale-DRS) is statistically significantly associated with medication adherence [90]. For every point increase on the DRS memory subscale (higher scores means better performance), there was an 11% decrease in the odds of medication non-adherence, OR 0.89, CI: 0.81-0.97, $p<0.001$[90]. Thirdly, quantitative data proved that the level of executive functioning is associated with medication adherence[76],[80]. Decreased executive functioning was associated with lower medication accuracy (OR 6.3, CI: 2.0-20.5 $p<0.01$); medication accuracy was evaluated by the "pill-dispensing" component of the Medication Management test-MMT which reflects the ability of the participant to transfer pills from prescription bottles to a medication organizer [94]. The ability to begin, switch and end an action with ease characterizes executive functioning which can be assessed with the initiation/perseveration subscale of the DRS[90]. For every point increase in the DRS initiation/perseveration subscale (higher values means better performance), there was a 7% decrease in the odds of medication non-adherence, (OR=0.93, CI: 0.87-1.00, $p<0.001$) suggesting a positive impact of high executive function on medication adherence[90]. Other specific cognitive functions significantly associated with adherence are psychomotor performance, verbal fluency and the ability to form abstract associations[90], [94]. A low score of psychomotor performance is associated with lower medication accuracy (OR 6.2, CI: 2.0-19.1 $p<0.01$)[94]; similarly, decreased verbal fluency is associated with lower medication accuracy ($p<0.01$) [94]. An increased ability to form associations between medications and associated

side-effects (which can trigger intentional non-adherence) is related to increased odds of medication non-adherence (OR=1.14, CI: 1.02-1.27, p<0.001)[90]. However, not all evaluated components of cognitive function have proved to be related to medication adherence. Choice reaction time was not associated with medication accuracy and consistency [94]. Performance on tasks related to visuospatial skills (reproduction of different designs of varying difficulty) has no impact on medication adherence[90], [94]. In summary, a higher awareness of the impact of some sub-components of cognitive function on medication adherence is important: level of memory awareness, executive functioning, psychomotor performance, verbal fluency and the ability to form abstract associations.

Behavioral

One of the concepts related to the acceptance of disease evolution is the perception of cognitively impaired individuals about the seriousness of their diseases. The perception about the seriousness of the disease was not significantly associated with adherence in a multilevel regression analysis model[89]. However, an accurate perception of the seriousness of their disease (disease is serious) positively correlates with an accurate perception of the outcome without medication (bad outcome) which in turn is a statistically significant predictor of good adherence[89]. In addition, considering the disease, for which one takes medications, not serious is associated with high reliance on oneself to take medications which in turn is a negative predictor of medication adherence[89].

An intentionally distorted reported level of self-adherence (lying) can flag a resisting care attitude. The self-reported medication adherence in HIV patients with cognitive impairment is not associated to adherence (measured by the level of medication accuracy) in HIV patients with cognitive impairment[94].

Treatment related beliefs were another identified determinant of medication adherence. Concerns related to medications (e.g. being anxious about the long term effect medications could have on one's health) were positively associated with increased medication adherence; concerned patients made fewer errors in the pill placement component of the Medication Management Test (r=0.52, p<0.001)[94].

Other treatment related beliefs such as: the perceived need for medications, the potential addictive effect of medications, the perception that higher milligrams of active ingredient per

dose medications are more efficient than lower milligram/dose and the perception that physicians prescribe too many medications were not statistically significantly correlated with medication adherence (medication accuracy)[94].

Treatment and support

A higher number of hospitalizations occurring in the context of Alzheimer's dementia (AD) increases the likelihood of discontinuation of AD specific treatment (HR=9.14, CI:2.69-31.07, p<0.001)[86]. Similarly, frequent hospitalizations unrelated to AD also increase the risk of discontinuation of AD treatment (HR=4.23, CI:1.54-11.59, p=0.005)[86].

Despite the important role the existence of social support plays in the management of dementia patients, there is no significant relationship between availability of social support and adherence to medications in general in this category of patients[90].

Socio-demographic

Quantitative evidence from observational studies pertaining to the impact of age on adherence is conflicting. Some studies found that age has no impact on discontinuation of acetylcholinesterase inhibitors[75], [86] or on the medication management decision capacity[91]. Other studies suggested that older age is either positively related to adherence to medications in general[89] or negatively related to adherence (lower medication accuracy)[94].

The influence of ethnicity was found to be not significant on the discontinuation of acetylcholinesterase inhibitors[75].

Evidence pertaining to the influence of education on medication adherence suggests that education has either no statistically significant influence on adherence[89], medication management decision capacity[91] or medication accuracy[94] or that education is strongly associated with discontinuation of acetylcholinesterase inhibitors (AChEI's) at 6 months (inverse relationship between the years of education and discontinuation) [75].

Gender has no impact on adherence to various medications prescribed to older adults with dementia[89], on discontinuation of AD specific medications (e.g. AChEI's)[75], [86] or on medication accuracy in HIV infected individuals with severe cognitive impairment[94].

Other socio-demographic factors, language[89], lifestyle determinants such as: level of physical exercise[75], smoking status[75], alcohol consumption[75], [90] and marital status[75] have not been statistically significantly associated with adherence to medications.

b. Patient and caregiver factors

Behavioral

The duration of acetylcholinesterase inhibitors (AChEI's) administration is multifactorial; one of the factors is represented by the perception of effectiveness of AChEI's. Based on one of the studies analyzed, the duration of AChEI's was not a significant predictor for treatment discontinuation[86]. Medication accuracy (as assessed based on the Medication Management Test) in HIV infected persons with dementia was not associated with the level of perceived need for medications[94]. In a study investigating the determinants of adherence to multiple medications in patients with dementia, participants were asked for each medication they took to rate their perception of the outcome of the corresponding disease without medication[89]. In this study, results of a multilevel regression analysis attested that patients' correct estimate of outcome of the disease without medication was positively related to adherence ($p<0.001$), meaning that a correct perception (bad outcome without medications) predicts a better adherence[89].

Treatment and support

Multiple medication adherence strategies have been described so far for improving the treatment process; one of them is represented by requesting external support. As opposed to this strategy, relying on oneself to take medications proved to be a significant negative predictor of medication adherence ($p<0.001$)[89].

c. Caregiver factors

Behavioral

The theme "Ability to cope" encompasses all determinants of the care-giving process which enables the caregivers to maintain a high level of care including: caregiver burden, caregiver status and living arrangements and caregiver satisfaction with medications. While caregiver burden (measured on the Zarit Burden scale) and caregiver status and living

arrangements had no impact on medication adherence[86], satisfaction with medication proved to be a significant factor[97]. The caregiver ‘s level of satisfaction with transdermal medication compared to oral therapies was significantly higher in adherent than in non-adherent patients (74 vs. 68, t test, $p<0.001$)[97]. The effect was significant on almost all domains of the questionnaire: "undesirable side effects", "treatment effectiveness", "convenience of use" and "impact on activities of daily living" and insignificant on the domain of "Medical care"[97].

Treatment and support

The success of the treatment endeavor is highly dependent on the skills displayed by the caregivers related to administering medicines. Efficient assistance is reflected by the number of episodes of medication non-adherence; having at least one previous episode of non-adherence (to any medication), increased the odds of subsequent non-adherence by over 2.6 as compared to having no previous occurrences (OR=2.61, CI: 1.18-5.62, $p<0.001$)[90].

Medication management skills are statistically significantly lower in dementia patients compared to controls[92]. Remarkably, medication adherence measured by pill count was not statistically different between the groups, being approximately 84% in both groups[92]. As both groups of participants received external assistance with medication administration (caregivers), the authors concluded that the caregiver support helped AD patients achieve a similar level of adherence as compared to the control group despite their lower medication management skills[92]. Additional evidence of the role and skills of caregivers is brought by the fact that while AD respondents showed no statistically significant difference between their predicted adherence and the final objective (pill count) adherence (84%), non cognitively impaired participants (control group) over-predicted their final adherence (predicted 97.6%, observed 83.9%, $t=3.23$, $p=0.004$)[92]. This can be explained by the fact that dementia patients benefited from caregivers’ skills and increased level of assistance in administering medications which was most probably not the case in the control group[92]. Conversely, another study investigating multiple factors hypothesized as having an impact on medication adherence suggested that receiving informal help with medications was not significantly associated with adherence (OR= 0.92, CI: 0.39-2.04)[90]. In this study participants lived alone and based on inclusion criteria, they had at least one weekly contact with a caregiver, either in person or by telephone. Therefore, we can speculate that the level of assistance with medications was rather low, which

may represent an explanation of the non-significant role of informal help with medications administering on adherence in this study.

While formal support for caregivers can be available to various degrees, there is no significant association between availability of formal help for CG (e.g. respite bed, home nursing, day hospital, etc) and adherence to medications[90]. The same study revealed that not even availability of social support was significantly associated with adherence[90].

d. Prescriber factors

Medications

It is the responsibility of the prescriber to individualize the treatment with medications by deciding on the class and name of medicines, route of administration, dosage and total number of medications for treating dementia and co-existing pathologies. For example, it is widely accepted that anticholinergic medications (e.g. hydroxyzine, urinary antispasmodics, anticholinergic antipsychotics, etc) are inappropriate for older adults and should be restricted to the highest extent possible (Fick DM et al, 2003). Exploring the factors of discontinuation of cholinesterase inhibitors has highlighted that concomitant use of anticholinergic medications increased the risk for discontinuation of AD treatment (HR 4.26, CI: 1.46-12.45, p=0.008)[86]. The same study suggested that concomitant use of antipsychotic drugs and benzodiazepines has no impact on AD medication discontinuation[86].

While administering an ineffective AChEI's dose has not been significantly linked to treatment discontinuation[86], the route of administration of acetylcholinesterase inhibitors was found as having significant impact on adherence[97]. Thus, comparing the adherence to oral AD medications with the adherence to transdermal formulation revealed that the proportion of patients adherent was significantly higher in the transdermal group (65%) compared to the oral group (41%) (OR 2.6, CI: 1.7-4.0, p<0.001)[97].

In polymedicated patients with dementia who live alone, taking four or more medications increases the likelihood of medication non-adherence (OR=2.58, CI: 1.31-5.29, p<0.001)[90]. However, patients followed–up in memory clinics were not susceptible to medication non-adherence based on the total number of medications prescribed[89]; authors concluded that the study failed to provide a significant link between the medication burden and adherence because

of a lower mean of medications per patient (3.7) compared to other studies[89]. Medication accuracy was not related to the number of medications in HIV patients[94].

Treatment and support

Monitoring medication adherence closely and being aware of previous episodes of medication non-adherence also reflects the physician's dementia care skills. Patients with at least one previous episode of medication non-adherence are 2.6 times more likely to be non-adherent compared to those without historical evidence of non-adherence (OR=2.61, CI: 1.18-5.62, p<0.001)[90].

e. Healthcare system

Evidence from a study reflecting particularities of the French healthcare system - study in which community-dwelling Alzheimer's dementia patients treated with acetylcholinesterase inhibitors were followed up for 2 years –found that medication cost burden was not significantly associated with discontinuation of acetylcholinesterase inhibitors[86].

In a study conducted in Germany, the adherence to dementia specific medications was not significantly different between the group of patients treated in a university affiliated memory clinic (Erlangen) compared to the patients followed up in a community hospital affiliated memory clinic (Nurnberg)[96].

B. Claim database studies

a. Patient factors

Medical

Patients' decreased level of independence in carrying out instrumental and other activities of daily living (Functional Assessment Questionnaire-FAQ score >9) was associated with lower likelihood of discontinuing cholinesterase inhibitors as opposed to those with FAQ scores <9 (HR= 0.82, CI: 0.69-0.99, p=0.036)[85].

General cognitive status as evaluated by MMSE significantly predicted AChEI's discontinuation [85]. Authors found an increased risk of discontinuation not only in patients with MMSE <15 as compared to those who scored above 20 (adjusted HR=2.52, CI: 2.01-3.17) but

also in those who scored between 15 and 20 (adjusted HR=1.55, CI 1.33-1.81)[85]. The increase risk of non-adherence is remarkable especially for patients with moderate (15-20) cognitive impairment as assessed by MMSE; authors speculated that probably low therapeutic benefits may have contributed to this effect, despite meeting the provincial health coverage requirements[85].

Results pertaining to the prediction of adherence to dementia specific treatments (oral and transdermal acetylcholinesterase inhibitors, respectively Memantine) in patients with dementia having other co-morbidities are conflicting; evidence exists that associated diseases either have no impact on discontinuation of AD specific therapy[84], [95], increase the likelihood of adherence[85] or decrease the probability of being adherent[99].

Results of two studies suggested that co-existing diseases (cardiovascular, stroke, diabetes mellitus, hypertension, cancer)[84] or the baseline co-morbidity score[95] was not statistically significantly associated with the level of adherence. Furthermore, quantile regression analysis -a unique analysis that permits assessing the impact of factors on different quantiles of adherence - has proved that across all values of adherence studied the co-morbidity score is not a significant determinant of adherence[95].

Patients with a Chronic Disease Score (CDS) over 7 as compared to those with a CDS between 0 and 3, have a lower risk of discontinuation of dementia medicines (adjusted HR 0.74, CI: 0.61-0.89, p=0.002)[85]. Similarly, having FAQ scores > 9 (compared to FAQ<9) was associated with a lower risk of discontinuation (adjusted HR 0.82, CI: 0.69-0.99, p=0.036)[85]. Based on the authors' opinions, CDS may represent a proxy for greater physician involvement, suggested by the fact that in this study participants with higher CDS scores were more likely to be seen by physicians[85].

Based on analyzing data from a large managed-healthcare plan in the United States, authors demonstrated that patients with AD or related dementia having higher baseline Charlson-co-morbidity scores were less likely to be adherent to oral AD therapy (OR=0.903, CI 0.859-0.95, p<0.001)[99].

Due to the fact that one of the most frequently encountered adverse effects of AD medications (AChEI's) is gastro-intestinal (GI), the GI functional status is considered a determinant of adherence to AChEI's in dementia patients. Thus, authors of a study who

explored the adherence to donepezil (oral therapy) and rivastigmine patch in terms of proportion of days covered (PDC) before and after switching from donepezil to rivastigmine concluded that: a) adherence was better for donepezil than for rivastigmine for patients having dysphagia at baseline but the difference was not statistically significant, b) in patients without dysphagia, the PDC was significantly better in patients treated with rivastigmine patch compared to those receiving donepezil (62.3% vs. 58.6%, p=0.0189) and c) the presence or absence of a GI complication at baseline had no impact on adherence[87].

Behavioral

A pro-active attitude of patients with dementia is represented by their willingness to undergo regular health checks by their physicians. This attitude has been hypothesized by researchers as being a determinant of medication adherence. Thus, a moderate increase of physician office visits (between 6 and 20) in the 12 months after the index date of AChEI's treatment[84] or in the year prior to index prescription[85] was associated with a decreased likelihood of treatment discontinuation. Compared to those who didn't visit their physician at all, patients who visited their physicians 6 or more times were 77% less likely to discontinue their therapy (RR=0.23, CI=0.17-0.30, p<0.01)[84]. Similarly, having 7-19 visits in the year preceding the index date (the date when AChEI's were first prescribed) was related to 22% decreased risk of treatment discontinuation (adjusted HR 0.78, CI: 0.66-0.93, p=0.004)[85].

Conversely, when adherence to AChEI's was measured based on the Medication Possession Rate (MPR ≥ 80%), authors concluded that the number of office visits in the baseline period (6 months before the index date) was not associated with the level of adherence[95]. In this study, quantile regression models showed that patients with lower adherence (65%) had significantly more baseline office visits. It is difficult to explain why those displaying lower adherence than the MPR cut-off (80%) visited their physician more often; it is possible that their health condition was worse but this sub-analysis was not provided in this study.

Treatment and support

Patients hospitalized at least once after the index date (compared to those not hospitalized at all) had a significantly lower risk of discontinuing acetylcholinesterase inhibitor therapy (adjusted RR=0.65, CI 0.42-0.99, p< 0.05)[84]. These results were contradicted by another study in which authors concluded that neither an increased number of inpatient or outpatient visits nor

an increased number of emergency room (ER) visits (in the 6 months preceding the index date) have significant impact on adherence[95]. In this study, quantile regression showed that highly adherent participants (MPR=95%) had lower likelihood of adherence if they had a higher frequency of baseline ER visits.

Socio-demographic

Quantitative evidence from claim database studies pertaining to the influence of age on medication adherence depends on a) how adherence was measured: discontinuation (gap of more than 60 days without a refill) or Medication Possession Rate (MPR $\geq$ 80%) and b) healthcare system specific regulations pertaining to reimbursement of dementia treatment and/or length of follow-up. Studies in which compliance was defined as discontinuation suggested either no impact of age[84], lower discontinuation rate in patients under 76 years of age as compared to those older than 76 (p=0.0008)[78] or even conflicting results within the same study depending on the length of follow up analyzed[85]. In another study in which adherence was defined as discontinuation (persistence), age > 80 was found to be associated with lower likelihood of AChEI's persistence at one year compared to those younger than 80 years (OR=0.74, CI: 0.57-0.96, p=0.02)[98]. It is possible that those aged 80 or more had more co-morbidities and needed hospitalizations; during the period of hospitalization they most likely continued taking AChEI's so there was no gap in the treatment. The sensitivity analysis-removing from the analysis patients who had gaps in AChEI's due to hospitalizations-, revealed that age was not a significant predictor anymore[98]. When adherence is assessed based on MPR, results suggest that older adults are more likely to be adherent to cholinesterase inhibitors[95], [99].

Lower discontinuation rate in younger patients (under 76 years) as compared to older adults was found in a Taiwanese study which included only mild to moderate Alzheimer's dementia patients[78]. In this study, a decrease in MMSE of more than 2 points or a CDR worsening of more than 1 grade as compared to baseline would disqualify respective patients from reimbursement[78]. Because of the restrictive inclusion criterion in this study pertaining to the grade of dementia and well known progressive deterioration of cognitive function with age, in this cohort of patients the 80-86 years threshold evaluated in other studies[95], [99] could not be reached.

Another study failed to associate age with discontinuation in analyses based on the entire follow-up period (40 months) but a sub-analysis on an interval of 6 months found that persons aged 70-79 had a lower risk of discontinuation as compared to persons <70 years (adjusted HR=0.58, CI:0.39-0.86, p=0.007)[85]. Over this 6 month period all patients met the healthcare plan coverage eligibility criteria which are based on evolution of dementia. Therefore, it is possible that the influence of age on discontinuation over the full 40 month follow-up period was confounded by patients' eligibility for reimbursement.

Assessment of adherence based on the MPR suggested that advanced age is associated with better adherence to medications. Thus, patients ≥ 86 years old were more likely to adhere to oral AD therapy compared to those aged ≤ 75 (OR=1.401, CI: 1.129-1.738, p<0.01)[99].

Results of a study exploring adherence to antihypertensive and dementia medications highlighted that- in a predominantly male population- being African American or Hispanic is associated with lower adherence to medications compared to whites[79]. This effect is especially important in African Americans who displayed significantly lower adherence (measured by MPR) in all drug classes except ARB's and potassium-sparing diuretics (p<0.05)[79]. On the other hand, Hispanics had a significantly lower mean of MPR for beta blockers, dihydropiridine Ca^{++} blockers and thiazide diuretics and AChEI's (p<0.05, t-test). Logistic regression models adjusted for age, sex marital status and geographic location in which the reference was adherence in whites, proved that: a) In African-Americans, the likelihood of being adherent was significantly lower in all medications (including AChEI's), except in loop diuretics, vasodilators and potassium sparing diuretics (p<0.05) and b) In Hispanics, the likelihood of being adherent was 31% lower for dihydropiridine Ca channel blockers (OR=0.69, p<0.05) and 23% lower for acetylcholinesterase inhibitors (OR=0.77, p<0.05)[79].

Evidence pertaining to the influence of gender on adherence is contradictory. Some authors have shown that adherence to medications is not significantly influenced by gender[78], [84], [98]. Others have proven that adherence to acetylcholinesterase inhibitors is better in males, based on a higher likelihood of therapy discontinuation in females (adjusted HR for females=1.34, CI: 1.16-1.55, P<0.001)[85], respectively higher likelihood of being adherent in males (OR1.175, CI: 1.001-1.378, p<0.05)[99].

b. Prescriber factors

Medications

Despite being hypothesized that the type of dementia specific medication would have an impact on adherence, the assumption was not validated[78], [84]. The proportion of patients who discontinued donepezil or rivastigmine was similar; sensitivity analyses for 30 day and 90 days gap confirmed the results obtained when discontinuation was defined as a gap of more than 60 days[84]. Similarly, being treated with rivastigmine, donepezil of galantamine had no significant impact on discontinuation or treatment duration (p=0.62)[78].

Central nervous system medications (CNS) are often prescribed in patients with dementia for various indications: anxiety, depression, sleep disorders, behavioral disorders, etc. The relative risk of discontinuation or switch of donepezil or rivastigmine was 30% higher in participants who used CNS medications before the index date (as compared to those who did not use CNS medications), after controlling for other patient factors (RR=1.3, CI 1.05-1.60, p<0.05)[84]. Conversely, authors of another claim database study found that taking antidepressants at initiation of AChEI's therapy was associated with increased likelihood of AChEI's persistence, OR 1.38, CI=1.05-1.82, p=0.02[98]. No other psychotropic medications or other classes (cardiovascular, antidiabetic, NSAID's, etc) were found to significantly influence AChEI's persistence at one year[98]. In a sensitivity analysis (removing from the analysis patients who had gaps in AChEI's due to hospitalizations), no medications (including antidepressants) were significant predictors of persistence anymore[98]. Authors explained the facilitator influence (before the sensitivity analysis) of antidepressant use on persistence to AChEI's by the fact that patients who present the most significant symptomatology tend to be the most adherent to therapies[98].

In patients suffering from both dementia and hypertension, physicians can expect variable levels of adherence based on the type of medicine and ethnicity[79]. In Hispanics, adherence to acetylcholinesterase inhibitors is lower than in whites (MPR mean= 0.84 vs. 0.88, p<0.05), while for Memantine the adherence is similar to whites[79]. Lower adherence levels for angiotensin-converting-enzyme inhibitors, beta-blockers, dihydropiridine calcium-channel blockers and thiazide diuretics have been found in Hispanics compared to whites (mean MPR, p<0.05)[79]. While the adherence to most antihypertensives is lower in African-Americans than

in whites, one should expect similar levels of adherence for angiotensin receptor blockers and potassium sparing diuretics in patients suffering from both dementia and hypertension[79].

The pill burden is associated with contradictory evidence pertaining to the level of adherence to medications in dementia patients[87], [95], [99]. In a US retrospective claim analysis evaluating factors related to adherence to oral AD medications in which the mean (SD) overall pill burden was 5.97(3.94), authors concluded that for every unit increase in the overall mean daily pill burden the odds of being adherent increases with 19%, (OR 1.192, CI: 1.163-1.222, $p<0.001$)[99]. According to the authors, it is possible that the level of assistance with medications from caregivers increases as the number of medications to be administered increases[99]. The number of medications at initiation of AChEI's (excluding AChEI's) is not associated with persistence of AChEI's at one year[98]. Two groups (5-9 and >10 medications) were tested against those receiving <5 medications and no statistical difference was obtained[98]. As opposed to the overall pill burden, the impact of index medication pill burden (number of pills for treating AD) on adherence is different. Hence, greater index medication daily pill burden (mean 1.24, SD 0.43) was associated with a significantly less likelihood of being adherent (OR=0.59, CI: 0.43-0.81, $p<0.05$)[95]. As revealed by quantile regression, this effect is more accentuated for patients with lower adherence (MPR about 65%)[95]. According to me, a possible explanation of the influence of index pill burden on adherence may be the presence of adverse effects of oral dementia medications which are dose dependent and diminish over time; less-adherent patients are probably not yet adapted to the adverse effects – and therefore more susceptible to higher doses- as compared to patients reaching higher levels of adherence who have adapted in time to the dementia treatment.

In patients with pill burden <10 the adherence (measured as proportion of days covered – PDC) was significantly better in patients treated with rivastigmine patch than in patients receiving donepezil (oral AD treatment), (PDC 62.3% vs. 57.2%, $p=0.0095$)[87]. The difference between the groups lost statistical significance for daily pill burden greater than 10[87]. It is possible that for pill burden >10, the advantage of administering rivastigmine patch on increasing compliance may be lost because of greater caregiver involvement which ensures that medications are administered according to the prescription.

Treatment and support

Switching from oral AChEI's (donepezil) to transdermal (rivastigmine patch) results in improved adherence as suggested by the mean PDC (proportion of days covered) for transdermal administration of 61.9% compared to 58.8%, for oral administration (p=0.0414)[87]. Results suggest that- in new AChEI's users who were started on donepezil and subsequently switched to rivastigmine- switching to transdermal in the first year of therapy is followed by an improved adherence (PDC donepezil 60.6, PDC rivastigmine 69.3%, p=0.0004). Furthermore, switching in the first 3 months results in even better results in terms of compliance (PDC donepezil 80.4%, PDC patch 90.7%, p=0.037)[87].

c. Healthcare system

While the type of insurance (commercial versus Medicare) was not associated with the level of adherence[99], the out-of pocket contribution[85], [87] and the cost of AD medications were significant determinants of adherence[95], [99]. Not benefiting from social assistance was associated with a higher likelihood of cholinesterase inhibitor therapy discontinuation compared to those receiving assistance (adjusted HR=1.25, CI:1.07-1.45, P=0.004)[85]. Patients' share of total prescription cost ≥ 65% was associated with a 51% higher likelihood of discontinuation of cholinesterase inhibitors (as opposed to those with shared cost <65%), adjusted HR=1.51, CI: 1.30-1.74, p<0.001[85]. Similarly, low cost sharing of rivastigmine was related to better adherence as suggested by a PDC difference of 4.2%, p=0.0389[87].

Based on price, medications can be categorized on a scale (Tier) from cheap to expensive with Tier 1 being the less expensive. Patients receiving Tier 2 oral AD medications were 1.33 times more likely to be adherent to their medication regimen than those receiving Tier 3 medications (OR=1.332, CI:1.133-1.567, p<0.001)[99]. Patients receiving Tier 2 medications were less likely to be adherent compared to patients treated with Tier 1 medications (OR=0.62, CI 0.46-0.83, p<0.05)[95]. Quantile regression analysis has revealed that adherence is not influenced by the cost of medications in patients who display a very good adherence (MPR around 99%); on the contrary, in patients with adherence levels of 65% (which is below the most frequently used 80% cut-off value for MPR) the price of medications is a significant determinant of adherence[95].

No clear influence of the area of residence on adherence exists. While a Canadian study[85] showed that residing in rural or urban areas was not a significant determinant of adherence, a large US database analysis revealed that the likelihood of being adherent to oral AD therapy (rivastigmine, donepezil, galantamine or Memantine) is lower for patients residing in the Southern US compared to those residing in the Western US (OR 0.78, CI: 0.563-0.995)[95], [99].

C. Interventional studies

The group of interventional studies consisted of 2 randomized controlled trials [72], [73] and 3 non-randomized trials [74], [82], [93].

a. Patient factors

Medical

Forgetfulness represents a determinant of poor adherence to AD medications[74]. Participants treated with tablets/capsules were 6.92 times more likely to report forgetfulness as a reason of non-adherence compared to those treated with transdermal rivastigmine (OR 6.92, CI: 4.27-11.2, $p<0.0001$) and those receiving acetylcholinesterase inhibitors in form of solution were 4.32 times more likely to report forgetfulness as a reason of non-adherence (OR:4.32, CI: 2.24-8.35, $p<0.0001$)[74].

Misinterpretation of instructions – another feature of cognitive impairment- was associated with poor adherence in patients treated with acetylcholinesterase inhibitors in form of solutions compared to those treated with patches (OR 7.31, CI:1.44-37.07, $p<0.02$)[74].

General cognitive status (evaluated by the MMSE score) was not significantly associated with adherence capacity[93]. Furthermore, the degree of cognitive impairment failed to be a predictor of adherence to oral acetylcholinesterase inhibitors; authors explained the lack of association based on the small sample size (27 participants)[73].

Some patients associated existing co-morbidities with their poor level of adherence; the relationship was stronger among those treated with capsules/tablets than in participants who received transdermal rivastigmine (OR 4.96, CI:1.59-15.43, $p<0.01$)[74].

None of the factors suggesting psychological co-morbidity have been found significantly related to adherence[72], [73]. The feeling of being more ill compared to others belonging to the same age segment or being more concerned about the health status was not associated with the level of adherence (P>0.3, Mann Whitney U test)[72]. Similarly, depression was not associated with compliance in an interventional study in which various factors with possible impact on adherence were analyzed[73].

Impairment of specific cognitive functions (e.g. executive functioning and delayed recall) represents a distinct entity evaluated in studies of adherence to medications. While executive functioning failed to reach statistical significance, better long term memory was positively associated with adherence to oral AD medications (p=0.02)[73].

Behavioral

A resisting care attitude (suggested by treatment refusal) and treatment related beliefs (suggested by the perception that treatment is not needed) are two behavioral factors with negative influence on adherence to medications. Participants treated with capsules/tablets were 36% more likely to name refusal of treatment as rationale of non-adherence compared to those using rivastigmine patches (OR 1.36, CI: 1.05-1.77, p<0.0001)[74]. Similarly, patients using solutions were 21.48 times more likely than those using patches to perceive that medication is not needed (OR:21.48, CI 6.25-72.95, p<0.0001)[74].

Socio-demographic

Besides age, none of the socio-demographic factors suggested in the final framework were found to be significantly related to adherence. In a study conducted by Ownby et al (2012), increased age was positively related to adherence to oral AD medications (p=0.002); health literacy, gender and patients' language were not significant determinants of medication compliance[73].

b. Patient and caregiver factors

Medications

Adverse effects of neither oral nor transdermal AD medications were associated with adherence[74]. In this study, adverse effects of AD medications were the second most frequently

mentioned reason for adherence at baseline; the non-significant association between adverse effects and non-adherence at 3 months was obtained by comparing the reasons for non-adherence between the galenic form groups (tablets, solutions, patches)[74]. Authors did not compare the impact of adverse effects on adherence at baseline with the impact at 3 months. Many patients treated with oral forms at baseline were switched to transdermal at 3 months (6.1% patches at baseline and 64.8% patches at 3 months) which may bias (in my opinion) the lack of association between adverse effects and adherence at 3 months.

Patients and caregivers rely sometimes on medication management strategies for facilitating compliance to medications. One possible strategy is the use of visual aids (e.g. a pictogram with all prescription medications and the number of doses to be administered according to the time of the day). Research has shown that usage of visual aids indeed has the capacity to significantly increase the comprehension of medication prescriptions $p<0.0001$; this applies to all aspects studied when assessing compliance: 1) the number of tablets to be taken during the day, 2) number of daily doses and 3) administration mode of medicines[93].

c. Caregiver factors

Behavioral

The factor "ability to cope" comprises various factors which permit caregivers to overcome difficulties associated with assisting patients with dementia and are reflected in assuring an optimal level of continuity of care. Caregiver burden represents an important reason of non-adherence in patients treated with oral AD medications as compared to the transdermal delivery form (OR 5.43, CI:2.54-11.17, $p<0.0001$)[74]. Likewise, caregiver change was significantly associated with non-adherence in patients treated with oral AD medications as compared to those treated with patches (OR 9.42, CI: 2.51-35.30, $p<0.001$)[74].

Treatment and support

The presence of a caregiver was positively associated with increased adherence, $p<0.001$[73]. A possible explanation is represented by an increased level of assistance with medication administration.

d. Prescriber factors

Medications

A modifiable factor for optimizing the level of adherence to medications is represented by individualizing the treatment based on the galenic form. Patients treated with capsules or tablets were less likely to adhere to the dementia specific treatment regimen compared to patients treated with rivastigmine patches; patients taking tablets/capsules were 80% less likely to be adherent due to missing medications (OR 0.201, 95%CI: 0.13-0.32; $p<0.0001$) and 77% less likely to be adherent as a result of not respecting the indicated dosage, timing and mode of administration (OR 0.236, CI: 0.15-0.37; $p<0.0001$)[74]. With regard to patients receiving AD specific therapy in form of solutions, they were 76% less likely to be compliant as compared with those treated with rivastigmine patch due to omitted medications (OR: 0.247, CI: 0.13-0.45; $p=0.041$)[74].

Another prescriber-dependent modifiable factor for improving adherence is represented by reducing the number of medications and simplifying the administration schedule. In patients treated with tablets/capsules, polymedication and complex dosing regimens were significantly associated with poor adherence[74]. At baseline 2.3% of patients receiving transdermal rivastigmine, 13% of those receiving tablets/capsules and 20.5% of those treated with solutions (for AD) reported polymedication as the cause of non-adherence ($p=0.0025$)[74]. At 3 months the association between polymedication and non-adherence remained significant; those treated with capsules/tablets were about 5 times more likely to report polypharmacy or complex dosing regimen as a reason of non-adherence than those using patches (OR 5.08, CI:1.2-21.54, $p<0.05$) while the likelihood in patients receiving solutions was almost 10 times higher (OR:9.91, CI: 2.16-45.45, $p<0.01$)[74].

One of the ways to address complex medication regimen issues is to reduce the number of daily administrations. It has been shown that one time per day administration results in significantly ($p<0.008$) better adherence to oral therapy than three times daily administration[72]. Medication adherence -measured by reading the number of pill bottle openings as recorded by a microchip incorporated in the cap of the bottle- was better in patients receiving one dose/day - in term of total number of administered doses and respecting the indicated dose schedule – compared to those receiving three doses per day[72].

Treatment and support

The following adherence promoting strategies have proved to be successful in patients with dementia: 1) switching the galenic form of specific AD treatment from oral to transdermal[74], 2) implementing psycho-education measures[74], 3) using video-monitoring techniques[82], 4) delivering patient-centered information about dementia and medication management options[73] and 5) employing automated phone reminding strategies[73]. Other interventions have not significantly changed the level of adherence, such as: 1) motivational support[74], and 2) change of concomitant (non dementia) treatment[74]. Surprisingly, in another study, (not automated) phone monitoring of medication was not found to be successful in improving adherence[82]. In this study, there was no significant difference in adherence between the phone group and the control group, nor between the phone group and the video-monitoring group[82].

In a study in which physicians implemented various adherence improving strategies in a cohort of baseline non-adherent patients, switching from oral AD treatment to patches was the most frequently chosen strategy by physicians, being applied to 74.5% of patients who improved medication compliance at 3 months ($p<0.0001$)[74]. In the same study, providing information about the disease with the purpose of helping participants understanding the disease and its management options (referred by authors as psycho-education) was successful in improving compliance at 6 months ($p<0.0001$)[74].

Employing a remote video monitoring procedure -in which investigators regularly contacted dementia patients living alone - with the purpose of facilitating medication administration, proved to be successful in improving adherence[82]. In the video monitoring group the compliance rate remained almost unchanged over time (80% initial and 81% final) while in the phone group and in the control group the compliance declined (85% initial and 80% final for the phone group and 75% initial and 62% final for the control group)[82]. The final adherence in the video monitoring group was significantly higher than the final adherence in the control group ($p<0.05$)[82]. These results are even more important considering the fact that the global cognitive status of the patients deteriorated over the length of the study follow-up (18 months)[82].

Providing tailored information about dementia and its treatment – adapted to patients' information needs, health literacy and language -was significantly associated (p=0.04) with better adherence to acetylcholinesterase inhibitors or memantine compared to controls who received usual care[73]. The same study succeeded to prove that patients receiving automated daily phone calls to remind them to take their AD medications had better end of phase adherence than their counterparts belonging to the control group (p=0.02)[73].

VI. Step three: integration of qualitative and quantitative evidence

So far, I have provided the output of the qualitative synthesis -represented by the final framework of factors impacting adherence to medications as described in Figure 4- and the quantitative synthesis of data pertaining to adherence, which was organized by study design – observational, claim database and interventional- based on the structure of factors proposed in the final framework. The purpose of integrating both qualitative and quantitative data in a common matrix is to provide a synthesis of the impact on adherence to medications of each factor (Appendix 4). The ultimate goal of the integration phase is to categorize the identified factors based on their impact on adherence as presented below in Table 1.

In the integration matrix (Appendix 4) factors are presented in the left column, in the same order as in the final framework (Figure 4). Thus, evidence is organized based on patient, patient and caregiver, caregiver, prescriber and healthcare system categories. In each category, factors are listed in the same order as in the final framework. The name of factors remained unchanged or suffered a slight adjustment as follows: a) if no quantitative data pertaining to the impact on adherence of a factor was found, the name remained unchanged, b) if a factor was quantitatively measured, then the name was slightly changed with the purpose of clearly presenting the impact trend (barrier or facilitator), c) if the name of the factor was suggestive of a broad concept, a name change could not be done and future details are provided. As an example, the name was changed from "functional status" to "decreased functional status" with the purpose of being able to evaluate if it represents a barrier or a facilitator. An example of the last scenario (c) is represented by "Class and name of medicines" that comprise of various names/classes of medicine, making further attempts to find a more suggestive name useless. The first row of the column header contains the study identification (reference) and the second row the appraisal

score for each study in which the impact of factors was measured (e.g. qualitative studies were excluded from the integration matrix).

The cells contain, in the majority of cases, one abbreviation per study but there are cases with two or three abbreviations for one factor; it occurred in studies in which multiple aspects (summarized in one factor) were evaluated and the impact of the aspects was different. For example, the factor "impairment of specific cognitive functions" includes: performance on verbal and visual tasks, executive functioning, ability to form associations, status of long term memory, etc. These individual aspects could have been found as having no impact or being a barrier or facilitator in the same study[90]. This study ([90]) represents an exception, being the only one in which all three possible values were present (in the same cell) and represent contradictory evidence; in all other cases where 2 annotations corresponding to a specific study are displayed (in the same cell), these point in one direction: either no impact/facilitator (possible facilitator) or no impact/barrier (possible barrier).

A synthesis of the direction of influence on adherence to medications of individual factors is provided in Table 1. For each category of the final framework, the impact on adherence is displayed from left to right. The interpretation of most factors is straight forwarding with the exception of three factors which need further clarification. Thus, the factor "Impairment of specific cognitive functions" was categorized as a "possible barrier" factor, despite the fact that study ([90]) suggests contradictory evidence (B and F and NI). The decision was based on the fact that impairment of all subcomponents of cognitive status are barriers of medication adherence with the exception of decreased ability to form associations (e.g. between medications and adverse effects) which is a facilitator of adherence because those with preserved ability display higher rates of intentional non-adherence. The factor "Class and name of medicines" either has no impact or represents a barrier or is a facilitator of adherence. Thus, no difference in adherence level was found between patients treated with rivastigmine, donepezil or galantamine[78], [84]. Another study found that Hispanics and African-Americans are less likely than whites to be adherent to acetylcholinesterase inhibitors[79]. Prescribing anticholinergic drugs represents a barrier of medication adherence in patients treated for dementia[86]. Evidence pertaining to central nervous system (CNS) medications is contradictory; these medications can be barriers[84], facilitators (antidepressants)[98] or "no impact" factors[86], [98]. Equally important is to adapt the type of antihypertensives prescribed in patients with dementia to the

ethnicity of the patient[79]. Pertaining to the area of residence, there is no impact of residing in urban or rural areas on adherence[85] while patients residing in the southern US were found to have a lower likelihood of adherence compared to those who live in the western part[95], [99].

Table 1- Impact of factors on adherence to medications in patients with Alzheimer's dementia and related disorders

	POSSIBLE BARRIER	POSSIBLE FACILITATOR	NO IMPACT	CONTRADICTORY	NOT MEASURED
PATIENT FACTORS	- General cognitive status impairment - Impairment of specific cognitive functions - Resisting care attitude	- Decreased functional status - Increased number of physician office visits - White race - High level of education and health literacy - Male gender	- Increased psychological co-morbidity - Acceptance of disease evolution - Patients support system - Language - Lifestyle - Marital status	- Increased physical co-morbidity - Negative treatment related beliefs - Increased number of hospitalizations - Age ≥ 76 (patient)	- Stage of dementia - Treatment effectiveness - Living alone
PATIENT AND CAREGIVER FACTORS	- Adverse effects of medications	- Employing medication management strategies - Positive perceptions of treatment effectiveness			- Expectations of treatment benefits
CAREGIVER FACTORS	- Decreased ability to cope	- Good caregiver skills - Increased level of assistance with medications	- Availability of caregiver support system		- Assuming an active role
PRESCRIBER FACTORS	- Oral AChEI's	- Good dementia care skills - Adherence promoting strategies		-Class and name of medicines -Increased complexity of medication regimen	- Quality of relationship with patients and caregivers
HEALTHCARE SYSTEM	- Increased medication cost burden - Area of residence		- Memory clinic structure		

CONCLUSION AND DISCUSSION

Mechanisms of medication adherence in general are multi-faceted and determined by complex interactions between patients, health-care providers and external factors. Providing a portrait of factors impacting medication adherence in patients with Alzheimer's dementia and related disorders should take into consideration not only general factors of adherence, but also factors specific to this category of patients such as: increased age, co-morbidities, changes in normal cognitive function, dependency on external support, and financial vulnerability.

I. Summary of results and discussion of factors

A. Qualitative synthesis

Providing a portrait of factors of adherence to medications in patients with dementia was based on a preliminary framework (Figure 3) that was improved, made more comprehensive and specific (Figure 4) through a deductive-inductive analysis of qualitative evidence extracted from studies of both qualitative and quantitative methodology.

Results confirm that in patient with dementia, factors of medication adherence can be categorized in five entities: 1) patient factors, 2) caregiver factors, 3) patient and caregiver factors, 4) prescriber factors and 5) healthcare system factors. These entities, rather than isolated, are highly inter-related as proved, for instance, by the newly emerged category "patient and caregiver factors". These results suggest the need of a holistic approach to adherence issues in dementia patients.

Two sub-categories of factors are of special importance, not only for patients but also for caregivers and prescribers: a) behavioral and b) treatment and support factors. Pertaining to the former, expectations of treatment benefits and the perception of treatment effectiveness are common factors of adherence for both patients and caregivers while on the part of prescribers, the quality of the relationship with patients and caregivers is a key factor. Other researchers have also highlighted the importance of behavioral factors in addressing medication adherence. Thus, based on behavioral medicine knowledge, Garfield and Caro (2000) have suggested that adherence can be improved in line with the following phases of change: "1) Preconception; the

patient is not intending to change, 2) Contemplation; the patient considers change 3) Preparation; small changes are initiated, 4) Action; active behavioral changes are made and 5) Maintenance; there is sustained long-term change in the behavior"[32]. Consequently, behavioral factors represent a central aspect of medication adherence and healthcare providers can address this aspect in a reflexive way (by improving their relationship with patients) and by finding solutions to improve adherence based on the preparedness of the patients (and caregivers) for improving adherence. Related to the latter sub-category (treatment and support), a central aspect is represented by dementia care skills- including being aware and making use of adherence improving strategies- and the availability of a support system for caregivers and patients.

B. Quantitative synthesis and integration

The assessment of the impact of identified factors on adherence suggested three possible main influences: a) possible facilitators, b) possible barriers and c) no impact of factors on medication adherence. Due to the heterogeneity of results, in the final interpretation model, a fourth category emerged: contradictory results. The final integration matrix shows that there are other aspects beyond study type (observational, claim database or interventional) that can explain discordant results pertaining to the impact on adherence of individual factors; one aspect could be individual study design characteristics. This conclusion is reinforced for example by the observation that in patients with dementia and related disorders increased psychological co-morbidity had no impact on medication adherence, as evaluated by both observational and interventional studies (5 observational and 2 interventional studies- Appendix 4). Similarly, increased physical co-morbidity was found to be a barrier by all three study types, a no-impact factor by observational and claim database studies or a facilitator in another claim database study (Appendix 4). Consequently, the integration matrix is a valuable method of analyzing the overall impact of individual factors by displaying the results from individual studies in a reader-friendly way.

For most determinants of adherence a clear-cut categorization of the influence on adherence could not be found. In other words, it is difficult to point at a specific factor and characterize it as a pure barrier or facilitator. Rather, we can affirm that a factor is probably a barrier or facilitator; this is the case of factors for which quantitative evidence (across analyzed studies) showed that they either have no impact or that they are barriers respectively facilitators.

The results of this review suggest that probable barriers of adherence are: patients' general cognitive status impairment, impairment of specific cognitive functions, resisting care attitude, area of residence, caregivers' decreased ability to cope, adverse effects of medications, prescription of oral versus transdermal acetylcholinesterase inhibitors for treating dementia and increased medication cost burden.

As expected, no evidence was found pertaining to the use of pharmacogenomics in the treatment of patients with dementia; a possible explanation is that it is an emerging area of research. Adapting medication administration based on pharmacogenomics evidence can facilitate medication adherence by individualizing therapies[49]. Based on the findings of this review, the class and name of medicines used to treat dementia as well as the pill burden have contradictory influence on adherence. A possible explanation could be the variable response to different medications and doses as determined by the genetic profile of each individual. Therefore, monitoring the progress in pharmacogenomics is important for optimizing adherence in patients with dementia in the future.

This review suggest that following factors can be viewed as key facilitators of medication adherence: patients' decreased functional status, increased number of physician office visits, positive perception of treatment effectiveness, high level of education and health literacy, white race, male gender as well as an increased caregivers' level of assistance with medications. Prescribers' recommendations of adherence promoting strategies and the willingness of both caregivers and patients to employ medication management strategies are also possible facilitators of medication adherence. Last but not least, good dementia care skills of both prescribers and caregivers have the potential of facilitating medication adherence

Among factors for which both positive and negative influence evidence was found (contradictory evidence) it is important to mention that only one study[85] found increased physical co-morbidity to be a facilitator of medication adherence; all other analyzed studies showed that increased physical co-morbidity represents a barrier or has no impact on adherence. Based on authors' explanations[85] the Chronic Disease Score (CDS) used in this claim database study to assess increased co-morbidity might have influenced the results because CDS is derived from patients' dispensed medications, thus indirectly reflecting a greater physician involvement; patients with higher CDS score also had a higher number of physician visits. Therefore, patients

with dementia who suffer from multiple diseases could be rather inclined to achieve lower levels of medication adherence. Most evidence related to increased complexity of medicating regimen point in the direction of impeding on medication adherence or of non-influence, with the exception of one study[99]. Interestingly, the same author published in 2013 another study[95] in which he concluded -based on analyzing data from the same pool of patients - that greater pill burden is associated with a decreased likelihood of being adherent. Excluding both studies (original and companion article) from the final analysis allows me to conclude that increased complexity of medication regimen is a probable barrier of adherence to medications.

The results of this review suggest that some factors have no impact on medication adherence, i.e. factors for which no statistically significant influence on adherence was found: increased psychological co-morbidity, acceptance of disease evolution, patients' support system, language, lifestyle, marital status, availability of caregiver support system and memory clinic structure.

Some factors have not been measured yet (stage of dementia, patient living alone, patients' and caregivers' expectations of treatment benefits, quality of prescribers' relationship with patients and caregivers) or their impact has not been tested using a statistical test: treatment effectiveness and caregivers' availability to assume an active role.

II. Strengths

The validity of the final framework of factors impacting adherence is ensured by the process of building it on a comprehensive preliminary framework -obtained based on existing reviews (Figure 3) - and by the fact that the qualitative evidence from the set of studies under scrutiny confirmed the general structure of the preliminary framework while permitting improvement and readjustment based on the latest evidence.

The good quality of included studies has contributed to the overall quality of the review; the majority of both qualitative and quantitative studies received at least a score of 3 out of 4.

The major strength of this review relies in its design. To my knowledge, this is the first systematic review using a mixed methods design to document and measure factors of medication adherence in ambulatory patients with Alzheimer's dementia and related disorders. The use of a mixed methods sequential exploratory design allowed to: 1) propose a comprehensive and

specific framework of key factors influencing medication adherence in patients with dementia and 2) evaluate their impact on adherence, despite the heterogeneity in the design of included studies.

III. Limitations

The majority of included studies (20 out of 34) explored medication adherence related exclusively to dementia specific medications. This is the result of the paucity of studies evaluating medication adherence in: a) dementia patients in general and b) of medications prescribed for associated co-morbidities in this population.

These review portraits medication adherence determinants in patients with mild to moderate dementia. Usually, patients with more advanced stages of dementia are institutionalized (and were not included in this study); medication adherence in this category of patients should be viewed from a different angle because of particularities of medication prescriptions and administration in long term care facilities. It is important to highlight that this review focused on dementia patients, leaving patients with mild cognitive disorders or other cognitive disorders not categorized as dementia out of the scrutiny. This may be an explanation why the present review included only one study of HIV caused dementia and no study of patients with dementia in the context of Parkinson's disease. Consequently, including all patients with cognitive impairment represents a potential path to follow in future research.

It is possible that existing evidence pertaining to patients with dementia has been omitted from the present review, because of two reasons: 1) sometimes dementia is not clearly stated as an inclusion criterion in the studies, even though the cognitive impairment of included patients range from mild cognitive impairment to advanced cognitive impairment, which is suggestive of dementia and 2) The snowballing approach of finding additional relevant articles from the bibliography of included articles was not used due to the lack of time.

Given the set of studies included, it was not possible to identify the lack of initiation of the drugs. Indeed, all the quantitative studies focused on persistence and compliance.

The heterogeneity of the tools used in measuring adherence in the set of studies under scrutiny my represent a limitation. Relying on physician's perceptions (estimation) about adherence and reports from patients have low validity. Thus, it is recommended to use higher

validity tools in measuring medication adherence such as: MPR (medication possession ratio), electronic monitoring of administration, Morisky Green questionnaire.

In the quantitative studies, it was not possible to identify the underlying process leading to an office visit. It can be argued that an office visit is a combination of a patient behavior, the quality of the relationship with the family physician and the characteristics of the healthcare system. No additional information was available on healthcare system accessibility in the qualitative studies. Given the lack of details provided in the studies, I put the number of physician visits in the category of patients factors.

In addition to the limitations linked with the included studies, there are some limitations with the methods used for this review. In particular, I did not search for grey literature (dissertations, thesis, and books). However, given the goal and the timeframe for my M.Sc, the inclusion of grey literature was not deemed essential. I based my preliminary framework on existing well-known and published frameworks and I adapted this framework based on the results of published studies. Consequently, I am confident that this review captures the essential factors influencing adherence.

IV. Implications for clinical practice

A. Assess the risk of non-adherence

The following predictors of better adherence could be used by physicians/prescribers for rapidly evaluating the risk of non-adherence: higher education and health literacy of patients, no previous episodes of medication non-adherence, regular physicians' office visits, decreased functional status, white ethnicity and male patients. Also, the results suggest that cognitive assessment should not be limited to evaluating the general cognitive function (MMSE). It is important to evaluate the level of impairment of specific cognitive functions, in particular: decreased memory awareness, lower awareness of medication management, deficit in psychomotor performance and impairment of executive function.

B. Optimize the medication regimen

It is advisable for prescribers to maintain a high level of reflexivity when treating dementia patients. Prescribers should keep the medication regimen at the lowest possible level and stop any non-essential medications. Special attention should be paid to avoiding adverse effects of medications - especially in the context of complex medication regimens- and to the advantages of switching from oral to transdermal drugs when possible.

C. Take into account the importance of the patient-caregiver dyad

The patient-caregiver dyad should be regarded as a unity as there are factors impacting adherence that are commonly shared between patients and caregivers. A good level of adherence cannot be achieved without taking into consideration caregiver related factors. Thus, increased caregiver burden, frequent caregiver change and low satisfaction with medications are all associated with low adherence. On the other hand, an increased level of caregivers' assistance with medication administration as well as being correctly informed about the disease evolution and treatment expectancies predict good adherence.

D. Increase the quality of information provided to patients, caregivers and prescribers

Information and educational interventions targeting the patient-caregiver dyad and the prescribers (physicians) might be efficient for increasing adherence to medications in patients with dementia. On the patient/caregiver side, providing information about disease evolution, treatment effectiveness and management of adverse effects can both address a possible resisting care attitude of patients and increase the assistance of caregivers with medications. On the prescriber side, organizing educational activities with the goal of increasing dementia care skills can increase the adherence to medications of patients with Alzheimer's dementia and related disorders.

E. Implement adherence promoting interventions:

Some adherence promoting interventions are effective in increasing adherence. Hence, utilization of visual aids, reminders, pill boxes, phone and or video monitoring have all been proven to be effective in increasing adherence to medications.

F. Increase support provided to patients and caregivers

Designing interventions to increase the availability of a support system for patients and caregivers might increase adherence to medications, despite the fact that the present review failed to prove an impact of the support system on adherence. It is reasonable to expect that providing information to patients about available support systems and providing formal help to caregivers -such as: respite bed, home nursing, day hospital- would have the potential to increase adherence levels.

V. Implications for future studies

A recommended direction for further studies is represented by exploring factors found in this review as having no impact, contradictory impact on medication adherence or factors for which the impact has not been measured at all.

A. "No impact" factors

It might not be useful to measure the "no impact" factors in future studies as this review was able to provide a synthetic view. However, two factors might be measured in future studies due to the paucity of studies having measured these factors. It is the case for the acceptance of disease evolution, including patients' awareness of the seriousness of the disease (measured in only one quantitative study) and the availability of support for caregivers and patients (only one quantitative study). Pertaining to the former, one could hypothesize that a better insight of the seriousness of the disease could facilitate the process of receiving external help (including medications), thus having a positive influence on medication adherence. Related to the second, it seems possible that an increased availability of health and social services, including services which could decrease caregiver's burden, could have a positive effect on medication adherence.

B. Factors with contradictory evidence

This review revealed contradictory evidence that requires future studies. Firstly, a tendency exists to consider increased age (>76 years) a facilitator of adherence, but confirmation is required. Secondly, increased number of hospitalizations can be the result of poor medication management or low accessibility to physicians – which in turn is related to poor adherence- or can be a facilitator of adherence because during hospitalizations medication regimens and

treatment benefits are reassessed and optimized, which in turn can increase adherence. Thirdly, increased complexity of medication regimen is generally viewed as a barrier of adherence; it is possible that caregivers' level of assistance with medication administration increases in parallel with the pill burden. This may explain why complex administration schedules are not always associated with poor adherence. Thus, it is important to further explore the relationship between the medication burden and the existence of medication administration support from caregivers.

Fourthly, negative treatment related beliefs of patients such as: long term adverse effects of medications, over-prescription of medications and potential addictive effects of medications might have a negative influence on the adherence to medications. Due to the paucity of quantitative data (evidence extracted from only two quantitative studies), further research is needed for confirming the influence of treatment related beliefs on adherence.

C. Factors not yet measured

The caregivers' health status (physical and cognitive) mentioned in the preliminary framework (Figure 3) was not confirmed based on the set of analyzed studies. Caregivers' health related factors represent a direction for further research

Current evidence suggests that the stage of dementia influences the medication management process[88]; specific features of medication management apply to early dementia as compared to late dementia. Consequently, it is necessary to study how dementia stage is related to medication adherence in order to apply specific medication management strategies.

The role of the quality of relationship between the prescriber and caregivers and patients could not be assessed in this review because of lack of quantitative evidence. It is possible that the level of adherence to medications parallels that of the quality of relationship between prescribers and patients/caregivers but this hypothesis awaits confirmation from further studies.

Assuming an active role of caregivers in medication management (e.g. caregivers' constant focus on respecting the medication administration schedule, making sure the patient has actually swallowed the medication, pro-actively requesting treatment) may represent a factor of medication adherence that could be studied in future studies. Moreover, it is appropriate to

further study the impact of living status of patients with dementia (living alone) on the level of adherence.

Expectations of treatment benefits- which can be realistic or unrealistic- have been identified as factors with potential influence on medication adherence in qualitative research studies but they have not been measured. We may hypothesize that realistic expectations of treatment benefits could have a possible influence on adherence to medications in patients with Alzheimer's dementia and related disorders.

VI. Key points

The review provides a comprehensive and specific framework of key factors which impact medication adherence in patients with Alzheimer's disease and related disorders.

Based on the proposed framework, a detailed description of the impact of identified factors on medication adherence is provided.

Our mixed studies review design permitted integrating qualitative with quantitative evidence. By using this technique, it was possible to provide a synthesis of the impact of factors on medication adherence.

The results of this review suggest avenues to improving the care provided to patients with Alzheimer's dementia and related disorders. In particular, the present review provides evidence for clinicians, managers and policy makers for designing or refining interventions to increase medication adherence in patients with Alzheimer's dementia and related disorders. The results of this review can be used for future research and for improving medication adherence in dementia patients.

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APPENDICES

I. Appendix 1 Search strategy for Medline

Research report

For Ovidiu Tatar (Isabelle Vedel Team)
By Muriel Guériton
24/09/2013
First extensive research in Medline : results 1254 references

Search strategy

Database: Ovid MEDLINE(R), Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid OLDMEDLINE(R) <1946 to Present>
Search Strategy:
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1 drug therapy/ or drug prescriptions/ or drug therapy, combination/ or drug therapy, computer-assisted/ or inappropriate prescribing/ or medication errors/ or polypharmacy/ or prescription drug misuse/ or self administration/ or self medication/ (224218)
2 Medication Therapy Management/ (633)
3 Medication Reconciliation/ (253)
4 Patient Medication Knowledge/ (35)
5 (medicat* or drug* or prescript* or prescrib* or pharmac* or polypharmac*).ti,ab. (1679615)
6 1 or 2 or 3 or 4 or 5 (1809408)
7 (dementia? or alzheimer*).mp. (160978)
8 exp dementia/ or exp aids dementia complex/ or exp alzheimer disease/ or exp aphasia, primary progressive/ or exp creutzfeldt-jakob syndrome/ or exp dementia, vascular/ or exp diffuse neurofibrillary tangles with calcification/ or exp frontotemporal lobar degeneration/ or exp huntington disease/ or exp kluver-bucy syndrome/ or exp lewy body disease/ or exp "pick disease of the brain"/ (121313)
9 7 or 8 (175300)
10 6 and 9 (22449)
11 Alzheimer Disease/dt (9787)
12 exp dementia/dt (14712)
13 11 or 12 (14712)
14 10 or 13 (30418)
15 (adherence* or complied or compliance? or discontinuation? or participat* or nonadherence? or noncompliance? or refusal).ti,ab. (519407)
16 "patient acceptance of health care"/ or patient compliance/ or patient participation/ or patient satisfaction/ or treatment refusal/ (159095)
17 Medication Adherence/ (7146)
18 15 or 16 or 17 (638178)
19 14 and 18 (1422)
20 limit 19 to (humans and (english or french or german)) (1254)

II. Appendix 2 General characteristics of included studies

Appendix 2 – Part 1- Qualitative studies - General characteristics

Basic study characteristics	Title	Objectives	Participants	MMAT score
Hutchings et al.[68], 2010, UK, (constructivist theory of knowledge)	"Good days and bad days: The lived experience and perceived impact of treatment with cholinesterase inhibitors for Alzheimer's disease in the United Kingdom"	To describe the lived experiences of patients treated with AChEI's, including the perceived impact of treatment.	12 patients and 11 informal caregivers	3/4
de Witt et al.[58], 2010, Canada (interpretive phenomenology)	"Living alone with dementia: an interpretive phenomenological study with older women"	To portrait the meaning of living alone from the point of view of older adults suffering from dementia	8 women	3/4
Kaasalainen et al.[88], 2011,Canada (grounded theory)	"The process of medication management for older adults with dementia"	To explore individual experiences related to medication management	11 patients, 20 informal caregivers, 10 pharmacists, 11 community health nurses, 6 family physicians	4/4
Lindstrom et al.[69], 2006, USA (qualitative description)	"Medication use to treat memory loss in dementia: Perspectives of persons with dementia and their caregivers"	To highlight practices and beliefs of patients with dementia and their informal caregivers pertaining to dementia medications	19 patients and 19 caregivers	3/4
Smith et al.[70], 2008, Australia (constructivist position)	"Quality of life and cholinesterase inhibitors: a qualitative study of patients with Alzheimer's Disease and their carers"	To investigate the consequence of AChEI's use on living and quality of life of patients with dementia and their caregivers	11 patient-caregiver dyads	2/4
Hutchings et al.[71], 2010, UK (constructivist or relativist position)	"Cholinesterase inhibitors and Alzheimer's disease: Patient, carer and professional factors influencing the use of drugs for Alzheimer's disease in the United Kingdom"	To understand which factors influence decisions to initiate, continue and discontinue treatment with donepezil, rivastigmine and galantamine.	12 patient-caregiver dyads	3/4

MMAT (Mixed Methods Appraisal Tool), AChEI's (acetyl cholinesterase enzyme inhibitors)

Appendix 2- Part 2- Quantitative studies - General characteristics

Basic study characteristics	Title	Objectives	Participants	Outcome	MMAT score
Suh et al.[84], 2005, USA (observational retrospective)	"Drug Persistency of Two Cholinesterase Inhibitors. Rivastigmine versus Donepezil in Elderly Patients with Alzheimer's Disease"	To comparatively assess persistency with rivastigmine or donepezil in AD patients and to assess factors influencing persistency	783 patients with AD, MarketScan database	Discontinuation and switching	4/4
Sun et al.[78], 2008, Taiwan (observational retrospective)	"How long can patients with mild or moderate Alzheimer's dementia maintain both the cognition and the therapy of cholinesterase inhibitors: a national population-based study"	To evaluate the duration of AChEI's use , factors influencing treatment duration and preservation of cognitive function	9877 AD patients, Bureau of National Health Insurance of Taiwan database	Treatment duration	3/4
Cotrell et al.[92], 2006, USA (observational prospective)	"Medical Management and Adherence Among Cognitively Impaired Older Adults"	To assess the relationship between medication adherence and factors influencing adherence: cognitive status, medication management skills and deficit awareness	27 persons with Alzheimer's disease and 20 health controls	Adherence (pill count), performance of medication management	3/4
Molinuevo et al.[74], 2012, Spain (observational prospective)	"Impact of transdermal drug delivery on treatment adherence in patients with Alzheimer's disease"	To highlight successful strategies for improving adherence in non-compliant AD patients	649 AD patients	Adherence evaluated based on missed doses and respecting the schedule	3/4
Amuah et al.[85], 2010, Canada (observational retrospective)	"Persistence with cholinesterase inhibitor therapy in a population-based cohort of patients with Alzheimer's disease"	To evaluate the factors of discontinuation of AChEI's therapy	1080 AD patients, administrative health data in Saskatchewan, Canada	HR of discontinuation	4/4
Poon et al.[79], 2009, USA (observational retrospective)	"Racial/Ethnic Disparities in Medication Use Among Veterans with Hypertension and Dementia: A National Cohort Study"	To assess adherence to dementia and antihypertensive drugs in patients with both dementia and hypertension	56,561 patients, Veterans Health Administration databases	Medication possession ratio (MPR)	3/4

MMAT (Mixed Methods Appraisal Tool), MPR (Medication Possession Ratio), PDC (Proportion of Days Covered), HR (Hazard Ratio), AD (Alzheimer Disease) AChEI's (Acetylcholinesterase enzyme inhibitors)

Appendix 2 - Part 2- Quantitative studies - General characteristics (continued)

Basic study characteristics	Title	Objectives	Participants	Outcome	MMAT score
Borah et al.[99], 2010, USA (observational retrospective)	"Predictors of adherence among Alzheimer's disease patients receiving oral therapy"	To assess determinants of oral AD medications adherence	3091 AD patients, Commercial and Medicare Advantage health plan database	MPR	4/4
Gardette et al.[86], 2010, France (observational prospective)	"Predictive Factors of Discontinuation and Switch of Cholinesterase Inhibitors in Community-Dwelling Patients with Alzheimer's Disease"	To discover factors of discontinuation and switch of AChEI's	686 patients enrolled as part of the multicentre REAL.FR cohort study.	HR of discontinuation	4/4
Boada et al.[97], 2013, Spain (observational, cross-sectional)	"Transdermal is Better than Oral: Observational Research of the Satisfaction of Caregivers of Patients with Alzheimer's Disease Treated with Rivastigmine"	To comparatively evaluate the level of caregivers' satisfaction and patients' adherence between oral and transdermal rivastigmine	1132 patients with AD	Adherence: Morisky Green questionnaire, satisfaction: SATMED-Q	4/4
Weih et al.[96], 2009, Germany (observational retrospective and cross-sectional survey)	"Comparison of Patient Therapy Adherence of Two Structural Different Memory Clinics"	To compare the influence of two differently structured memory clinics on adherence and therapeutic outcome	483 patients with dementia syndrome	Reports of discontinuation from patients ad caregivers	3/4
Oswald et al.[72], 1993, Germany (randomized controlled trial)	"Compliance of patients with dementia syndrome treated with Encephabol forte and Encephabol 600"	To evaluate the comparative adherence between once versus three times per day administration of Encephabol	45 patients with dementia syndrome	Adherence measured based on pill counting, microchip bottle, patients and physicians reports	2/4
Tian et al.[87], 2013, USA (observational retrospective)	"Patient Adherence to Transdermal Rivastigmine After Switching from Oral Donepezil"	To examine patient compliance before and after switching from donepezil to transdermal rivastigmine	772 patients with AD	Proportion of days covered PDC	4/4

MMAT (Mixed Methods Appraisal Tool), MPR (Medication Possession Ratio), PDC (Proportion of Days Covered), HR (Hazard Ratio), AD (Alzheimer Disease) AChEI's (Acetylcholinesterase enzyme inhibitors), SATMED-Q (Treatment Satisfaction with Medicines Questionnaire)

Appendix 2- Part 2- Quantitative studies - General characteristics (continued)

Basic study characteristics	Title	Objectives	Participants	Outcome	MMAT score
Ownby et al.[73], 2012, USA (randomized controlled trial)	"Tailored Information and Automated Reminding to Improve Medication Adherence in Spanish and English Speaking Elders Treated for Memory impairment"	To assess the effectiveness of an information and an automated reminding intervention for improving compliance to AChEI's	27 participants with significant memory problems	Adherence measured by MEMS pill bottle recordings	2/4
Cosentino et al.[91], 2011, USA (cross-sectional controlled trial)	"Memory Awareness Influences Everyday Decision Making Capacity about Medication Management in Alzheimer's Disease"	To investigate the influence of various aspects of memory awareness on medication management	42 participants with AD and 50 healthy elders	Decision making capacity for medication management	4/4
Barry et al.[80], 2013, UK (observational, cross-sectional)	"Community pharmacists and people with dementia: a cross-sectional survey exploring experiences, attitudes and knowledge of pain and its management"	To investigate the experiences and attitudes of community pharmacists related to dementia patients	182 community pharmacists	Questionnaire developed by researchers	3/4
Dhikav et al.[81], 2013, India (observational cross-sectional)	"Medication adherence survey of drugs useful in prevention of dementia of Alzheimer's type among Indian patients"	To measure the compliance to antihypertensive, diabetes and dyslipidemia drugs in dementia patients and to highlight factors with influence on adherence	67 patients with dementia or MCI and their caregivers	Adherence measured based on reports from caregivers (number of doses, frequency of administration)	2/4
Saleh et al.[75], 2013, Canada (prospective cohort quasi-exp.)	"Less Education Predicts Anticholinesterase Discontinuation in Dementia Patients"	To evaluate the predictors of adherence to AChEI's	63 patients with dementia naive to AChEI's therapy	Discontinuation of medications by six months	3/4
Ownby et al.[89], 2005, USA (observational cross-sectional)	"Factors related to medication adherence in memory disorder clinic patients"	To understand medication adherence with the help of an existent integrative model of compliance	75 patients with dementia or memory disorders and 63 corresponding caregivers	Adherence measured based on responses (to a standardized question) from patients and caregivers	2/4

MMAT (Mixed Methods Appraisal Tool), AChEI's (Acetylcholinesterase enzyme inhibitors), MEMS (Medication Event monitoring System) MCI (Mild Cognitive Impairment)

Appendix 2- Part 2- Quantitative studies - General characteristics (continued)

Basic study characteristics	Title	Objectives	Participants	Outcome	MMAT score
Gauthier et al.[100], 2013, Canada (observational prospective)	"Real-life effectiveness and tolerability of the rivastigmine transdermal patch in patients with mild-to-moderate Alzheimer's disease: the EMBRACE study"	Primary objective: to evaluate the effectiveness and tolerability of transdermal rivastigmine. Secondary objective: to assess compliance compared to oral rivastigmine	1204 AD patients	Caregiver reported compliance	4/4
Park et al.[76], 1994, USA (quasi-experimental)	"Cognitive Function and Medication Usage in Older Adults. Comprehension of Medical Information in Normal and Demented Elderly"	To evaluate the ability of cognitively impaired patients to understand and solve problems related to drug label information	Normal and Alzheimer's disease patients	Responses to inferential versus literal questions	1/4
Borah et al.[95], 2013, USA (observational retrospective)	"Highlighting differences between conditional and unconditional quantile regression approaches through an application to assess medication adherence"	To assess the impact of different factors on medication adherence	3091 patients with AD or related dementia from Medicare Advantage health plan database	MPR	4/4
Monfort et al.[93], 2010, France (controlled, non-randomized trial)	"Contribution of pictorial help to the understanding of medical prescriptions in elderly adults and in patients with Alzheimer's disease"	To evaluate the impact of visual aids on understanding of medical prescriptions	30 AD patients and 29 healthy elderly participants	Responses to specially designed (3) questions	4/4
Albert et al.[94], 2003, USA (observational prospective)	"Medication Management Skill in HIV: I. Evidence for Adaptation of Medication Management Strategies in people with Cognitive Impairment. II. Evidence for a Pervasive Lay Model of Medication Efficacy"	To observe the association between cognitive deficit and medication accuracy respectively consistency and to explore beliefs about medications	100 HIV patients and 25 healthy individuals	Medication accuracy and consistency	4/4
Thiruchselvam et al.[90], 2012, Canada (observational prospective)	"Risk factors for medication non-adherence in older adults with cognitive impairment who live alone"	To assess the association between cognitive, medical, behavioral and social risk factors on med. adherence	339 cognitively impaired patients living alone and their CG	Reports of medication non-adherence	4/4

MMAT (Mixed Methods Appraisal Tool), MPR (Medication Possession Ratio), AD (Alzheimer Disease), CG (caregiver)

Appendix 2- Part 2- Quantitative studies - General characteristics (continued)

Basic study characteristics	Title	Objectives	Participants	Outcome	MMAT score
Kamimura et al.[77], 2012, Japan (interventional)	"Medication Reminder Device for the Elderly Patients With Mild Cognitive Impairment"	To study the efficacy of a medication reminder system in patients with very mild to mild dementia	17 patients living alone and their caregivers	Self administered medication rate (SAMR)	2/4
Pariente et al.[98], 2010, France/Canada (observational retrospective)	"Factors associated with persistence of cholinesterase inhibitor treatments in the elderly."	To evaluate factors related to persistence of AChEI's treatments	947 patients, data from French National Healthcare system's 'Echantillon Generaliste des beneficiares (EGB)	One year persistence	3/4

MMAT (Mixed Methods Appraisal Tool), AChEI's (Acetylcholinesterase enzyme inhibitors), AD (Alzheimer's disease)

Appendix 2-Part 3 - Mixed methods studies - General characteristics

Basic study characteristics	Title	Objectives	Participants	Outcome	MMAT score
Smith et al.[82], 2007, USA (qualitative: post-positivistic approach, quantitative: prospective, interventional)	"Telehealth Home Monitoring of Solitary Persons with Mild Dementia"	To assess the efficacy of a tele-video intervention in improving medication self-administration accuracy	14 patients living alone and their caregivers	Medication accuracy-pill count	6/11
Abetz et al.[83], 2009, UK (qualitative: grounded theory, quantitative: observational prospective)	"Alzheimer's disease treatment: assessing caregiver preferences for mode of treatment delivery."	To develop a questionnaire for measuring the satisfaction and preference of caregivers for oral or transdermal dementia medications	24 caregivers of patents with AD and 6 clinicians, psychometric testing on 986 patients enrolled in the IDEAL trial	Opinions about AD treatment, including adherence adherence	8/11

III. Appendix 3 Distribution of factors by study

PATIENT FACTORS (part 1)

	[84]	[78]	[92]	[74]	[85]	[79]	[99]	[86]	[82]	[97]	[96]	[72]	[87]	[73]	[68]	[58]	[88]	[69]	[70]	[71]	[91]	[80]	[81]	[75]	[89]	[100]	[76]	[95]	[93]	[94]	[90]	[77]	[98]	[83]
Stage of dementia																	**X**																	
Functional status					**X**			**X**																**X**							**X**			
General cognitive status (MMSE)		**X**	**X**	**X**	**X**			**X**						**X**	**X**						**X**			**X**	**X**				**X**			**X**		
Physical co-morbidity	**X**			**X**	**X**		**X**	**X**					**X**							**X**			**X**	**X**				**X**		**X**	**X**	**X**		
Psychological co-morbidity								**X**				**X**		**X**			**X**				**X**			**X**	**X**						**X**			
Impairment of specific cognitive functions			**X**											**X**							**X**						**X**			**X**	**X**			
Acceptance of disease evolution																		**X**							**X**									
Resisting care attitude				**X**							**X**	**X**			**X**			**X**												**X**				
Treatment related beliefs				**X**																										**X**				

Appendix 3 Distribution of factors by study

PATIENT FACTORS (part 2)

	[84]	[78]	[92]	[74]	[85]	[79]	[99]	[86]	[82]	[97]	[96]	[72]	[87]	[73]	[68]	[58]	[88]	[69]	[70]	[71]	[91]	[80]	[81]	[75]	[89]	[100]	[76]	[95]	[93]	[94]	[90]	[77]	[98]	[83]
Number of physician office visits	**X**				**X**																							**X**						
Treatment effectiveness											**X**													**X**										
Number of hospitalizations)	**X**							**X**																				**X**						
Patient support system																															**X**			
Age	**X**	**X**			**X**		**X**	**X**						**X**							**X**			**X**	**X**			**X**		**X**		**X**	**X**	
Ethnicity						**X**												**X**						**X**										
Education and health literacy														**X**							**X**		**X**	**X**	**X**					**X**				
Gender	**X**	**X**			**X**		**X**	**X**						**X**										**X**	**X**			**X**		**X**		**X**	**X**	
Language														**X**											**X**									
Lifestyle																								**X**							**X**			
Living alone																	**X**															**X**		
Marital status																								**X**										

Appendix 3 Distribution of factors by study

PATIENT AND CAREGIVER FACTORS

	[84]	[78]	[92]	[74]	[85]	[79]	[99]	[86]	[82]	[97]	[96]	[72]	[87]	[73]	[68]	[58]	[88]	[69]	[70]	[71]	[91]	[80]	[81]	[75]	[89]	[100]	[76]	[95]	[93]	[94]	[90]	[77]	[98]	[83]
Adverse effects of medications				**X**											**X**			**X**						**X**	**X**									**X**
Expectations of treatment benefits															**X**	**X**		**X**		**X**														**X**
Perception of treatment effectiveness								**X**							**X**	**X**			**X**	**X**					**X**					**X**				**X**
Medication management strategies															**X**		**X**								**X**				**X**			**X**		

Appendix 3 Distribution of factors by study

CAREGIVER FACTORS

	[84]	[78]	[92]	[74]	[85]	[79]	[99]	[86]	[82]	[97]	[96]	[72]	[87]	[73]	[68]	[58]	[88]	[69]	[70]	[71]	[91]	[80]	[81]	[75]	[89]	[100]	[76]	[95]	[93]	[94]	[90]	[77]	[98]	[83]
Ability to cope				**X**				**X**		**X**					**X**		**X**						**X**									**X**		**X**
Assuming an active role									**X**						**X**		**X**						**X**									**X**		
Caregiver skills			**X**												**X**								**X**								**X**			**X**
Level of assistance with medications			**X**											**X**																	**X**	**X**		
Caregiver support system									**X**						**X**		**X**			**X**											**X**			

Appendix 3 Distribution of factors by study

PRESCRIBER FACTORS

	[84]	[78]	[92]	[74]	[85]	[79]	[99]	[86]	[82]	[97]	[96]	[72]	[87]	[73]	[68]	[58]	[88]	[69]	[70]	[71]	[91]	[80]	[81]	[75]	[89]	[100]	[76]	[95]	[93]	[94]	[90]	[77]	[98]	[83]
Class and name of medicines	**X**	**X**				**X**		**X**			**X**																						**X**	
Administration route and dosage	**X**			**X**				**X**	**X**	**X**							**X**																	
Complex medication regimen				**X**			**X**					**X**	**X**												**X**	**X**		**X**		**X**	**X**		**X**	
Quality of relationship with patients and caregivers																	**X**			**X**		**X**												
Dementia care skills											**X**	**X**					**X**			**X**		**X**									**X**		**X**	
Adherence promoting strategies				**X**					**X**				**X**	**X**			**X**					**X**				**X**	**X**					**X**		

Appendix 3 Distribution of factors by study

HEALTHCARE SYSTEM

	[84]	[78]	[92]	[74]	[85]	[79]	[99]	[86]	[82]	[97]	[96]	[72]	[87]	[73]	[68]	[58]	[88]	[69]	[70]	[71]	[91]	[80]	[81]	[75]	[89]	[100]	[76]	[95]	[93]	[94]	[90]	[77]	[98]	[83]
Medication cost burden		**X**			**X**		**X**	**X**					**X**					**X**					**X**					**X**				**X**		
Memory clinic structure											**X**																							
Area of residence					**X**		**X**																					**X**						

IV. Appendix 4- Integration matrix of qualitative and quantitative evidence

Reference	[84]	[78]	[92]	[74]	[85]	[79]	[99]	[86]	[82]	[97]	[96]	[72]	[87]	[73]	[91]	[75]	[89]	[98]	[95]	[93]	[94]	[90]
Quality appraisal score	4/4	3/4	3/4	3/4	4/4	3/4	4/4	4/4	6/11	4/4	3/4	2/4	4/4	2/4	4/4	3/4	2/4	3/4	4/4	4/4	4/4	4/4
<u>PATIENT</u>-Medical																						
Stage of dementia	-																					
Decreased functional status					**F**			**NI**								**NI**						**NI**
General cognitive status impairment				**B**	**B**			**NI**						**NI**	**NI**	**NI**	**NI**			**NI**		
Increased physical co-morbidity	**NI**			**B**	**F**		**B**	**B**					**NI**			**NI**			**NI**		**NI**	**NI**
Increased psychological co-morbidity								**NI**				**NI**		**NI**	**NI**	**NI**	**NI**					**NI**
Impairment of specific cognitive functions			**B**											**B** **NI**	**B**						**B** **NI**	**B** **F*** **NI**

*Obs: In case of study[90], decreased ability to form or abstract associations (e.g. between medication and associated side-effects) precludes intentional non-adherence. Thus, an impairment of a specific cognitive function is followed by a positive effect on adherence (facilitator).

Reference	[84]	[78]	[92]	[74]	[85]	[79]	[99]	[86]	[82]	[97]	[96]	[72]	[87]	[73]	[91]	[75]	[89]	[98]	[95]	[93]	[94]	[90]
Quality appraisal score	4/4	3/4	3/4	3/4	4/4	3/4	4/4	4/4	6/11	4/4	3/4	2/4	4/4	2/4	4/4	3/4	2/4	3/4	4/4	4/4	4/4	4/4
<u>PATIENT</u>- Behavioral																						
Acceptance of disease evolution																	**NI**					
Increased number of physician office visits	**F**				**F**														**NI**			
Negative treatment related beliefs				**B**																	**F NI**	
Resisting care attitude				**B**																	**NI**	
<u>PATIENT</u>- Treatment and support																						
Increased number of hospitalization	**F**							**B**											**NI**			
Patients support system																						**NI**
Treatment effectiveness	**-**																					

Reference	[84]	[78]	[92]	[74]	[85]	[79]	[99]	[86]	[82]	[97]	[96]	[72]	[87]	[73]	[91]	[75]	[89]	[98]	[95]	[93]	[94]	[90]
Quality appraisal score	4/4	3/4	3/4	3/4	4/4	3/4	4/4	4/4	6/11	4/4	3/4	2/4	4/4	2/4	4/4	3/4	2/4	3/4	4/4	4/4	4/4	4/4
<u>PATIENT</u>-Socio-demographic																						
Age ≥ 76	**NI**	**B**			**NI**		**F**	**NI**						**F**	**NI**	**NI**	**F**	**B**	**F**		**B**	
White race						**F**										**NI**						
High level of education and health literacy														**NI**	**NI**	**F**	**NI**				**NI**	
Male gender	**NI**	**NI**			**F**		**F**	**NI**						**NI**		**NI**	**NI**	**NI**	**NI**		**NI**	
Language														**NI**			**NI**					
Lifestyle																**NI**						**NI**
Living alone	**-**																					
Marital status																**NI**						

Reference	[84]	[78]	[92]	[74]	[85]	[79]	[99]	[86]	[82]	[97]	[96]	[72]	[87]	[73]	[91]	[75]	[89]	[98]	[95]	[93]	[94]	[90]
Quality appraisal score	4/4	3/4	3/4	3/4	4/4	3/4	4/4	4/4	6/11	4/4	3/4	2/4	4/4	2/4	4/4	3/4	2/4	3/4	4/4	4/4	4/4	4/4
PATIENT&CAREGIVER FACTORS - Medications																						
Adverse effects of medications				**NI**													**B**					
PATIENT&CAREGIVER FACTORS- Behavioral																						
Expectations of treatment benefits	**-**																					
Positive perceptions of treatment effectiveness								**NI**									**F**				**NI**	
PATIENT&CAREGIVER FACTORS- Treatment and support																						
Employing medication management strategies																	**F**			**F**		

Reference	[84]	[78]	[92]	[74]	[85]	[79]	[99]	[86]	[82]	[97]	[96]	[72]	[87]	[73]	[91]	[75]	[89]	[98]	[95]	[93]	[94]	[90]
Quality appraisal score	4/4	3/4	3/4	3/4	4/4	3/4	4/4	4/4	6/11	4/4	3/4	2/4	4/4	2/4	4/4	3/4	2/4	3/4	4/4	4/4	4/4	4/4
CAREGIVER FACTORS- Behavioral																						
Decreased ability to cope				**B**				**NI**		**B**												
Assuming an active role	-																					
CAREGIVER FACTORS- Treatment and support																						
Good caregiver skills			**F**																			**F**
Increased level of assistance with medications			**F**											**F**								**NI**
Availability of caregiver support system																						**NI**

Reference	[84]	[78]	[92]	[74]	[85]	[79]	[99]	[86]	[82]	[97]	[96]	[72]	[87]	[73]	[91]	[75]	[89]	[98]	[95]	[93]	[94]	[90]
Qual. score	4/4	3/4	3/4	3/4	4/4	3/4	4/4	4/4	6/11	4/4	3/4	2/4	4/4	2/4	4/4	3/4	2/4	3/4	4/4	4/4	4/4	4/4
<u>PRESCRIBER FACTORS</u>- Medications																						
Class and name of medicines	**B NI**	**NI**				**B**		**B NI**										**F NI**				
Oral AChEI's				**B**				**NI**		**B**												
Increased complexity of medication regimen				**B**			**F NI**					**B**	**B**				**NI**	**NI**	**B**		**NI**	**B**
<u>PRESCRIBER FACTORS</u>- Behavioral																						
Quality of relationship with patients and caregivers	-																					
<u>PRESCRIBER FACTORS</u>- Treatment and support																						
Good dementia care skills																						**F**
Adherence promoting strategies				**F NI**					**F NI**				**F**	**F**								

Reference	[84]	[78]	[92]	[74]	[85]	[79]	[99]	[86]	[82]	[97]	[96]	[72]	[87]	[73]	[91]	[75]	[89]	[98]	[95]	[94]	[94]	[90]
Quality appraisal score	4/4	3/4	3/4	3/4	4/4	3/4	4/4	4/4	6/11	4/4	3/4	2/4	4/4	2/4	4/4	3/4	2/4	3/4	4/4	4/4	4/4	4/4
HEATHCARE SYSTEM																						
Increased medication cost burden					**B**		**B NI**	**NI**					**B**						**B**			
Memory clinic structure											**NI**											
Area of residence					**NI**		**B**												**B**			

OBS: B= barrier, F=facilitator, NI= no impact. Factors not measured in quantitative studies or measured but without significance test done are considered not measured and the boxes are left blank