Inappropriate medication use in long-term care facility residents with advanced Alzheimer's disease and other dementias

Mémoire

Mehrdad Yazdanmehr

Maîtrise en sciences pharmaceutiques – Pharmaco-épidémiologie
Maître es sciences (M. Sc.)

Québec, Canada

Inappropriate medication use in long-term care facility residents with advanced Alzheimer's disease and other dementias

Mémoire

Mehrdad Yazdanmehr

Sous la direction de :

Danielle Laurin, directrice de recherche

Edeltraut Kröger, codirectrice de recherche

Résumé

Les personnes atteintes de démence sévère, résidant dans un centre d'hébergement et de soins de longue durée (CHSLD) et approchant la fin de leur vie, ne reçoivent pas systématiquement des soins palliatifs, malgré que ce niveau de soins soit le plus approprié. La plupart de ces personnes reçoivent également un grand nombre de médicaments dont les effets indésirables peuvent contribuer à des souffrances évitables. Une approche axée sur les soins palliatifs serait possiblement associée à une réduction de la charge médicamenteuse et, du même coup, à une prescription plus appropriée. Les objectifs de ce projet de recherche étaient de décrire l'usage des médicaments chez les résidents atteints de démence sévère en CHSLD, de comparer leur usage de médicaments à des critères de pertinence et d'évaluer si la mise en œuvre d'une approche axée sur les soins palliatifs était associée aux médicaments prescrits. Cette étude décrit l'usage des médicaments chez 215 sujets atteints de démence sévère et en fin de vie qui ont participé à une étude d'intervention quasi expérimentale menée dans quatre CHSLD du Québec sur la mise en œuvre d'une approche axée sur les soins palliatifs. L'utilisation des médicaments a été comparée à trois listes de critères pertinents publiés, soit ceux de Holmes, Rancourt et Kröger, en utilisant des statistiques descriptives. Les analyses sur l'usage de 412 médicaments différents chez 120 sujets du groupe expérimental et 95 sujets du groupe témoin ont montré que cette approche axée sur les soins palliatifs n'est pas associée à une prescription plus appropriée des médicaments chez ces personnes particulièrement vulnérables.

Abstract

Individuals with severe dementia in long-term care facilities (LTCFs) near the end of life do not systematically receive palliative care, although this would be the appropriate care level. Most of these people also receive large numbers of medications, and prescribing for them is often challenging. Implementing a palliative care approach may be an important step towards more appropriate medication use. The objectives of this research project were to describe medication use in LTCF residents with severe dementia, to compare this use to criteria of appropriateness, and to assess whether implementation of a palliative care approach was associated with medication prescribing. This study describes medication use in 215 LTCF residents with severe dementia near the end of life who participated in a quasi-experimental clinical trial on the implementation of a palliative care approach in four LTCFs in Quebec province. Using descriptive statistics, medication use has been compared to three sets of published criteria on appropriateness including those of Holmes, Rancourt and Kröger. Analysis on the use of 412 different medications on 120 subjects in the experimental LTCF and 95 subjects in the control LTCF showed that the palliative care approach was not associated with changes in medication prescribing for these particularly vulnerable individuals.

Table of contents

List of tables

List of figures

List of abbreviations

AD	Alzheimer's disease
AGS	American Geriatrics Society
ATC	Anatomical Therapeutic Chemical
ADE	Adverse drug effect
ADR	Adverse drug reaction
CHSLD	Centre d'hébergement et de soins de longue durée
CSHA	Canadian Study of Health and Aging
DS-DAT	Discomfort scale - dementia of the Alzheimer type
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders – 4th edition
FAST	Functional Assessment Staging Tool
IPET	Improved Prescribing in the Elderly Tool
LTCF	Long-term care facility
MAI	Medication Appropriateness Index
NORGEP	Norwegian General Practice
NSAIDs	Nonsteroïdal anti-inflammatory drugs
PEACE	Palliative Excellence in Alzheimer Care Efforts
PRN	Latin phrase for pro re nata medication (as needed)
SD	Standard deviation
STOPP	Screening tool of older people's prescriptions

Special thanks

I would like to express my appreciation to my thesis supervisor, Dr. Danielle Laurin,[1,2] and my co-supervisor, Dr. Edeltraut Kröger,[1,2] for their scholarly advice and all their support. I also appreciate Drs. René Verreault[1, 2] and Marcel Arcand[3] for giving the authorisation for using the study database. I would also like to thank all who helped me throughout the preparation of this thesis, especially Mr. Pierre-Hugues Carmichael[1] (biostatistician), Madam Martine Marcotte[1] and Madam Annie Frappier[1] for their valuable cooperation.

I am also using this opportunity to express my gratitude and love to my family, especially my mother, who supported and encouraged me throughout my life.

[1] Centre d'excellence sur le vieillissement de Québec (CEVQ), Centre de recherche du CHU de Québec, Québec, Canada

[2] Université Laval, Faculté de pharmacie, Québec, Québec, Canada

[3] Institut universitaire de gériatrie de Sherbrooke, Québec, Canada

Foreword

I would like to underline that as a graduate student that comes from different baccalaureate background, I have learned and enjoyed substantially during the course of my present research work and enriched my knowledge in the field of epidemiology and medication therapy especially in relations for the subjects with advanced dementia.

During the course of my graduate studies, I was responsible for the codification of the 412 medications according to the World Health Organization – Anatomical Therapeutic Classification (WHO-ATC) system in Excel software. I was also responsible for the validation of the descriptive analyses. I suggested to show graphically the medications identified inappropriate according to three set of criteria in a Venn diagram to highlight the most inappropriate medication' names in my thesis.

This study project has been presented through a poster presentation in three conferences including: la 15e édition de la Journée de la Recherche de la Faculté de pharmacie (Université Laval – April 2015), la Journée de la recherche des étudiants de l'axe Santé des populations – Pratiques optimales en santé (SP-POS, CHU de Québec – May 2015), and la 5ème Journée Scientifique du Réseau Québécois de Recherche sur les Médicaments (RQRM) (Hôtel Hilton - Quebec City – June 2015).

Chapter 1. General introduction

Dementia is a global public health problem that will continue to grow as demographic trends shift towards an increased proportion of older people in the population [1]. Individuals with advanced dementia at the end of life are at greater risk of receiving overly aggressive care that may not align with the intended goals of therapy [2], whereas these individuals often have a prolonged terminal phase of advanced illness and may experience many physical and psychological symptoms, including agitation, depression, constipation, and pain [3, 4].

Because of the age-related changes in drug pharmacokinetics and pharmacodynamics, older people are more at risk for adverse medication outcomes, so inappropriate medication use can be a major health care issue for individuals with advanced dementia [5].With advancing Alzheimer's disease (AD) and dementia, the goal of care should switch from curative and preventive care to a comfort care approach [6]. Within such an approach the potential benefits of preventive medications become questionable in the final stages of dementia [7].In spite of the importance of this issue, few intervention studies have been performed regarding ceasing or continuing of medication within the context of a palliative care and quality of life approach in long term-care residents with advanced dementia at the end of life [7].

This research project aimed at describing medication use within a palliative care approach to examine the use of inappropriate medications among residents with advanced dementia at the end of life in four LTCFs in Quebec City and Sherbrooke. Following the general introduction, this thesis includes a literature review in Chapter 2, a methodology section in Chapter 3, a results section in Chapter 4 and the discussion of the results and a final conclusion in Chapter 5.

Chapter 2. Literature review

2.1 Dementia

2.1.1 Definition of dementia

Dementia is a syndrome characterized by a variety of multiple cognitive deficits, which includes memory impairment and at least one of the following symptoms: aphasia, apraxia, agnosia or disturbance in executive functioning [8]. These deficits must be severe enough to affect social or occupational functioning, and represent a decline from a previously higher level of functioning [8-10]. Based on etiology, the four most prevalent forms of dementia include AD, its most common type, vascular dementia, Lewy body dementia and fronto-temporal dementia [11]. The fast growth in the prevalence of conditions leading to dementia is the result of increasing life expectancy and demographic changes in population, generally leading to the aging of the population [1]. Dementia is an important health challenge facing the global community in the 21st century.

2.1.2 Epidemiology of dementia

Estimates from the Canadian Study of Health and Aging showed that 8% of all individuals aged 65 and over in 1991-1992 met the criteria for dementia, including 5% of AD [12]. These subjects were equally divided between the community and institutions. It has been estimated that there were 44.4 million people with dementia worldwide in 2013 [13]. Dementia incidence increases exponentially with age and doubles nearly every five years over the age of 65 years [14]. Due to the aging of the population, it is projected that there will be 75.6 million dementia sufferers in 2030, and 135.5 million in 2050 [15]. Meanwhile, 62% of them currently live in developed countries. This figure is expected to rise to 71% by 2050 [16].

In Canada, there were nearly 104 000 new dementia cases per year in the older population, and there will be over a quarter million of individuals by 2038 [15]. In Quebec, 25 000 cases of advanced dementia are diagnosed each year [17], a number that will grow to more than 50 000 annually by 2050 [17].

2.1.3 Advanced dementia in long-term care facilities (LTCFs)

Nearly 75% of LTCF residents have a diagnosis of dementia [18], and approximately half of them are at an advanced stage, generally leading to immobility, loss of independence and eventually to death [17]. LTCFs are important providers of end-of-life care for residents with advanced dementia. Nearly 70% of them are in advanced stages of this illness or even in the dying process [19].

Individuals with advanced dementia frequently have comorbidities and are treated intensively. They often have a prolonged phase of advanced disease and may encounter numerous physical and mental symptoms [18, 20]. Previous studies showed that individuals with advanced dementia had an average of 21 different medical problems over a six-month interval [4]. Notably, serious therapeutic issues were found in 80% or more of these such as pain, shortness of breath, gastrointestinal difficulties, depression, congestive heart failure, hypertension, anxiety, diabetes, delirium, falls, febrile episodes, psychiatric disturbances, infections including pneumonia and urinary tract infections [3, 4]. This high rate of morbidities at this stage of life normally implies that these individuals receive more medications than any other group of older people and concurrently use complex long-term medication regimens to treat their medical and psychological conditions [5].

Unlike other individuals with terminal illness, older people with advanced dementia have severe impairments of activities of daily living and may have limited decision-making capacity in regard to their choices and preferences for treatment at the end of life [21, 22]. Also, individuals with advanced dementia are generally at more serious danger of receiving aggressive care that may not be adjusted to the objectives of their therapy [2].

2.2 Challenges for medication use in frail older people

2.2.1 Physiological changes

Significant physiological changes occur with advancing age [23]. Lean body mass and total body water progressively decrease, resulting in a relative increase in total body fat [24]. These changes in volume of distribution combined with changes in pharmacokinetics and pharmacodynamics result in clinical importance for the older individuals [25, 26], most notably for the frail who take several medications for numerous morbidities.

Pharmacokinetics changes with advancing age include the decline in hepatic and renal clearance and the increase of distribution of lipid soluble medications, which often leads to a longer elimination half-life [25]. Pharmacodynamics changes comprise generally increased sensitivity to several classes of medications. These physiological changes concern drug absorption, distribution, elimination and adverse events [15, 27-29]. Few data are available on pharmacodynamics differences specifically in very old persons. The pharmacodynamics changes that occur with aging depend upon both receptor density, signal transduction (e.g. via cyclic AMP in the case of β-adrenergic receptors) and intracellular response (e.g. biochemical changes or induction of protein transcription) [30]. Reported changes include increased response to warfarin, benzodiazepines and opiates and reduced inotropic and chronotropic responses to β1-adrenergic stimulation [31]. Other changes contributing to a diminished volume of circulation for hydrophilic drugs such as lithium [32], ethanol and digoxin [33], can result in higher plasma concentrations, consequently increasing the potential for adverse effects. On the contrary, lipid-soluble medications such as long-acting benzodiazepines have an increased volume of distribution, which may delay their maximal effect, bringing about accumulation effects with continued use [5].

There is also a reduction in hepatic mass and blood flow with aging [26]. Drugs such as beta-blockers, nitrates and tricyclic anti-depressants that have a first pass effect in the liver may have a higher bioavailability in older people and thus be effective at lower doses [5]. Cytochrome P450 oxidation declines with aging [34] and drug–drug interactions involving these enzymes are important to recognize [35]. Excretion is altered as a result of age-related changes in renal structure [36]. Larger drug storage reservoirs and decreased clearance

prolong drug half-lives and lead to increased plasma drug concentrations in older people [5]. If serum albumin is further decreased, there will be an increase in the active unbound drug concentration for highly protein-bound drugs such as phenytoin, theophylline, warfarin and digoxin [37]. Aging is also associated with changes in the end-organ responsiveness to drugs at receptor or post-receptor level [37]. There is also a decreased sensitivity to beta-receptors along with a possible decreased clinical response to beta-blockers and beta-agonists [38-40].

In addition to pharmacokinetics and pharmacodynamics changes, impairment of homeostatic mechanisms may occur with aging [25]. Mechanisms that are particularly affected include baroreceptor responses, control of body sway, thirst, volume regulation, glucose and electrolyte control, and thermoregulation. It is therefore not surprising that older people are particularly sensitive to drugs which may cause postural hypotension (e.g. antihypertensive or antiparkinsonian medication), ataxia (e.g. benzodiazepines), volume depletion and electrolyte imbalance (e.g. diuretics) or hypothermia (e.g. phenothiazines) [41, 42].

Older individuals with advanced dementia often tolerate medications less favorably than healthy older adults [43]. This is because of increased sensitivity to certain side effects, difficulty with adhering to drug regimens, and decreased ability to recognize and report adverse events. Older demented individuals are also more prone than healthy individuals to develop drug-induced cognitive impairment [43]. All in all, aging and changes in medical status of demented individuals over time can cause medications that have been used chronically to become unsafe or ineffective.

2.2.2 Adverse drug reactions

Adverse drug reactions (ADRs) can be defined as a noxious and unintended response to a drug reaction, which occurs from an intervention related to the use of a medication, for the purpose of prevention or treatment of a disease or the modification of an organic function [44]. Age-related changes in pharmacodynamics and pharmacokinetics are the main causes of ADRs in older individuals [45, 46]. Older individuals are major drug consumers, and resulting polypharmacy is known as an indicator of ADRs [47].

ADRs are at least three times more common in individuals over 90 years than in those under 50 years [48]. The prevalence of ADRs in the AD population is estimated to be between 5 and 10% [49-51]. It has also been reported that ADRs are the fourth to sixth greatest cause of death [52].

Many adverse drug interactions are predictable and, therefore, avoidable by adjustment of dose or administration times, or by selection of an appropriate alternative drug [46]. The drugs most often involved in ADRs are not necessarily new and exotic drugs, but old and well-known chronic care drugs [53]. The occurrence of avoidable ADRs is the most serious consequence of inappropriate drug prescribing in LTCFs [54]. ADRs occur most often in LTCF residents with several pathologies and receiving multiple drugs [54].These are usually considered type A or dose-related adverse events rather than type B or idiosyncratic. This fact implies that they are largely preventable [48]. In 1992, Lindley *et al*. found that 50% of older subjects' admissions to one hospital in Manchester were actually due to inappropriate prescribing [55, 56].

ADRs can be difficult to detect in older individuals because these often exhibit non-specific symptoms such as lethargy, confusion, light-headedness, falls, constipation and depression [57]. In a review and meta-analysis of hospitalizations caused by ADRs, older people were four times more likely to be admitted to a hospital as a result of an ADR (16.6% versus 4.1%) and were more likely to have preventable ADRs (88% versus 24%) [58]. Indeed, ADRs are a major cause of hospitalization in older people and may account for as much as 20 to 30% of hospital admissions in this age group. In contrast, drug-related hospitalizations have been estimated to account for 2.4 to 6.7% of all medical admissions in the general population [52, 55, 59].

In a study of people over 75 years, 30.4% of emergency medical admissions were secondary to ADRs, half of which was considered preventable [58]. Harugeri *et al*. reported a prevalence of 32.2% of ADRs in older people, which increased the duration of hospital stays in 5.9% of them [60]. Other studies reported that 27% of ADR in primary care and 42% of ADRs in long-term settings were preventable, with most problems occurring at the prescribing and monitoring level. [2]. Bero *et al*. found that 20% of re-admissions to hospital in a geriatric population of 706 patients were drug-related. Seventy-five (75) percent of these

admissions could have been prevented had medications been used properly [61]. Col *et al*. reported that 17% of older patients in hospital were admitted as a result of non-adherence to medications or of ADRs [62].

A meta-analysis of 39 studies in older patients found an in-hospital incidence of ADRs of 6.7% and an incidence of fatal ADRs of 0.3%, placing fatal ADRs amongst the six leading causes of death in the USA [52, 55]. A study of ADRs found that 35% of ambulatory older adults experienced an ADR and 29% required healthcare services (physician, emergency department, or hospitalization) for ADRs [63]. Cooper *et al*. found that almost two-thirds of LTCF residents experienced ADRs over a 4-year period, with one in seven of these resulting during hospitalization [64]. These figures indicate the magnitude of the morbidity and resource utilization associated with ADR in older people.

2.2.3 Polypharmacy in older people

Polypharmacy is defined as the use of multiple concomitant medications by an individual. This phenomenon is due to multimorbidity, increasing life expectancy and the implementation of evidence-based guidelines for many diseases [65]. The number of medications used to define "polypharmacy" is variable, but it is generally considered more than five concomitant medications [65]. Polypharmacy is considered as a risk factor for increased morbidity and mortality, particularly among older people who have comorbid conditions, are subsequently be prescribed multiple medications but also are more vulnerable to ADRs [66, 67]. As a specific example, a large proportion of LTCF residents who suffer from dementia are treated with psychotropic drugs for neuropsychiatric symptoms. These medications present a narrow benefit-risk profile and another addition to their drug burden [66].

Polypharmacy has been considered the most important factor related to an increased risk of ADRs, of drug–drug and drug–disease interactions [68, 69]. It has been shown that patients taking two drugs confront a 13% risk of adverse drug interactions, which climbs to 38% when taking four drugs and to 82% if seven or more drugs are given concomitantly [70]. In addition, polypharmacy has been identified as a significant predictor of the prevalence of

potentially inappropriate medications. Polypharmacy can be troublesome for patients with dementia, particularly when there is dysphagia or resistance to taking medications [68, 69].

Elderly people living in LTCFs are at high risk for polypharmacy since they are often frail and suffer from multiple illnesses. These individuals are frequently prescribed preventive medications in accordance with best practice guidelines for individual chronic diseases [71, 72]. It is estimated that more than 50% of older people living in LTCFs and 27% of those in the community take more than five medications a day in Canada [73]. The average LTCF resident is prescribed seven to eight separate medications daily, many of which target chronic conditions, but the potential benefits of continuing many of these drugs are questionable in the final stages of dementia [74-76].

High medication use poses a significant risk of ADRs to older people, given higher comorbidity and greater medication consumption [77]. Older patients have increased chances of exposure to potentially inappropriate medications, such as drug–disease and drug–drug interactions [76, 77]. Polypharmacy is a specific concern when medications may be added to manage symptoms during the dying process [78], because their altered physiological drug metabolism heightens the residents' sensitivity to various drug effects [79-81]. Some researches in older LTCF residents have showed the risks associated with polypharmacy including frailty, disability, mortality and falls [74].

Moreover, with polypharmacy, duplicative prescribing within the same drug class is prevalent and unrecognized drug adverse-effects are often treated with more drugs thus leading to prescribing cascades (e.g. using Levodopa to treat the Parkinsonian adverse effects of neuroleptic medications) [5]. Polypharmacy also makes adherence to medications more challenging [5]. Non-adherence with prescribed medications can result in sub-optimal therapeutic effectiveness, and can have major clinical consequences [62, 82]. If the existence of non-adherence is not recognized, the physician may increase the dose of the initial medication or add a second agent, increasing both the risk and the cost of treatment. A recent survey of 2 590 non-institutionalized older adults in the USA showed an increased use of all types of medications with advancing age, with the highest prevalence of drug use in women 65 years of age and older, 12% of whom took 10 or more medications, and 23% took at least 5 prescribed drug therapies [83].

Older people are the greatest consumers of medications and healthcare resources in developed countries. In most industrialized nations, older people consume three times as many prescription medications as younger people and purchase 70% of non-prescription medications [84]. In the USA, 12.5% of the population is over 65 years of age, but they consume 32% of all prescription medications and account for 25% of drug expenditure and 30% of total national healthcare expenditure [85-87].

2.2.4 Potentially inappropriate medication

The terms *potentially inappropriate medications* describe a number of suboptimal prescribing practices, where the risk of adverse effects outweighs the expected clinical benefit, and particularly, when a safer or more effective therapy option is accessible to treat the same condition [88-90]. This definition of inappropriateness is usually considered to be relative rather than absolute. It depends on the quality and relevance of the evidence, viewpoints of the clinician, the patient's circumstances and treatment goals [91, 92]. Inappropriate prescribing also includes the use of medications at a higher dosage or frequency and for longer periods than clinically indicated, the use of multiple medications that have recognised drug-drug interactions and drug-disease interactions, and the under-use of beneficial medications that are clinically indicated but not prescribed for other reasons [5].

In older people, potentially inappropriate medications have resulted in adverse effects, significant morbidity, hospitalization and mortality [89]. It has been reported that older people who reside in LTCFs are particularly vulnerable to potentially inappropriate medications [76, 93]. Compared to community-dwelling seniors, LTCF residents suffer from an increased incidence of functional disabilities and from more intense and co-morbidities. A higher prevalence of inappropriate medication use by LTCF residents compared with community-dwelling older people (33.2% vs. 24.4%, respectively) has been previously reported [94].

2.2.5 Challenges in prescribing for older people with advanced dementia in LTCFs

Older people with advanced dementia often have a wide variety of physical and psychological needs, leading to the prescribing of multiple medications [74]. In individuals suffering from advanced dementia near the end of life, some medications may be of restricted benefit. Prescribing is complicated by various factors which need to be taken into account, like comorbidities and concurrent use of numerous medications to meet their medical and psychological needs [95-97]. The use of polypharmacy in older people with advanced dementia is of particular concern [98]. It is often challenging and complex, as any new medication must be considered in the context of altered pharmacokinetics, altered pharmacodynamics and age-related changes in body composition and physiology [99].

Individuals with advanced dementia nearing the end of life and living in LTCFs do not receive sufficient palliative care [2, 21, 22, 100]. The objective of care for people with advanced dementia should change from preventive or curative care to a comfort care approach [101]. At the same time, these individuals would benefit from more appropriate medication use, in accordance with the comfort care approach [101-103]. For individuals in comfort care, it would be reasonable to reconsider and review the medication regimens with the objective of adjustment or discontinuation of prescriptions to avoid or reduce suffering and to meet the true needs [104]. Within such an approach the potential advantages of preventive medications become questionable in the last phases of dementia or the dying process. A re-orientation process is required in the therapy of chronic conditions, including the adjustment of medications or the removal of unnecessary drugs since complex drug therapies and the resulting polypharmacy may increase the risk of adverse drug events [20, 105, 106].

As the objective of care shifts from life-prolonging measures toward comfort measures, several challenges may arise [107]. The use of less-familiar medications, barriers to medication administration, and inappropriate pharmacotherapy at the end of life can have deleterious results [107]. For example, if an individual's life expectancy is short and the goals of care are palliative, then prescribing a prophylactic medication that requires a long time to produce a benefit may not be considered appropriate. Additionally, some therapeutic

medications (e.g., antibiotics for pneumonia) may not increase comfort or quality of life when palliative care is the objective [6].

Moreover, it is more challenging to discover adverse effects if the individual is not capable to communicate verbally. Alternatively, the decision to continue or discontinue medication or to withhold treatment for an individual with advanced dementia nearing the end of life may be difficult to make for the physician if the resident's family does not approve this decision. The opinions of the patient's family may thus influence the physician's decision process regarding treatment [108]. The physician must consider various ethical issues, as most of the time, his/her patients are unable to make decisions for themselves. It can also be hard to estimate the life expectancy of a patient with severe dementia as the progression of the disease is unpredictable and another condition or illness may trigger death.

It is of interest that monitoring medication used in LTCF residents near the end-of-life may also relate to the fact that under certain circumstances, medications which are deemed generally inappropriate in older persons, might in fact have an appropriate indication in a particular patient, e.g. furosemide as monotherapy to treat hypertension when other anti-hypertensives have failed [92]. Moreover, many medications and classes of medications commonly prescribed for people at the end of life (e.g. psychotropic drugs, cardiovascular agents and pain medications) are often followed by a higher danger of antagonistic occasions [109]. All in all, with many medications prescribed, LTCF residents with advanced dementia often do not receive optimal medication care or sufficient palliative care, resulting in a large proportion of their medications meeting the criteria for potentially inappropriate medications.

2.2.6 Special considerations for optimal palliative prescription in patients near the end-of-life

Frail older patients at the end-of-life tend to take more medications and have more adverse outcomes related to medications than other older people [110]. Because of increased sensitivity to certain side effects, difficulty with adhering to drug regimens, and decreased ability to recognize and report adverse events, older patients with advanced dementia often tolerate drugs less favorably than healthy older adults [43]. Optimisation of the drug regimen for an older patient with advanced near the end-of-life is a dynamic process [6]. When

approaching end-of-life care, as in the case of advanced dementia, both the number of and the indication for the medication should be evaluated, with the priority placed on symptomatic care and the alleviation of suffering versus preventive care [111-113]. In spite of the significance of this issue, research into medication during palliative care for patients with advanced dementia in the end-of-life care is lacking [20]. Hence, there are few guidelines for appropriateness of medication treatment among such patients [114].

Some published recommendations for end-of-life pharmacotherapy provide guidance on individualizing drug therapy regimens [6, 115, 116]. One model of prescribing for patients late in life that takes into account important factors to better individualize prescribing practices was previously described [115]. It included considering whether a patient is likely to benefit from a particular medication by comparing this patient's estimated remaining life expectancy with the time until the medication benefit is achieved [115]. In addition, the medication had to fit into a logical treatment plan as determined by the concordance between the patient's goals of care and the treatment targets of the medications [115]. Medications commonly used in palliative and end-of-life care can have adverse effects such as confusion, drowsiness, constipation and fatigue [117]. To optimize the use of these medications, it may be prudent to minimize the use of other medications that could potentially worsen these effects. For example, ferrous gluconate may no longer provide achievable benefit for anemia, but may exacerbate constipation caused by opiates [117].

For reasons described above, specific populations, such as patients with advanced dementia, may particularly benefit from such an approach. Consequently, these patients could benefit from the personalization of their medication therapy by a multidisciplinary team, leading to better agreement between a clinical objective prioritizing symptomatic control and the patient’s medication profile [6, 116].

Clinicians working in LTCFs are often faced with the challenge of knowing when it might be best to withhold or discontinue medications [115]. While the Beers criteria identify medications that should be avoided in older people, they do not address such considerations as when to discontinue certain medications late in life [118]. The oral administration of multiple medications in patients with end-stage dementia with feeding problems or repeated

venipunctures needed to monitor certain drugs (e.g. warfarin) are additional burdensome consequences of polypharmacy in this population [106].

Estimating a patient's life expectancy is an important issue in determining the goals of care and potential long-term value of many preventive medications. Patients with a limited lifespan (12 months or less) because of marked frailty, advanced dementia, or end-stage organ disease, should have more conservative care goals and their preferences may call for reduction in medications [115]. Medications that may take several years to gain benefits, such as bisphosphonate therapy to prevent osteoporotic fractures, have clearly limited opportunity to benefit patients whose projected life expectancy is short [119].

In general, drugs prescribed to improve longevity can be avoided since the focus of pharmacotherapy in end-of-life is optimal symptom control for the remaining weeks or months of life [6]. This process should be discussed between the physician and the patient and, where necessary, the patient’s primary carer. The drug regimen may require several changes before medications have been rationalised effectively. When drugs should be discontinued, it is preferable to withdraw one drug at a time [6]. In this way, adverse symptoms after particular drug discontinuations can be attributed more readily and the necessary corrective action taken. Fewer daily tablets and doses should be a core aim of drug regime review, including the use of once-daily, long-acting preparations [6]. Best clinical practice would involve an open and frank discussion between the physician and the patient or the patient’s family if communication with the patient has become extremely challenging, as to the reasons for withdrawal of preventive drug therapies [6]. Such a discussion may in turn facilitate more in-depth dialogue about overall prognosis with the patient and his/her carers. There is an important distinction to be made between drugs that should generally not be initiated and drugs that should be discontinued when encountered in end-of-life patients [6].

Drugs for primary prevention have, in general, no place in the treatment of end-of-life patients, since the time-to-benefit usually exceeds life expectancy [115]. Drugs for secondary prevention require careful scrutiny and should be prescribed only where ongoing benefit is to be expected within a patient's life expectancy [6]. In general, prescribing more than five regular daily drugs to a patient with end-of-life status should be avoided. Six or more daily

drugs heighten the risk of adverse effects [46, 66] as well as poor medication adherence [120] in older people. Close collaboration liaison with the responsible pharmacist is also important, particularly with regard to the presentation of prescribed drugs to end-of-life patients e.g. blister packs arranged at times most convenient for consumption by the patient [6].

Identification of end-of-life should normally be accompanied by a significant reduction in the number of daily drugs [115]. Thus, lipid-lowering drugs are almost always inappropriate in end-of-life. Similarly, most medications used for minimisation of fragility fracture risk in these patients are usually inappropriate. Likewise, ACE-inhibitors and angiotensin receptor blockers to prevent diabetic nephropathy or to reduce mortality from heart failure are of little value when an individual's life expectancy is severely curtailed as a result of other irreversible disorders [89].

2.3 Defining medication inappropriateness in older people

There are two common tools for assessing the appropriateness of medications for older people, and they can be divided into implicit and explicit tools [89, 121].

2.3.1 Implicit criteria

In an implicit method, medical knowledge and information from the individual are used to determine whether a treatment is appropriate [89]. These methods are individually tailored and allow leading a complete and adaptable appraisal of an individual pharmacotherapy [122]. Examples of validated, implicit screening tools are the Medication Appropriateness Index (MAI) and the prescription optimization method [123]. These methods are fairly time consuming, costly [89] and dependent on clinical judgment and knowledge of geriatric pharmacotherapy, factors that may vary between physicians [54]. Of note, implicit criteria cannot easily be replicated by other investigators [86] or compared to explicit criteria [54, 89].

2.3.2 Explicit criteria

Explicit criteria are typically developed by a process of expert consensus using results from published reviews and comprising the lists of medications or drug classes that should usually be avoided in older people because of limited effectiveness or risk of ADRs [124]. The Delphi technique is a frequently used technique to obtain consensus between experts on a matter. According to this technique [125], the research group constructs questions about the appropriateness of the use of specific medications based on a review of the literature. Selected experts are then asked to rate their agreement with statements about candidate potentially inappropriate medications, using, for instance, a five-point Likert scale. Statements with agreement above certain cut-points are circulated again for second or third ratings. Finally, potentially inappropriate medications that generate a high degree of agreement about their inappropriateness among the experts are listed [126].

Various criteria have been developed by expert panels to assess the quality of prescribing practices and medication use in older adult individuals in different countries. For example, Beers criteria and McLeod criteria were respectively developed in the USA and Canada on the basis of those countries' national drug formularies [127, 128].

Explicit criteria need to be regularly updated as new drugs come to the market, as new evidence emerges related to the use of these medications, and as new methods to assess the evidence develop. Being able to update these criteria quickly and transparently is crucial to their continued use as decision-making tools, because regular updates will improve their relevancy, dissemination, and usefulness in clinical practice [129]. Advantages of explicit criteria are that they are simple, quick to apply, objective and do not require specific clinical expertise and can often be applied to large prescribing databases [91]. The structure of these tools makes it possible to incorporate them easily into software packages, and they can be used as so-called *clinical rules* [130]. Because of their ease of use, several explicit criteria tools have been developed and widely used in studies exploring the prevalence of potentially inappropriate medication use [89].

Given significant differences in national drug formularies, specific criteria for potentially inappropriate medication use should be adapted or developed for the context of particular jurisdictions. Beers criteria thus have been adapted to France (Laroche) [80], Quebec

(Rancourt) [131], Ireland (STOPP) [132] and Norway (NORGEP) [133] among others. A number of European studies have adopted Beers and McLeod criteria to investigate the prevalence of potentially inappropriate medications use by older people in Europe and to determine the risk factors for receiving such prescriptions [90]. Although several studies on potentially inappropriate medication use in older people have been published, few of these focused on individuals with advanced dementia. Most of the studies investigating prescribing practices in AD were performed in America where the healthcare policy and cultural background context, as well as the potentially inappropriate medication lists differ from other countries. Few of them have also investigated factors associated to potentially inappropriate medications [7, 134-136].

2.3.3 Published explicit criteria and their outcome studies

2.3.3.1 Beers criteria (1991, 1997, 2003 and 2012)

Beers *et al*. published in 1991 the first set of explicit criteria for determining inappropriate medication use in LTCF residents in the USA [127]. This tool is the most commonly used explicit criteria set to review drug treatments and to identify potentially inappropriate medications in older patients [127]. A modified Delphi technique was employed to derive consensus opinion on prescribing indicators from a panel of 13 experts in geriatric medicine, long-term care, geriatric and psychogeriatric pharmacology and pharmacoepidemiology. The expert panel produced a list of 30 medications to be avoided in LTCF residents regardless of diagnoses, dose and frequency of medication use. This list incorporated certain psychotropic medications, anti-hypertensives, oral hypoglycaemic agents, non-steroidal anti-inflammatory drugs and analgesic agents [127].

These criteria include the list of inappropriate drugs that should be avoided in older patients because of toxicity relating to the agent, too frequent doses or too large accumulative daily doses (independent of diagnosis), plus a list of criteria considering diagnoses with possible drug-disease interactions. For over 20 years, Beers criteria, updated several times, have been the most widely consulted list for evaluating the prescription of medication to the older people [130, 137].

Although the Beers criteria have been applied in many studies, several authors considered that these criteria present several flaws, particularly for certain circumstances: e.g. many prescribed drugs are not used in some European formularies, inclusion of some drugs is subject to controversy, and the criteria do not contemplate problems involving under-use of beneficial medicines) or are of doubtful relevance to routine geriatric pharmacotherapy, especially in European countries [132]. For instance, many medications listed in the Beers criteria are obsolete and no longer available in Europe [90]. Thus international researchers have declared difficulties in applying the Beers criteria in their own countries [89]. Also, several experts did not agree with some statements in these lists [80]. Furthermore, the first version of the Beers criteria do not include some important instances of potential potentially inappropriate medications (e.g. drug-drug interactions or drug class prescription duplication) in older people. Importantly, Beers criteria take no account of prescribing omission errors which may be just as important as prescribing commission errors in the overall consideration of appropriateness, e.g. failure to prescribe anticoagulant drugs in older people with chronic atrial fibrillation considered at high risk for arterial embolism [5]. Therefore, several country-specific potentially inappropriate medication criteria have been developed to improve the prescription quality for older adults in different specific regions [80, 90, 114, 131, 138].

The revised Beers criteria in 1997 were designed to be applicable to all older people regardless of their place of residence (community or institution) or level of frailty [88]. The 1997 Beers criteria have been used widely in their original or revised version [139].The 2003 version of the Beers criteria has been applied in clinical studies in many countries as a geriatric healthcare quality indicator to reflect newly attained evidence on efficacy and safety of various medications. The 2003 edition was published by Fick *et al*. after the elimination of 15 outdated statements and the addition of 44 new statements to the 1997 list [114]. The revised criteria comprised two categories of potentially inappropriate medications: (i) 48 medications or medication classes to be avoided irrespective of diagnosis or condition; and (ii) 20 diseases or conditions with corresponding medications or medication classes to be avoided in individuals with these conditions [114]. Among the 68 medications or medication classes identified as constituting potentially inappropriate medications, 52 were classified as being of high severity and 16 as low severity [114].

In the 2003 Beers criteria, medications such as nitrofurantoin, doxazosin and amiodarone were added to the general list of inappropriate medications. Medications and medication classes removed include the use of beta-blockers (with exception of propranolol) in those with chronic obstructive pulmonary disease, asthma, peripheral vascular disease and syncope or falls [114]. The co-morbidity list included new diagnoses such as depression, Parkinson's disease and cognitive impairment and incontinence [5]. However, the updated criteria do not identify all important causes of potentially inappropriate prescribing (e.g. drug–drug interactions are not included). Furthermore, controversy exists over some of the medications that are considered to be potentially inappropriate by Beers criteria, e.g. amitriptyline – a tricyclic antidepressant that is useful in a broad range of pain syndromes. Finally, the criteria only deal with the prescribing of inappropriate medications and not with the under-prescribing of clinically indicated drugs and other drug management issues [5].

In 2012, the American Geriatrics Society (AGS) supported a major revision, and upgraded the Beers criteria. The AGS recommends the consistent, straightforward, methodical overhauls and the backing for the more extensive data and encourages dispersal of the criteria by expert clinicians for their utilization in examination, strategy, and practice. The updated 2012 AGS Beers criteria are current with other methods for determining best-practice guidelines to keep this instrument applicable [129].

The revised criteria differ from earlier versions in a few ways. The 2012 criteria include 53 medications or drug classes. Medications that are no more accessible in the USA, e.g. propoxyphene, and several other medications, e.g. stimulant laxatives, have been removed and new medications, e.g. zolpidem, have been added [129]. Other notable additions include glibenclamide, benzotropine, metoclopramide, prazosin, sliding scale insulin, glitazones with heart failure, acetylcholinesterase inhibitors in the presence with a history of syncope, and serotonin reuptake inhibitors in the presence of a history of falls and fractures. Dabigatran has also been listed and is to be used with caution in people aged more than 75 years or with renal impairment [129].

2.3.3.2 STOPP criteria

The Screening Tool of Older Persons potentially inappropriate Prescriptions (STOPP) has been developed by a multidisciplinary team of Irish geriatricians, pharmacists, pharmacologists, and primary care physicians in 2008 [90]. This criteria provides a more comprehensive explicit process measure of potentially inappropriate medications. These criteria are adapted for use in European countries, and have overcome some of the limitations inherent to the Beers criteria. STOPP is a physiological system-based screening tool comprising 65 clinically significant criteria which take drug-drug and drug-disease interactions, drug doses and duration of treatment into consideration. It considers clinical effectiveness and the removal of any potentially unnecessary drugs as well as drug duplication [90, 132].The advantage of the STOPP consist of good inter-rater reliability, inclusion of both American and European medications, organization and structure based physiological system and short time to complete [132].

2.3.3.3 McLeod criteria

McLeod *et al*. [128] published a Canadian consensus panel list of potentially inappropriate medications in 1997. These potentially inappropriate medications were categorized as cardiovascular, psychotropic, non-steroidal anti-inflammatory drugs (NSAIDs)/other analgesics and miscellaneous drugs. The 38 medications and medication classes included 16 drugs generally to be avoided, 11 drug-disease interactions and 11 drug-drug interactions [128]. Mean clinical significance ratings were given for each drug by the experts to a maximum of four points. Most potentially inappropriate medications scored greater than three points. These criteria also contained suggestions for alternative medications. Naugler *et al*. identified the most frequently encountered 14 of the 38 potentially inappropriate medications identified in these criteria and used these to develop the Improving Prescribing in the Elderly Tool (IPET) [140]. These Canadian criteria require diagnostic information which is not easily accessible in most long-term care settings [128].

2.3.3.4 Rancourt criteria

In 2004, the Rancourt criteria were developed by clinical and scientific experts of geriatric care in Quebec City, Canada, using a modified Delphi method [139]. The criteria of appropriateness were based on the 1991 and 1997 Beers and the 1997 McLeod criteria and adapted to the province of Quebec context. They comprise four categories of potentially inappropriate medication treatment for a total number of 111 statements: (i) medication type (n=42); (ii) duration (n=12); (iii) dosage (n = 20); and (iv) drug-drug interactions (n=37). The most commonly identified inappropriate medication classes were analgesics & antipyretic, anxiolytics and antipsychotics. These criteria were focussed towards the assessment of psycholeptic drugs. An interesting feature of these criteria is that the generic name and Anatomical Therapeutic Chemical (ATC) classification code for each medication available in Canada is listed and matches the data on an international level [131].

2.3.3.5 Laroche criteria

In 2007, the Laroche criteria were published by Laroche *et al*. for application to the population aged ≥ 75 in France. These criteria were developed using a Delphi method [125] consulting 15 French experts from various backgrounds. They were based on the 1997, 2001 and 2003 Beers criteria, the McLeod criteria and various prior French adaptations of lists of inappropriate medications. The final three statements were categorized into unfavourable benefit-risk ration (n=25), questionable efficacy (n=1), both unfavorable benefit-risk ratio and questionable efficacy (n=6), and drug-drug interactions (n=2). Similarly to the Rancourt criteria, all generic medications used in France were clearly listed and alternative drugs were suggested [80].

Table 1 demonstrates the potentially inappropriate medication and medication classes in a descriptive study according to the criteria of Beers 2003 [114], McLeod 1997 [128], Rancourt 2004 [131], Laroche 2007 [80] and STOPP 2008 [132].

Table 1. Comparison of potentially inappropriate medications/medication classes according to the criteria of Beers 2003, McLeod 1997, Rancourt 2004, Laroche 2007 and STOPP 2008 (Adapted from Chang *et al*. 2010)

Medication class/medication	Beers 2003	McLeod 1997	Rancourt 2004	Laroche 2007	STOPP 2008
Analgesics					
Indometacin	✓	✓	✓	✓	
Phenylbutazone		✓	✓	✓	
Muscle relaxants					
Methocarbamol	✓	✓	✓	✓	
Carisoprodol	✓		✓	✓	
Antispasmodics			✓	✓	
Hyoscyamine	✓				✓
Hypnotics and sedatives			✓	✓	
Long-acting benzodiazepines	✓	✓	✓		
Barbiturates	✓	✓			✓
Antidepressants			✓	✓	
Tricyclic antidepressants	✓	✓			✓
First-generation antihistamines			✓	✓	✓
Chlorphenamine	✓		✓	✓	
Diphenydramine	✓		✓	✓	✓
Hyroxyzine	✓		✓	✓	
Promethazine	✓		✓	✓	
Dexchlopheniramine	✓		✓		
Cardiovascular drugs					
Dipyridamole	✓	✓	✓	✓	✓
Digoxin	✓		✓	✓	✓
Methyldopa	✓		✓	✓	
Reserpine	✓	✓	✓	✓	
Oral antihyperglycaemic drugs					

Table 1. Comparison of potentially inappropriate medications/medication classes according to the criteria of Beers 2003, McLeod 1997, Rancourt 2004, Laroche 2007 and STOPP 2008 (Adapted from Chang *et al*. 2010) (continued)

Medication class/medication	Beers 2003	McLeod 1997	Rancourt 2004	Laroche 2007	STOPP 2008
Chlorpropamide	✓		✓		✓
Antipsychotics					
Chlorpromazine	✓	✓		✓	
Miscellaneous					
Cimetidine	✓	✓	✓	✓	
Theophylline	✓				✓

2.3.3.6 Holmes criteria

In 2008, Holmes *et al.* [7] categorized the appropriateness of the most commonly used medications in patients with advanced dementia, as a part of the Palliative Excellence in Alzheimer Care Efforts (PEACE) program in the USA. There were 12 geriatricians who participated in the consensus survey. The inclusion of 81 medications and medication classes was based upon the classification system of the British National Formulary, the United States Pharmacopeia and National Formulary, and the Lexi-Comp alphabetical drug index. Out of 221 total medications, 69 (31%) were considered always appropriate, 82 (37%) were considered sometimes appropriate, whereas 8 (4%) and 11 medications (5%) were respectively considered rarely and never appropriate [7].

2.3.3.7 Kröger criteria

In 2015, Kröger *et al.* [141] published three lists of criteria for appropriate medications in LTCF residents with advanced dementia. They used a validation process to categorize appropriate medications for these patients in the province of Quebec, based on a scoping review of the literature on medication optimization among seniors with advanced dementia.

A consensus reaching method was used, consisting of a two-round Delphi panel of 15 experts (3 geriatricians, 3 family physicians, 3 pharmacists, 3 nurses, 2 social workers and one ethicist) and an in between teleconference between panelists and researchers, following a modified consensus reaching method, developed by the Research and development (RAND) corporation, the RAND/UCLA appropriateness method [125]. The lists of generally, sometimes or rarely appropriate medications were submitted to this interdisciplinary Delphi panel. This process led to three lists of 12 generally, 27 sometimes and 22 exceptionally appropriate medications or medication classes [141].

Table 2 demonstrates the medication appropriateness of several medication classes in older people with advanced dementia according to the criteria of Holmes 2008 [7] and Kröger 2015 [141].

Table 2. Comparison of potentially inappropriate medications by medications/medication classes according to the criteria of Holmes 2008 and Kröger 2015

Medications	Criteria	
	Holmes 2008	Kröger 2015
GENERALLY appropriate		
1. Inhaled bronchodilators	✓	✓
2. Antiepileptic drugs	✓	✓
3. Anxiolytics/benzodiazepines	✓	✓
4. Narcotic analgesics	✓	✓
5. Non-narcotic analgesics: Acetaminophen	✓	
6. Lubricating eye drops	✓	✓
7. Pressure ulcer products	✓	✓
8. Lidoderm	✓	
9. Antifungal creams	✓	
10. Nutritional supplements such as Ensure		
SOMETIMES appropriate		
11. Antidiarrheals	✓	✓
12. Laxatives	✓	✓
13. Antiemetic (eg, diphenhydramine)	✓	✓
14. Proton pump inhibitors	✓	✓
15. Beta-blockers	✓	✓
16. Calcium channel blockers	✓	✓
17. Diuretics	✓	✓
18. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers	✓	✓

Table 2. Comparison of potentially inappropriate medications bymedications/medication classes according to the criteria of Holmes 2008 and Kröger 2015 (continued)

Medications	Criteria	
	Holmes 2008	**Kröger 2015**
SOMETIMES appropriate		
19. Nitrates/Nitroglycerin	✓	✓
20. Antipsychotics	✓	✓
21. Antidepressants other than (TCA)	✓	✓
22. Antibacterials	✓	✓
23. Antivirals	✓	✓
24. Antiparasitic agents	✓	✓
25. Oral hypoglycemics	✓	✓
26. Thyroid hormones	✓	✓
27. Antithyroid medications	✓	✓
28. Corticosteroids, oral or inhaled	✓	✓
29. Insulin	✓	✓
30. Antihistamines second generation	✓	✓
31. Electrolytes	✓	✓
32. Antiglaucoma drops	✓	✓
33. Anti-inflammatory eye drops	✓	✓
34. Allopurinol	✓	✓
35. Uroselective alpha-blockers: tamsulosin, silodosin	✓	
36. Antiplatelet agent: Aspirin		✓

Table 2. Comparison of potentially inappropriate medications by medications/medication classes according to the criteria of Holmes 2008 and Kröger 2015 (continued)

Medications	Criteria	
	Holmes 2008	Kröger 2015
RARELY, or EXCEPTIONALLY appropriate		
37. TCA	✓	✓
38. Colchicine	✓	✓
39. Digoxin	✓	✓
40. Clonidine	✓	✓
41. Antiarrhythmics class I and III	✓	
42. Hydralazine	✓	✓
43. Bisphosphonates	✓	✓
44. Antiplatelet agents excluding aspirin: heparins, clopidogrel	✓	✓
45. Vitamin K antagonists: warfarin, acenocoumarol		✓
46. Anticoagulants excluding vitamin K antagonists: dabigatran, rivaroxaban, apixaban		✓
47. Appetite stimulants	✓	✓
48. Bladder relaxants	✓	✓
49. Antispasmodics: glycopyrrolate, scopolamine or ipratropium or tiotropium as inhalators		✓
50. Lipid-lowering medications	✓	✓
51. Leukotriene receptor antagonists	✓	✓
52. Antiestrogens	✓	✓
53. Sex hormones	✓	✓
54. Cytotoxic chemotherapy	✓	✓

Table 2. Comparison of potentially inappropriate medications by medications/medication classes according to the criteria Holmes (2008) and Kröger (2015) (continued)

Medications	Criteria	
	Holmes 2008	Kröger 2015
RARELY, or EXCEPTIONALLY appropriate		
55. Hormone antagonists	✓	✓
56. Immunomodulators	✓	✓
57. Nonsteroidal analgesics: NSAIDS		✓
58. Tricyclic antidepressant (TCA)		✓
59. Antihistamine first generation		✓

2.4 Prevalence of potentially inappropriate medications among older people using different criteria

Previous studies of medication use in older people with a reduced life expectancy, although not always specific to dementia patients, have highlighted the prevalence of suboptimal and inappropriate medication use in LTCF residents [89, 142]. Studies in the USA and Canada have reported the high prevalence of potentially inappropriate medications (at least one) among LTCF residents (up to 40%) and community-dwelling elderly person (14-37%) according to the 2003 Beers criteria [5, 143, 144]. Using these criteria, the estimated prevalence of potentially inappropriate medications was 28% in the United Kingdom in general older population [145]. Australian studies have also reported similar levels of potentially inappropriate medication use, ranging from 19 to 50% [146, 147]. One study in Switzerland in 2010 showed that the prevalence of potentially inappropriate medication use was 77% while there was a prevalence of prescribing omissions of 65% among ill older hospital patients, according to the STOPP criteria [148]. In Japan, Niwata *et al*. found the potentially inappropriate medications prevalence rate was about 21.1% in general LTCFs [149].

Using various methodologies, several studies have investigated the extent of the problem in Canada. In Quebec, in 1995-1996, Rancourt *et al*. [131] carried out a study of inappropriate medication use among LTCF residents (n=2 633 with an average age = 82 ± 8 years) living in the Quebec City area. Rancourt *et al*. found that 54.7% of these patients had a potentially inappropriate medication. The prevalence of questionable high-risk prescribing among the study sample was 52.6% [131].

In another Canadian study, Dhalla *et al.* [150] performed a pre-post retrospective, cohort study to examine the prevalence of inappropriate prescribing in old patients before and after LTCF admission. Their definition of potentially inappropriate medications was based on the 1997 Beers criteria. Their study showed that the prevalence of potentially inappropriate medications decreased from 25.4 to 20.8% after LTCF admission [150].

Another retrospective review of insurance claims for medications used in the last year of life in the USA showed that 44% of beneficiaries (n=4 602) received at least one medication considered inappropriate according to Beers 1997 criteria, although the appropriateness of a medication may vary depending on the life-limiting condition for which it is prescribed [151]. However, the prevalence of potentially inappropriate medications detected according to the Beers criteria varied from 18 to 42% among studies performed in different countries [152-154]. Van Der Hooft *et al.* studied the computer based records of a group of 150 general practitioners in the Netherlands from 1997 to 2001. The results showed that between 16.8 and 18.5% of older people received at least one inappropriate medication according to Beers 1997 criteria and between 19.1 and 20% according to the updated Beers 2003 criteria [155].

A study of hospitalized older people in Italy found the prevalence rate of potentially inappropriate medications to be 14.6% using Beers 1997 criteria. In this Italian study, age and cognitive impairment were associated with less inappropriate drug use, whereas a direct relationship was observed for a number of drugs used during hospital stay and the Charlson co-morbidity index [144]. These studies showed a somewhat lower prevalence of inappropriate medication use in Europe than in the USA. However, because of different study populations, time horizons and methodologies, these international comparisons are of limited value.

There are few studies that have examined the drug use and potentially inappropriate medications in patient with advanced dementia specifically, and most of them had some limitations such as small sample sizes [7, 20] cross-sectional design [7], and a focus only on anti-dementia agents [156].

Chan *et al.* identified suboptimal medication use as a potential source of decreased function in older patients with dementia [157]. Giron *et al.* studied appropriateness of drug use in an older non-demented and demented population, and found that while there was substantial exposure to presumably inappropriateness of drug use in both populations, demented persons were more commonly exposed to drugs with potent anticholinergic properties, the most commonly involved drugs being psychotropic (namely antipsychotics, antidepressants and anxiolytics) [153]. The use of anti-cholinergic medications in dementia patients can be problematic as they may counteract the benefits of anti-dementia medications [153].

One study found that polypharmacy was associated with a number of specific diseases including congestive heart failure, hypertension, depression, anxiety, and diabetes [71]. Others have found less inappropriate medication usage among LTCF residents with dementia than among those without dementia [72, 150, 158].

Tjia *et al.* defined medications of questionable benefit as those deemed *never appropriate* in advanced dementia according to Holmes criteria as previously published research [105]. They found that residents were prescribed six daily medications and that they were receiving at least one medication considered *never appropriate* in advanced dementia. The most commonly used medications with questionably beneficial were acetylcholinesterase inhibitors (15.8 %) and lipid-lowering agents (12.1%) [105].

2.5 Conclusion

LTCF residents with advanced dementia are particularly vulnerable to inappropriate medication use. These frail older patients typically have functional disabilities and acute and chronic medical histories that require complex medication regimens. This results in an increase in both the incidence and degree of polypharmacy in these patients. Age-related

changes in pharmacokinetics and pharmacodynamics are strongly effected by dose regimes and together with coexisting diseases, they contribute to a significant increase in sensitivity to particular drugs and a corresponding increase in the incidence of ADRs. ADRs are particularly common in these patients [159]. In addition, some of these reactions may be confused with the progression of a given pathology or with some typical age-related syndromes. As physicians may be unaware of these factors, their prescribing may sometimes be suboptimal or inappropriate.

2.6 Research objectives

The general objective of this research project is to evaluate the appropriateness of medication use among LTCF residents with advanced dementia, using data from an intervention study on the implementation of a palliative care approach in Quebec City and Sherbrooke.

The specific objectives are:

a) To measure the prevalence of inappropriate medications among subjects with advanced dementia at baseline and at the end of the intervention study in four LTCFs, two experimental and two control LTCFs, according to three sets of criteria of inappropriate medications, namely those of Rancourt *et al*. [131], Holmes *et al.* [7] and Kröger *et al*. [141].

b) To assess whether there is a difference in the prevalence of inappropriate or potentially inappropriate medications, or medication classes, between the control group and the experimental group (palliative care intervention), among subjects with advanced dementia living in LTCFs, at study begin and at study ending.

Chapter 3. Methodology

3.1 Study design and intervention program

This research project was carried out using data from an intervention study with a quasi-experimental design which was conducted between November 1st, 2013 and October 30, 2014 in four LTCFs. A comprehensive intervention program to foster the palliative care approach among residents with advanced dementia at the end of their life was implanted in two randomly chosen experimental facilities, one in Quebec City and one in Sherbrooke. This intervention program included a period of six months for staff training, and then its effects were evaluated over 12 months in comparison with two other control LTCFs, one in Quebec City and one in Sherbrooke, where usual care was applied during this same period, but without implementation of the intervention program [160].

For the present study, several characteristics of the subjects and their medication dispensing histories over the duration of the study were collected from the patients' profile. More specifically, through using the subject's identification number (ID), the following characteristics were abstracted: gender, city of residence, intervention group, the date of admission to the LTCF, type of dementia, level of care and changes of care level during the study, number and type of active medications at study beginning and study end or date of death. Medications used by subjects were coded according to the World Health Organization ATC classification system.

3.2 Study population

The intervention sites comprised one LTCF in Quebec City, where 320 residents, at the time of the study, were living in nine care units, and a LTCF in Sherbrooke, where 216 residents were living in three care units. The control centers were a LTCF in Quebec City where 284 residents were living in four care units, and another LTCF in Sherbrooke where 144 residents were living in two units. These LTCFs were considered similar with regard to residents' profiles and care teams. More than 75% of the residents had AD/dementia while approximately a third had advanced AD/dementia.

To be included in the intervention study, subjects had to be 65 years or over, and have AD/dementia of at least stage 7B on the Reisberg Functional Assessment Staging Tool (FAST). The FAST scale is a well validated and widely used tool to assess the course of AD [161].

3.3 Description of the intervention program

This study used data from a palliative care intervention program aimed at increasing knowledge and skills of health care teams to improve the quality of palliative care for residents of LTCFs with advanced dementia at the end of life. In general, this intervention program included the following components: 1) involvement of the nurses of LTCFs as the local agents of change; 2) awareness sessions for staff at LTCFs; 3) a training program for physicians and staff; 4) systematic family meetings with distribution of information booklets; and 5) systematic clinical monitoring for symptom management [160].

3.4 Determining the prevalence of potentially inappropriate medications

Use of inappropriate medications was compared among the subjects of the experimental and the control groups of LTCFs before and after the intervention. Potentially inappropriate medications were defined as those medications listed in the Rancourt criteria [131]. Further, the appropriateness of medication use was compared to the criteria developed by Holmes [7] and Kröger [141], two criteria sets adapted for individuals with advanced dementia at the end of life. All medications used in this study were compared with these three lists and the prevalence of inappropriate or potentially inappropriate medications was determined.

3.5 Measurements

Outcome (dependent) variables. The presence of active inappropriate medications according to three criteria sets (Holmes, Kröger, Rancourt) at baseline and end of study (specific objective a); and the mean difference between the number of inappropriate medications in the intervention and control groups at baseline and end of study according to three sets of criteria (specific objective b).

Exposure (independent) variables. Patient information and other characteristics included: gender, age (continuous), type of dementia (AD, vascular dementia, mixed dementia or other types), level of care (optimal curative care, proportional curative care, palliative care), change of level of care during the study, hospital transfer during the study (yes/no), length of stay in the LTCF before study begin (years) and type of active medications at study beginning and at study end (specific objective a); and being in the intervention group or in the control group (specific objective b).

The current study included data on all prescribed medications, i.e. active medications (regular or as needed (PRN)). For each subject, the number of inappropriate medications according to the three sets of criteria has been calculated at baseline and at the end of the study. Active medications have been considered for the first Monday following admission into the study and medications given only once a week have been considered active for that day, as did PRN medications.

3.6 Ethical considerations

All collected information has been kept confidential and the anonymity of subjects has been preserved throughout the study. This study has been directed at members of the care team and was designed for long-term care staff to improve care practices and in turn, possibly medication appropriateness. Medication optimization and appropriateness are an integral part of the medical quality review in any center and considered as part of a center's «usual mandate». No direct intervention of the research team on subjects themselves occurred during this study. The study was submitted to the Ethics review board of the CSSS-VC (Ministère de la santé et des services sociaux du Québec) in Quebec City and to the Ethics review board of the CSSS-IUGS (Institut universitaire de gériatrie de Sherbrooke). Written and informed consent has been obtained from the legal representative or most significant family member of each resident to be included in the study. Written and informed consent has also been obtained from the family and care-team members who participated in the focus groups.

3.7 Statistical analysis

Baseline characteristics of subjects in experimental and control LTCFs were compared using Student's *t*-test for continuous variables and Chi square χ^2 (Fisher' exact test) test for categorical variables. The individual active medications and number of medications (continuous variable) for all subjects in the experimental or the control LTCFs have been compared to each of the three sets of criteria of inappropriateness by using the Student's *t*-test for these two groups. An approximate test for two independent proportions was used to compare the mean difference in inappropriate active medications at study beginning and end of study in the intervention and the control groups. A significance level of 0.05 for a two-sided test was applied. Data analyses were performed using SAS version 9.4.

Chapter 4. Results

4.1 Description of the characteristics of study sample

Overall, 215 subjects completed the study; 109 subjects were recruited in Quebec City, and 106 subjects, in Sherbrooke. There were 95 subjects in the control group, and 120 subjects in the intervention group. Selected characteristics of subjects are given in Table 3. The majority of subjects were women (73.5%) and the overall mean age was 87.9 years with a standard deviation (SD) of 8.0 years. AD and mixed dementia were the most frequent types of dementia with 36.7% and 39.1%, respectively. Almost a third of the subjects (30.7%) were receiving proportional curative care at study beginning while the other two-thirds (67.9%) were receiving palliative care. These proportions changed to 11.2% and 89% for proportional curative care and palliative care respectively at the end of the study. So, nearly 9 out of 10 subjects were receiving palliative care at study ending. Subjects had stayed on average 2.6 years (SD=4.2 years) in LTCFs before starting the study. Only 5 patients out of 215 have been transferred to a hospital during the study. In total, 412 different medications were used during the study.

Levels of care at study beginning and study ending were somewhat similar between the intervention and control at study beginning. A lower proportion of subjects in the intervention group was receiving palliative care as compared to the control group (53.3% versus 86.3%), with a *p*-value near the significance level (p=0.055). This difference of care level between the control and intervention groups decreased during the study (p=0.08 at study ending). No difference between the two groups for age, gender, type of dementia, hospital transfer during study and duration of stay in LTCFs before study begin was noted (all p values>0.05)

Table 3. Characteristics of subjects by city of study and by intervention group

Characteristic	All (n=215)	Quebec City (n=109)	Sherbrooke (n=106)	Control (n=95)	Intervention (n=120)	*p*-value[1]
Age at baseline (years ± standard deviation)	87.9 ± 8.0	87.2 ± 8.6	88.5 ± 7.1	87.7 ± 6.1	88.0 ± 9.2	0.74
Gender (women)	158 (73.5)	83 (76.2)	75 (70.7)	67 (70.5)	91 (75.8)	0.44
Type of dementia						0.76
Alzheimer's disease	79 (36.7)	37 (33.9)	42 (39.6)	33 (34.7)	46 (38.3)	
Vascular dementia	30 (14.0)	14 (12.8)	16 (15.0)	15 (15.8)	15 (12.5)	
Mixed dementia	84 (39.1)	44 (40.3)	40 (37.7)	39 (41.1)	45 (37.5)	
Other types	20 (9.3)	13 (11.9)	7(6.6)	8 (8.4)	12 (10.0)	
Not specified	2 (0.9)	1 (0.9)	1 (0.9)	0 (0.0)	2 (1.7)	
Level of care at study beginning						0.055
Optimal curative care	3 (1.3)	0 (0.0)	3 (2.8)	0 (0.0)	3 (2.5)	
Proportional curative care	66 (30.7)	44 (40.4)	22 (20.8)	13 (13.7)	53 (44.2)	
Palliative care	146 (67.9)	65 (59.6)	81 (76.4)	82 (86.3)	64 (53.3)	
Level of care at study ending						0.08
Optimal curative care	0.0	0.0	0.0	0.0	0.0	
Proportional curative care	24 (11.2)	20 (18.3)	4 (3.7)	6 (6.3)	18 (15.0)	
Palliative care	191 (89.0)	89 (81.6)	102 (96.2)	89 (93.7)	102 (85.0)	

Table 3. Characteristics of subjects by city of study and by intervention group (continued)

Characteristic	All (n=215)	Quebec City (n=109)	Sherbrooke (n=106)	Control (n=95)	Intervention (n=120)	*p*-value[1]
Hospital transfer during study (yes)	5 (2.6)	2 (2.4)	3 (2.8)	3 (3.2)	2 (2.1)	0.68
Duration of stay in LTCFs before study begin (years)	2.6 ± 4.2	3.0 ± 5.3	2.1 ± 2.8	3.0 ± 5.6	2.32.8	0.25

Values are n (%) if not otherwise stated.

[1] For the comparison between control and intervention groups

LTCFs: Long-term care facilities

4.2 Description of medication use before and after intervention

Table 4 summarizes the medications used per subject in the control and experimental groups, before and after the intervention. The mean number of medications prescribed per subject was 14.3 (SD=8.8) before the intervention. On average, subjects in the control group were taking more medications than in the intervention group (16.5 versus 12.6 medications, respectively, $p<0.001$) with a total number of 412 different medications prescribed. The mean number of medications prescribed per subject was 14.8 (SD=9.1) after the intervention. At study ending, subjects in the control group were still taking more medications than in the intervention group (17 versus 13 medications, respectively, $p<0.002$) with a total number of 412 different medications prescribed.

Before the intervention, the most frequent *potentially inappropriate medication* use was identified by the Rancourt criteria with an average of 5.8 (SD=3.6) medications. This can be compared to the categories of *rarely or never appropriate medications* according to the Holmes criteria with a mean of 1.7 medication and to a mean of 1.1 (SD=1.3) medication in the category of *exceptionally appropriate medications* by the Kröger criteria. After the intervention, these numbers were a mean of 5.9 (SD=3.6) potentially inappropriate medications as identified by the Rancourt criteria versus 1.7 medications (sum of *rarely and never appropriate medications)* by the Holmes criteria and 1.1 (SD=1.3) medications (*exceptionally appropriate medications*) by the Kröger criteria.

There was a significant difference in use of *potentially inappropriate medication*s according to the Rancourt criteria between the control and the intervention groups before the intervention (6.7 versus 5.2 medications, respectively; $p<0.002$). The same mean estimates were observed after the intervention ($p<0.003$).

The results also showed that there was a statistically significant difference between intervention and control groups in the mean number of medications per subject identified as *rarely or never appropriate* medications according to the Holmes criteria ($p<0.03$) and in the mean number of *exceptionally appropriate* medications according to the Kröger criteria ($p<0.04$) after the intervention, whereas no significant difference was observed before the intervention ($p=0.08$ and 0.052, respectively).

Table 4. Numbers of medications used per subject, according to the categories of different criteria, before and after the intervention

Category of the respective set of criteria	Before the intervention			*p*-value	After the intervention			*p*-value
	All n=215	Control n=95	Intervention n=120		All n=215	Control n=95	Intervention n=120	
Mean number of ALL different medications used per subject	14.3 ± 8.8	16.5 ± 9.4	12.6 ± 8.0	0.001	14.8 ± 9.1	17.0 ± 9.5	13.0 ± 8.5	0.002
Medications used according to four categories of Holmes criteria[1]								
Always appropriate medications	4.1 ± 2.6	4.7 ± 2.9	3.7 ± 2.3	0.007	4.2 ± 2.6	4.7 ± 2.8	3.8 ± 2.3	0.009
Sometimes appropriate medications	5.4 ± 3.3	6.1 ± 3.7	4.8 ± 2.9	0.008	5.6 ± 3.5	6.3 ± 3.8	5.0 ± 3.1	0.01
Rarely appropriate medications	0.9 ± 1.2	0.9 ± 1.2	0.8 ± 1.3	0.51	0.9 ± 1.1	0.9 ± 1.1	0.8 ± 1.2	0.26
Never appropriate medications	0.8 ± 0.8	0.9 ± 0.9	0.7 ± 0.8	0.08	0.8 ± 0.9	1.0 ± 1.0	0.7 ± 0.9	0.03
Medications used according to three categories of Kröger criteria[2]								
Always appropriate medications	2.7 ± 1.4	2.9 ± 1.6	2.6 ± 1.3	0.17	2.9 ± 1.4	2.9 ± 1.4	2.9 ± 1.3	0.85

Table 4: Mean numbers of medications used per resident, according to the categories of different criteria, before and after the intervention (continued)

Category of the respective set of criteria	Before the intervention			*p*-value	After the intervention			*p*-value
	All n=215	Control n=95	Intervention n=120		All n=215	Control n=95	Intervention n=120	
Sometimes appropriate medications	6.7 ± 4.3	7.6 ± 4.7	5.9 ± 3.8	0.005	6.7 ± 4.4	7.8 ± 4.7	5.8 ± 3.9	0.001
Exceptionally appropriate medications	1.1 ± 1.3	1.2 ±1.3	0.9 ± 1.2	0.052	1.1 ± 1.3	1.3 ± 1.4	0.9 ± 1.3	0.04
Used medications considered as potentially inappropriate according to Rancourt criteria[3]								
Potentially inappropriate medications	5.8 ± 3.6	6.7 ± 3.9	5.2 ± 3.2	0.002	5.9 ± 3.6	6.7 ± 3.9	5.2 ± 3.2	0.003

Values correspond to mean ± standard deviation.

[1] Holmes HM, Sachs GA, Shega JW, Hougham GW, Cox Hayley D, Dale W. (2008) "Integrating palliative medicine into the care of persons with advanced dementia: identifying appropriate medication use." J Am Geriatr Soc 56(7): 1306-1311;

[2] Kröger E, Wilchesky M, Marcotte M, Voyer P, Morin M, Champoux N, Monette J, Aubin M, Durand PJ, Verreault R, Arcand M. (2015) Medication use among nursing home residents with severe dementia: Identifying categories of appropriateness and elements of a successful intervention." J Am Med Dir Assoc 16(7): 629 e621-617.

[3] Rancourt C, Moisan J, Baillargeon L, Verreault R, Laurin D, Grégoire JP. (2004) Potentially inappropriate prescriptions for older patients in long-term care. BMC Geriatr 4: 9.

Table 5 summarizes the proportions of subjects exposed to medications according to the different categories of appropriateness for the control and intervention groups, at the beginning and at the end of the intervention. Before the intervention, 50.7% and 55.8% of subjects respectively were receiving one or more inappropriate medications according to the categories of *rarely and never appropriate medications* of Holmes criteria. This difference was not statistically significant. After the intervention, 50.7% and 52.1% of subjects were receiving one or more inappropriate medications based on the categories of rarely and never appropriate medications of Holmes criteria, respectively. Subjects in the intervention group were receiving a lower proportion of never appropriate medications compared to the control group (45.8% versus 60.0%; $p<0.04$). Similar results were observed between groups for rarely appropriate medications, but the result was not significant (45.0% versus 57.9%; $p=0.06$).

According to the Kröger criteria, 54.4% of subjects had at least one potentially inappropriate medication in category of exceptionally inappropriate medications before the intervention, and 57.2% of them after the intervention. Before the intervention, subjects in the intervention group were receiving a lower proportion of exceptionally appropriate medications compared to the control group (48.3% versus 62.1%; $p<0.04$). Similar results were observed after the intervention (50.0% versus 66.3%; $p<0.02$).

According to the Rancourt criteria, 98.1% of subjects were receiving at least one medication classified as *potentially inappropriate* before the intervention and 99.1% of them after the intervention. No difference between the control and intervention groups was noted before and after the intervention.

Table 5. Proportions of subjects exposed to respective categories of different criteria, before and after the intervention

Category of the respective set of criteria	Before the intervention			*p*-value	After the intervention			*p*-value
	All n=215	Control n=95	Intervention n=120		All n=215	Control n=95	Intervention n=120	
Medications used according to four categories of Holmes criteria[1]								
Always appropriate medications	206 (95.8)	91 (95.8)	115 (95.8)	0.99	210 (97.7)	92 (96.8)	118 (98.3)	0.47
Sometimes appropriate medications	209 (97.2)	92 (96.8)	117 (97.5)	0.77	211 (98.1)	93 (97.9)	118 (98.3)	0.81
Rarely appropriate medications	109 (50.7)	54 (56.8)	55 (45.8)	0.11	109 (50.7)	55 (57.9)	54 (45.0)	0.06
Never appropriate medications	120 (55.8)	56 (59.0)	64 (53.3)	0.41	112 (52.1)	57 (60.0)	55 (45.8)	0.04
Medications used according to three categories of Kröger criteria[2]								
Always appropriate medications	205 (95.3)	88 (92.6)	117 (97.5)	0.09	208 (96.7)	88 (92.6)	120 (100)	0.003
Sometimes appropriate medications	210 (97.7)	93 (97.9)	117 (97.5)	0.85	211 (98.1)	94 (98.5)	117 (97.5)	0.43
Exceptionally appropriate medications	117 (54.4)	59 (62.1)	58 (48.3)	0.04	123 (57.2)	63 (66.3)	60 (50.0)	0.02
Used medications considered as potentially inappropriate according to Rancourt criteria[3]								
Potentially inappropriate medications	211 (98.1)	94 (98.9)	117 (97.5)	0.43	213 (99.1)	95 (100)	118 (98.3)	0.21

Values correspond to n (%).

[1] Holmes HM, Sachs GA, Shega JW, Hougham GW, Cox Hayley D, Dale W. (2008) Integrating palliative medicine into the care of persons with advanced dementia: identifying appropriate medication use. J Am Geriatr Soc 56(7): 1306-1311.

[2] Kröger E, Wilchesky M, Marcotte M, Voyer P, Morin M, Champoux N, Monette J, Aubin M, Durand JP, Verreault R, Arcand M. (2015) Medication use among nursing home residents with severe dementia: Identifying categories of appropriateness and elements of a successful intervention. J Am Med Dir Assoc 16(7): 629 e621-617.

[3] Rancourt C, Moisan J, Baillargeon L, Verreault R, Laurin D, Grégoire JP. (2004) Potentially inappropriate prescriptions for older patients in long-term care. BMC Geriatr 4: 9.

Figure 1 shows the list of inappropriate medication used based on Kröger, Holmes and Rancourt criteria. As it can be seen, there is some overlaps in individual medications and classes among the three sets of criteria. The eight common inappropriate medications identified by the three sets of criteria comprise: Atorvastatin, Cholestyramine, Digoxin, Fenofibrate, Hydralazine, Pravastatin, Rosuvastatin, and Simvastatin.

The use of Holmes and Kröger criteria identified 26 additional inappropriate medications: Alendronate, Amethopterin, Amiodarone, Anastrozole, Calciferol, Clonidine, Clopidogrel, Conjugated estrogens, Dalteparin, Dutasteride, Enoxaparin, Estradiol, Etidronate disodium, Finasteride, Fluorouracil, Heparin, Hydroxyurea, Medroxyprogesterone, Montelukast, Pentosan, Risedronate, Solifenacin, Tamoxifen, Tolterodine, Warfarin and Zoledronic acid. The use of Rancourt and Kröger criteria identified six additional inappropriate medications: Amitriptyline, Cyproheptadine, Dimenhydrinate, Diphenhydramine, Doxepin and Loratadine .The use of Holmes and Rancourt criteria identified just one inappropriate medication: Dipyridamole. Finally, 13 medications, 11 medications and 12 medications were considered inappropriate medications according only the set of criteria of Rancourt, Holmes and Kröger, respectively.

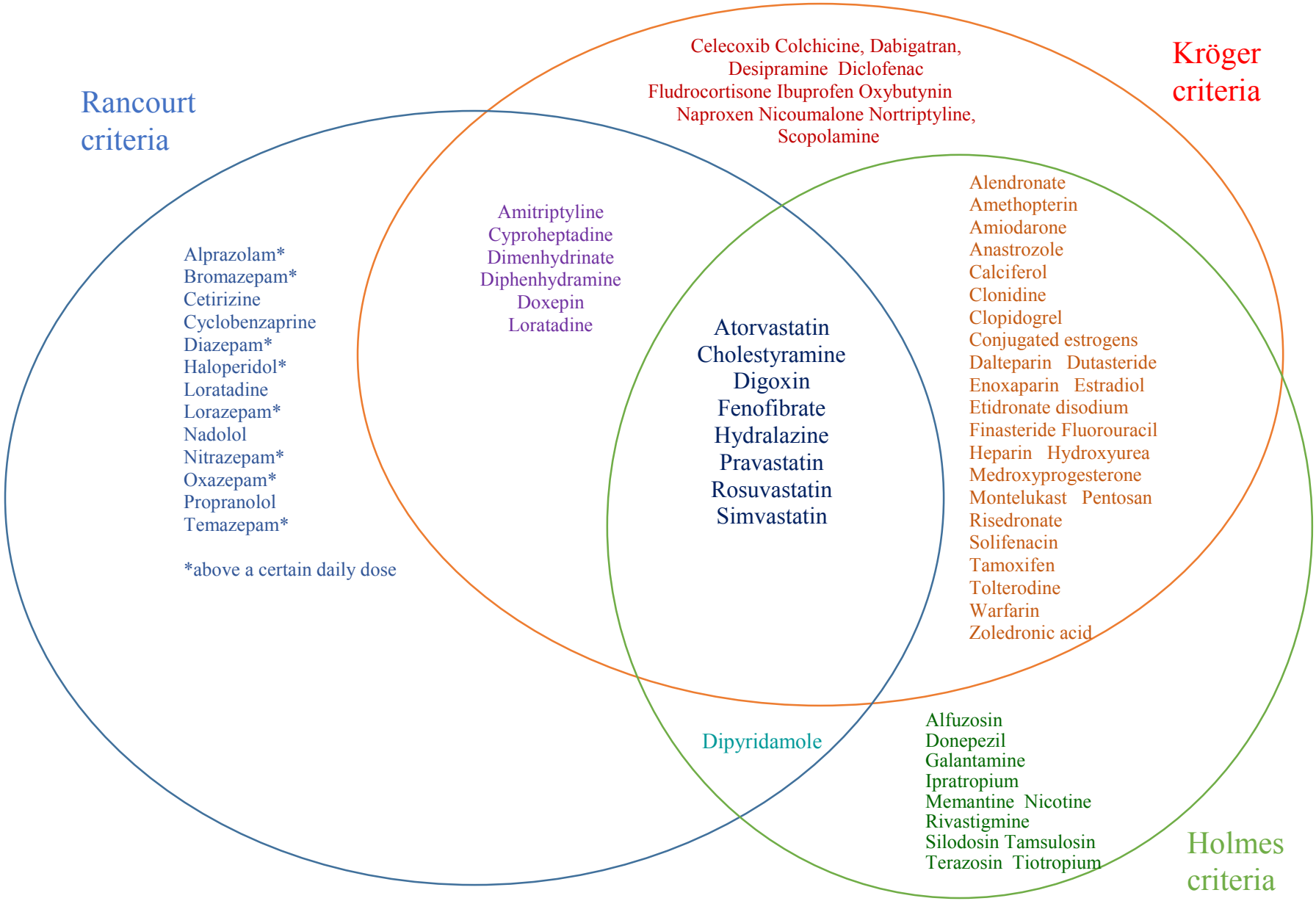

Figure 1. List of inappropriate medication use based on Kröger 2015, Holmes 2008 and Rancourt 2004 criteria

Table 6 summarizes the proportion of subjects exposed to five specific medication classes, including antipsychotics, cholinesterase inhibitors, statins, other lipid modifiers and bisphosphonates. These classes were selected because their use has frequently been questioned (cholinesterase inhibitors, antipsychotics) or they are frequently used yet classified as never appropriate according to Holmes criteria or as exceptionally appropriate according to Kröger criteria (statins and other lipid modifiers, bisphosphonates) in LTCF residents with advanced dementia at the end of their life.

The two most commonly used medications before the intervention were cholinesterase inhibitors and antipsychotics with 22.8% and 18.6% of subjects, respectively. These results remained similar after the intervention with 20.5% and 16.7%, respectively. There was no significant difference between control and intervention groups before and after the intervention.

Relatively few subjects were receiving bisphosphonates (7.9%), statins (5.2%) and other lipid modifiers (1.9%) before the intervention and after the intervention (8.0%, 4.6% and 3.1%, respectively). No difference was observed between control and intervention groups before and after the intervention (all p values>0.05).

Table 6. Proportions of subjects exposed to five specific medication classes, before and after the intervention

Medication classes	Before the intervention			*p*-value	After the intervention			*p*-value
	All n=215	Control n=95	Intervention n=120		All n=215	Control n=95	Intervention n=120	
Antipsychotics	40 (18.6)	15 (15.8)	25 (20.8)	0.35	36 (16.7)	15 (15.8)	21 (17.5)	0.74
Cholinesterase inhibitors	49 (22.8)	21 (22)	28 (23.4)	0.83	44 (20.5)	21 (22)	23 (19.2)	0.60
Statins	11 (5.2)	7 (7.5)	4 (3.5)	0.18	10 (4.6)	7 (7.4)	3 (2.5)	0.09
Other lipid modifiers	4 (1.9)	2 (2)	2 (1.7)	0.81	8 (3.7)	3 (3.1)	5 (4.2)	0.70
Bisphosphonates	17 (7.9)	5 (5.3)	12 (10)	0.20	17 (8.0)	5 (5.3)	12 (10)	0.20

Values correspond to n (%).

[1] Holmes HM, Sachs GA, Shega JW, Hougham GW, Cox Hayley D, Dale W. (2008) Integrating palliative medicine into the care of persons with advanced dementia: identifying appropriate medication use. J Am Geriatr Soc 56(7): 1306-1311.

[2] Kröger E, Wilchesky M, Marcotte M, Voyer P, Morin M, Champoux N, Monette J, Aubin M, Durand JP, Verreault R, Arcand M. (2015) Medication use among nursing home residents with severe dementia: Identifying categories of appropriateness and elements of a successful intervention. J Am Med Dir Assoc 16(7): 629 e621-617.

[3] Rancourt C, Moisan J, Baillargeon L, Verreault R, Laurin D, Grégoire JP. (2004) potentially inappropriate prescriptions for older patients in long-term care. BMC Geriatr 4: 9.

Chapter 5. Discussion and conclusion

The present research project aimed at evaluating the appropriateness of medication use among LTCF residents with advanced dementia, using, data from an intervention study designed to determine the effect of a palliative care intervention program in such residents. To this end, this research project compared medication use according to three pertinent sets of criteria on appropriateness, i.e. Holmes, Rancourt and Kröger criteria. Overall, results showed that appropriateness of medication according to these criteria did not differ significantly between control and intervention groups, either before or after the intervention program. Little change was observed in the use of *potentially*, *rarely*, *never* of *exceptionally appropriate* medications before and after the study.

There isn't much information in the literature on the effects of this type of palliative care approach on appropriate use of medications. Since this approach leads to a shift from a proportional curative to a comfort care approach, it should comprise a review of the resident's medication list. A change of medication appropriateness according to criteria for residents with advanced dementia near the end of life was thus hoped for.

Results from previous studies are somewhat different from the present study with regard to methodology, study location and population. For instance, Holmes *et al*. examined medication use in 34 persons with advanced dementia who were registered in a palliative care program and assessed the appropriateness using a Delphi panel of 13 geriatricians. They reported that 29% were receiving a medication that was classified as *never appropriate* [7]. In our study, 53.3% were receiving at least one medication categorized as *never appropriate* according to Holmes criteria in the intervention group at study beginning, whereas 45.8% of them were receiving one at the end of study. The mean number of medications used in Holmes' study was 6.5, and only 18% of subjects used 10 or more medications, whereas the mean number of medications was 14.3 in the present study.

The mean number of medications taken before and after the intervention remained nearly unchanged (14.8 versus 14.3 medications). Some previous studies reported shifts away from medications for comorbid medical conditions (e.g. osteoporosis) toward palliative and symptom specific medications (e.g. opioids, scopolamine), but in the present study the period

of the last two weeks before the death of a participant were excluded to avoid this type of bias [20, 79, 105]. Our results contrast with some other studies in patients with advanced dementia living in other healthcare settings where significant reductions in overall medication use were found [76, 162, 163]. For example, Garfinkel *et al*, had reported a reduction of 10% of all drugs used by their subjects in their palliative care approach.

This study showed that nearly 50% of subjects used at least one questionably medication after comparison with three sets of criteria. This result is consistent with the work of Tjia *et al*. in the USA in 2014 [164], where 53.9% (n=5 406) of the study sample were prescribed at least one questionably beneficial medication during the 90-day observation period.

In our study, the prevalence of inappropriate medication use differs significantly between the application of the category *rarely inappropriate* according to Holmes criteria (45%) and *potentially inappropriate* according to Rancourt criteria (100%). This may be explained in part by the fact that more medications are potentially inappropriate in older people than are rarely appropriate in LTCF residents with advanced dementia.

The prevalence of potentially inappropriate medications according to Rancourt criteria is higher than for *rarely, never* or *exceptionally appropriate* medications according to the criteria of Holmes and Kröger. After applying the three sets of criteria, the maximum number of inappropriate medications were identified by Rancourt criteria (5.8 and 5.9 medications) before and after the intervention, respectively. An explanation for this phenomenon could be that the Rancourt criteria were introduced to identify potentially inappropriate medications in institutionalized older persons in general, including those potentially inappropriate at a specific duration or dosage, and therefore a much larger group of medications is included. Holmes developed criteria specifically for persons with advanced dementia near the end of life, and only the categories *rarely* or *never appropriate* were included here. Kröger criteria are similar to Holmes and only the category *exceptionally appropriate* was included.

In general, as the end of life approaches, the types of medications prescribed change. Logically, the palliative medication use (opiate analgesics and pulmonary agents) should increase, whereas most other medications such as psychotropic medication should decrease [20]. It is thus interesting to note that the proportions of using five specific classes, the most common questionably medications used in residents in LTCFs, have not changed at

beginning and end of the study (all *p* values>0.05). It is nevertheless reassuring to note that the proportions for some of those classes were relatively low (statins, other lipid modifiers, bisphosphonates). Likewise, the use of lipid-lowering medications in individuals with advanced dementia at the end of life is a challenging issue for physicians. It is now generally accepted to discontinue these types of medications near the end of life [20]. Our findings support these ideas.

Approximately one in five subjects (22.8%) with advanced dementia at the end of life were using cholinesterase inhibitors at the beginning of study. This estimate is lower than those reported previously for residents of LTCFs (30-40%) [165-167]. This estimate remained similar after the intervention (20.5%). Interestingly, the proportion of residents using lipid-lowering agents was much higher in other studies, e.g. the study done by Tjia (4.2% versus 22.4%) [164]. In our study, the use of antipsychotics decreased slightly (from 20.8% to 17.5%) during the intervention, for a relative reduction of 15.9%. This result is somewhat comparable to findings of previous studies, which showed relative reductions between 19% and 56% in the intervention group compared with the control group [168-171].

Results of this study show that use of potentially inappropriate medications (Rancourt) or medications of questionable benefit (Holmes, Kröger) were common among the LTCF residents in this study, both before and after the intervention to foster a palliative care approach in residents with advanced dementia near the end of their lives.

One of the strengths of our study was applying three sets of criteria of appropriateness. Two of these criteria, those of Holmes [7] and Kröger [141], were specifically developed for determining inappropriate medications for these patients with advanced dementia.

Limitations of this study must be recognized. First, given the quasi experimental study design of the intervention, it is not possible to exclude a potential selection bias. Such a bias is possible given that recruitment was based on only four units in LTCFs from (Quebec City and Sherbrooke). This selection procedure could also limit the generalizability of the results to Canada and other countries.

As shown in table 3, characteristics of subjects between the control and intervention groups are not exactly similar. The subjects in the control group were receiving more palliative care at the beginning of the intervention and less proportional curative care. Second, some of the

data on pertinent medical and sociodemographic variables for our analysis were not available for our analysis. For example, we do not have information on a previous history of depression or other comorbidities, living arrangements, education level, etc. In addition, the medication information of this study was only analysed with respects to the medication type, but not regarding medication dose, duration or way of administration. Such analyses are, however feasible and would be interesting for a future project. One also has to note the conceptual differences between Rancourt criteria on one side and Holmes or Kröger's criteria on the other side, as specified above.

The present study has important implications because it highlights the burden of medication use overall and of medications of questionable benefit in LTCF residents with advanced dementia, as well as the burden this use poses on the health system and these vulnerable residents. An economic assessment of the use of questionably beneficial medications could also be an important issue when aiming at the reduction of the average resident's annual medication cost to the health care system in LTCF.

Further research is required to establish how to reduce exposure to medications of questionable benefit in residents with advanced dementia and to improve clinical guidance on optimal medication use in this population. This new approach could include other research designs, qualitative approaches on decision making regarding medication use, as well as a combination of implicit and explicit criteria on medication appropriateness. Continued efforts to monitor medication use in older people with advanced dementia at the end of life needs the full attention of decision makers. This could lead to a more standardised clinical decision making and better practice guidelines based on the best available evidence.

References

1. Ferri, C.P., et al., *Global prevalence of dementia: a Delphi consensus study.* Lancet, 2005. **366**(9503): p. 2112-7.
2. Mitchell, S.L., D.K. Kiely, and M.B. Hamel, *Dying with advanced dementia in the nursing home.* Arch Intern Med, 2004. **164**(3): p. 321-6.
3. McCarthy, M., J. Addington-Hall, and D. Altmann, *The experience of dying with dementia: a retrospective study.* Int J Geriatr Psychiatry, 1997. **12**(3): p. 404-9.
4. Black, B.S., et al., *Health problems and correlates of pain in nursing home residents with advanced dementia.* Alzheimer Dis Assoc Disord, 2006. **20**(4): p. 283-90.
5. Gallagher, P.F., P. Barry, and D. O'Mahony, *Inappropriate prescribing in the elderly.* J Clin Pharm Ther, 2007. **32**(2): p. 113-21.
6. O'Mahony, D. and M.N. O'Connor, *Pharmacotherapy at the end-of-life.* Age Ageing, 2011. **40**(4): p. 419-22.
7. Holmes, H.M., et al., *Integrating palliative medicine into the care of persons with advanced dementia: identifying appropriate medication use.* J Am Geriatr Soc, 2008. **56**(7): p. 1306-11.
8. American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)*. 4 ed. 1994, Washington DC: American Psychiatric Association.
9. Alzheimer's Association, *Dementia Care Practice Recommendations for Assisted Living Residences and Nursing Homes.Phase 3 End-of life Care*. 2007, Alzheimer's Association: Washington D.C USA.
10. World Health Organization. *Dementia*. 2014 [cited 2015 10 October]; Available from: http://www.who.int/mental_health/neurology/dementia/dementia_thematicbrief_executivesummary.pdf.
11. Alzheimer Society of Canada. *About dementia*. 2014 [cited 2015 10 November]; Available from: http://www.alzheimer.ca/en/About-dementia.
12. Canadian Study of Health and Aging Working Group, *Canadian Study of Health and Aging: study methods and prevalence of dementia.* CMAJ, 1994. **150**(6): p. 899-913.
13. Alzheimer's Disease International. *World Alzheimer Report 2014: Dementia and Risk Reduction*. 2013 [cited 2015 September 25]; http://www.alz.co.uk/research/world-report-2014]. Available from: http://www.alz.co.uk/research/world-report-2014.
14. Alzheimer Society of Canada. *Dementia numbers in Canada*. 2010 [cited 2015 September 25]; Available from: http://www.alzheimer.ca/en/About-dementia/What-is-dementia/Dementia-numbers.
15. Smetanin, P., et al., *Rising Tide: The Impact of Dementia in Canada 2008 to 2038*. 2008, Alzheimer Society of Canada.
16. Prince, M., R. Bryce, and C. Rerri, *World Alzheimer Report 2011. The benefits of early diagnosis and intervention*, in *World Alzheimer Report*, A.s.D. International, Editor. 2011, Institute of Psychiatry, King's College London, UK: London, UK.
17. Douglas Mental Health University Institute. *Alzheimer's Disease, a critical situation*. 2015 [cited 2015 11 September 2015]; Available from: http://www.douglas.qc.ca/page/prevent-alzheimer
18. Shega, J.W., et al., *Patients dying with dementia: experience at the end of life and impact of hospice care.* J Pain Symptom Manage, 2008. **35**(5): p. 499-507.
19. Mitchell, S.L., et al., *A national study of the location of death for older persons with dementia.* J Am Geriatr Soc, 2005. **53**(2): p. 299-305.

20. Blass, D.M., et al., *Medication use in nursing home residents with advanced dementia.* Int J Geriatr Psychiatry, 2008. **23**(5): p. 490-6.
21. Ahronheim, J.C., et al., *Treatment of the dying in the acute care hospital. Advanced dementia and metastatic cancer.* Arch Intern Med, 1996. **156**(18): p. 2094-100.
22. Morrison, R.S. and A.L. Siu, *Survival in end-stage dementia following acute illness.* JAMA, 2000. **284**(1): p. 47-52.
23. Turnheim, K., *When drug therapy gets old: pharmacokinetics and pharmacodynamics in the elderly.* Exp Gerontol, 2003. **38**(8): p. 843-53.
24. Fülöp, T.J., et al., *Body composition in elderly people. Determination of body composition by multiisotope method and the elimination kinetics of these isotopes in healthy elderly subjects.* Gerontology, 1985. **31**(1): p. 6-14.
25. Mangoni, A.A. and S.H. Jackson, *Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications.* Br J Clin Pharmacol, 2004. **57**(1): p. 6-14.
26. Meyer, B., et al., *Clinical pharmacology and aging.Oxford textbook of geriatric medicine.* 2nd ed. Oxford textbook of geriatric medicine. 2003, Oxford, UK: Oxford University Press.
27. Hilmer, S.N., A.J. McLachlan, and D.G. Le Couteur, *Clinical pharmacology in the geriatric patient.* Fundam Clin Pharmacol, 2007. **21**(3): p. 217-30.
28. Ouslander, J.G. and I. Tamai, *Drug treatment for elderly patients.* Compr Ther, 1987. **13**(5): p. 62-73.
29. Brooks, T.R., *Drug prescribing for the elderly outpatient and for those confined to convalescent hospitals. How the new OBRA laws will change some established habits.* J Natl Med Assoc, 1993. **85**(12): p. 921-7.
30. Abernethy, D.R., *Altered pharmacodynamics of cardiovascular drugs and their relation to altered pharmacokinetics in elderly patients.* Clin Geriatr Med, 1990. **6**(2): p. 285-92.
31. McLean, A.J. and D.G. Le Couteur, *Aging biology and geriatric clinical pharmacology.* Pharmacol Rev, 2004. **56**(2): p. 163-84.
32. Morike, K., M. Schwab, and U. Klotz, *Use of aminoglycosides in elderly patients. Pharmacokinetic and clinical considerations.* Drugs Aging, 1997. **10**(4): p. 259-77.
33. Miura, T., et al., *Effect of aging on the incidence of digoxin toxicity.* Ann Pharmacother, 2000. **34**(4): p. 427-32.
34. Hunt, C.M., W.R. Westerkam, and G.M. Stave, *Effect of age and gender on the activity of human hepatic CYP3A.* Biochem Pharmacol, 1992. **44**(2): p. 275-83.
35. Hunt, C.M., et al., *Hepatic cytochrome P-4503A (CYP3A) activity in the elderly.* Mech Ageing Dev, 1992. **64**(1-2): p. 189-99.
36. Miller, M., *Fluid and electrolyte homeostasis in the elderly:physiological changes of aging and clinical consequences.* Baillier's Clinical Endocrinology &Metabolism, 1997. **11**: p. 367-387.
37. White, M., et al., *Age-related changes in beta-adrenergic neuroeffector systems in the human heart.* Circulation, 1994. **90**(3): p. 1225-38.
38. Vestal, R.E., A.J. Wood, and D.G. Shand, *Reduced beta-adrenoceptor sensitivity in the elderly.* Clin Pharmacol Ther, 1979. **26**(2): p. 181-6.
39. O'Malley , K., J.R. Docherty, and K. J.G., *Adrenoreceptor status and cardiovascular function in ageing.* Journal of hypertension, 1988. **6(Supp.1)**: p. S59-62.
40. Feldman, R.D., et al., *Alterations in leukocyte beta-receptor affinity with aging. A potential explanation for altered beta-adrenergic sensitivity in the elderly.* N Engl J Med, 1984. **310**(13): p. 815-9.
41. Williamson, J. and J.M. Chopin, *Adverse reactions to prescribed drugs in the elderly: a multicentre investigation.* Age Ageing, 1980. **9**(2): p. 73-80.

42. Cunningham, G., et al., *Drug-related problems in elderly patients admitted to Tayside hospitals, methods for prevention and subsequent reassessment.* Age Ageing, 1997. **26**(5): p. 375-82.
43. Roe, C.M., M.J. Anderson, and B. Spivack, *Use of anticholinergic medications by older adults with dementia.* J Am Geriatr Soc, 2002. **50**(5): p. 836-42.
44. Edwards, I.R., *Spontaneous ADR reporting and drug safety signal induction in perspective. To honour Professor Jens Schou.* Pharmacol Toxicol, 2000. **86 Suppl 1**: p. 16-9.
45. Walker, J. and H. Wynne, *Review: the frequency and severity of adverse drug reactions in elderly people.* Age Ageing, 1994. **23**(3): p. 255-9.
46. Routledge, P.A., M.S. O'Mahony, and K.W. Woodhouse, *Adverse drug reactions in elderly patients.* Br J Clin Pharmacol, 2004. **57**(2): p. 121-6.
47. Viktil, K.K., et al., *Polypharmacy as commonly defined is an indicator of limited value in the assessment of drug-related problems.* Br J Clin Pharmacol, 2007. **63**(2): p. 187-95.
48. Hughes, S., *Compliance with drug treatment in the elderly.* Prescriber, 1998. **9**: p. 45-54.
49. Mjorndal, T., et al., *Adverse drug reactions as a cause for admissions to a department of internal medicine.* Pharmacoepidemiol Drug Saf, 2002. **11**(1): p. 65-72.
50. Mannesse, C.K., et al., *Contribution of adverse drug reactions to hospital admission of older patients.* Age Ageing, 2000. **29**(1): p. 35-9.
51. Atkin, P.A. and G.M. Shenfield, *Medication-related adverse reactions and the elderly: a literature review.* Adverse Drug React Toxicol Rev, 1995. **14**(3): p. 175-91.
52. Lazarou, J., B.H. Pomeranz, and P.N. Corey, *Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies.* JAMA, 1998. **279**(15): p. 1200-5.
53. Lamy, P.P., *Drug interactions and the elderly.* J Gerontol Nurs, 1986. **12**(2): p. 36-7.
54. Jansen, P.A. and J.R. Brouwers, *Clinical pharmacology in old persons.* Scientifica (Cairo), 2012. **2012**: p. 723678.
55. Lindley, C.M., et al., *Inappropriate medication is a major cause of adverse drug reactions in elderly patients.* Age Ageing, 1992. **21**(4): p. 294-300.
56. Becker, J.T., et al., *The natural history of Alzheimer's disease. Description of study cohort and accuracy of diagnosis.* Arch Neurol, 1994. **51**(6): p. 585-94.
57. Bootman, J.L., D.L. Harrison, and E. Cox, *The health care cost of drug-related morbidity and mortality in nursing facilities.* Arch Intern Med, 1997. **157**(18): p. 2089-96.
58. Chan, M., F. Nicklason, and J.H. Vial, *Adverse drug events as a cause of hospital admission in the elderly.* Intern Med J, 2001. **31**(4): p. 199-205.
59. Onder, G., et al., *Adverse drug reactions as cause of hospital admissions: results from the Italian Group of Pharmacoepidemiology in the Elderly (GIFA).* J Am Geriatr Soc, 2002. **50**(12): p. 1962-8.
60. Harugeri, A., et al., *Prescribing patterns and predictors of high-level polypharmacy in the elderly population: A prospective surveillance study from two teaching hospitals in India.* Am J Geriatr Pharmacother, 2010. **8**(3): p. 271-80.
61. Bero, L.A., H.L. Lipton, and J.A. Bird, *Characterization of geriatric drug-related hospital readmissions.* Med Care, 1991. **29**(10): p. 989-1003.
62. Col, N., J.E. Fanale, and P. Kronholm, *The role of medication noncompliance and adverse drug reactions in hospitalizations of the elderly.* Arch Intern Med, 1990. **150**(4): p. 841-5.
63. Hanlon, J.T., et al., *Adverse drug events in high risk older outpatients.* J Am Geriatr Soc, 1997. **45**(8): p. 945-8.
64. Cooper, J.W., *Adverse drug reaction-related hospitalizations of nursing facility patients: a 4-year study.* South Med J, 1999. **92**(5): p. 485-90.
65. Sergi, G., et al., *Polypharmacy in the elderly: can comprehensive geriatric assessment reduce inappropriate medication use?* Drugs Aging, 2011. **28**(7): p. 509-18.

66. Hanlon, J.T., et al., *Incidence and predictors of all and preventable adverse drug reactions in frail elderly persons after hospital stay.* J Gerontol A Biol Sci Med Sci, 2006. **61**(5): p. 511-5.
67. Simonson, W. and J.L. Feinberg, *Medication-related problems in the elderly : defining the issues and identifying solutions.* Drugs Aging, 2005. **22**(7): p. 559-69.
68. Stevenson, J., et al., *Managing comorbidities in patients at the end of life.* BMJ, 2004. **329**(7471): p. 909-12.
69. Riechelmann, R.P., et al., *Potential drug interactions in cancer patients receiving supportive care exclusively.* J Pain Symptom Manage, 2008. **35**(5): p. 535-43.
70. Goldberg, R.M., et al., *Drug-drug and drug-disease interactions in the ED: analysis of a high-risk population.* Am J Emerg Med, 1996. **14**(5): p. 447-50.
71. Chiang, L., S.H. Hirsch, and D.B. Reuben, *Predictors of medication prescription in nursing homes.* J Am Med Dir Assoc, 2000. **1**(3): p. 97-102.
72. Perri, M.r., et al., *Adverse outcomes asspciated with inappropriate drug use in nursing homes.* Ann Pharmacother, 2005. **39**(3): p. 405-411.
73. Ramage-Morin, P.L., *Medication use among senior Canadians*, in *Health Rep*. 2009, Statistics Canada: Ottawa Canada. p. 37-44.
74. Gnjidic, D., et al., *Deprescribing trials: methods to reduce polypharmacy and the impact on prescribing and clinical outcomes.* Clin Geriatr Med, 2012. **28**(2): p. 237-53.
75. Doshi, J.A., T. Shaffer, and B.A. Briesacher, *National estimates of medication use in nursing homes: findings from the 1997 medicare current beneficiary survey and the 1996 medical expenditure survey.* J Am Geriatr Soc, 2005. **53**(3): p. 438-43.
76. Beers, M.H., et al., *Inappropriate medication prescribing in skilled-nursing facilities.* Ann Intern Med, 1992. **117**(8): p. 684-9.
77. Gurwitz, J.H., et al., *Incidence and preventability of adverse drug events in nursing homes.* Am J Med, 2000. **109**(2): p. 87-94.
78. Lee, S.P., K.T. Bain, and V. Maio, *Appropriate discontinuation of medications at the end of life: a need to establish consensus criteria.* Am J Med Qual, 2007. **22**(6): p. 393-4.
79. Currow, D.C., et al., *Prescribing in palliative care as death approaches.* J Am Geriatr Soc, 2007. **55**(4): p. 590-5.
80. Laroche, M.L., J.P. Charmes, and L. Merle, *Potentially inappropriate medications in the elderly: a French consensus panel list.* Eur J Clin Pharmacol, 2007. **63**(8): p. 725-31.
81. Koh, N.Y. and W.H. Koo, *Polypharmacy in palliative care: can it be reduced?* Singapore Med J, 2002. **43**(6): p. 279-83.
82. Monane, M., S. Monane, and T. Semla, *Optimal medication use in elders. Key to successful aging.* West J Med, 1997. **167**(4): p. 233-7.
83. Kaufman, D.W., et al., *Recent patterns of medication use in the ambulatory adult population of the United States: the Slone survey.* JAMA, 2002. **287**(3): p. 337-44.
84. Everitt, D.E. and J. Avorn, *Drug prescribing for the elderly.* Arch Intern Med, 1986. **146**(12): p. 2393-6.
85. Arnett, R.H.3rd, et al., *National health expenditures, 1988. Office of National Cost Estimates.* Health Care Financ Rev, 1990. **11**(4): p. 1-41.
86. Gupta, S., H.M. Rappaport, and L.T. Bennett, *Inappropriate drug prescribing and related outcomes for elderly medicaid beneficiaries residing in nursing homes.* Clin Ther, 1996. **18**(1): p. 183-96.
87. Golden, A.G., et al., *Inappropriate medication prescribing in homebound older adults.* J Am Geriatr Soc, 1999. **47**(8): p. 948-53.
88. Beers, M.H., *Explicit criteria for determining potentially inappropriate medication use by the elderly. An update.* Arch Intern Med, 1997. **157**(14): p. 1531-6.
89. Spinewine, A., et al., *Appropriate prescribing in elderly people: how well can it be measured and optimised?* Lancet, 2007. **370**(9582): p. 173-84.

90. Gallagher, P. and D. O'Mahony, *STOPP (Screening Tool of Older Persons' potentially inappropriate Prescriptions): application to acutely ill elderly patients and comparison with Beers' criteria.* Age Ageing, 2008. **37**(6): p. 673-9.
91. Elliott, R.A. and P. Stehlik, *Identifying Inappropriate Prescribing for Older People.* J Pharm Pract Res, 2013. **43**(4): p. 312-19.
92. Fialova, D., et al., *Potentially inappropriate medication use among elderly home care patients in Europe.* JAMA, 2005. **293**(11): p. 1348-58.
93. Chutka, D.S., et al., *Symposium on geriatrics--Part I: Drug prescribing for elderly patients.* Mayo Clin Proc, 1995. **70**(7): p. 685-93.
94. Liu, G.G. and D.B. Christensen, *The continuing challenge of inappropriate prescribing in the elderly: an update of the evidence.* J Am Pharm Assoc (Wash), 2002. **42**(6): p. 847-57.
95. O'Mahony, D. and P.F. Gallagher, *Inappropriate prescribing in the older population: need for new criteria.* Age Ageing, 2008. **37**(2): p. 138-41.
96. Lau, D.T., et al., *Medicare Part D and quality of prescription medication use in older adults.* Drugs Aging, 2011. **28**(10): p. 797-807.
97. Parsons, C., et al., *Withholding, discontinuing and withdrawing medications in dementia patients at the end of life: a neglected problem in the disadvantaged dying?* Drugs Aging, 2010. **27**(6): p. 435-49.
98. Juurlink, D.N., et al., *Drug-drug interactions among elderly patients hospitalized for drug toxicity.* JAMA, 2003. **289**(13): p. 1652-8.
99. Meyer, U.A., *Pharmacogenetics and adverse drug reactions.* Lancet, 2000. **356**(9242): p. 1667-71.
100. Sampson, E.L., et al., *A systematic review of the scientific evidence for the efficacy of a palliative care approach in advanced dementia.* Int Psychogeriatr, 2005. **17**(1): p. 31-40.
101. Fox, E., *Predominance of the curative model of medical care. A residual problem.* JAMA, 1997. **278**(9): p. 761-3.
102. Hogan, D.B., et al., *Diagnosis and treatment of dementia: 5. Nonpharmacologic and pharmacologic therapy for mild to moderate dementia.* CMAJ, 2008. **179**(10): p. 1019-26.
103. Teno, J.M., et al., *Validation of toolkit after-death bereaved family member interview.* J Pain Symptom Manage, 2001. **22**(3): p. 752-8.
104. Luchins, D.J. and P. Hanrahan, *What is appropriate health care for end-stage dementia?* J Am Geriatr Soc, 1993. **41**(1): p. 25-30.
105. Tjia, J., et al., *Daily medication use in nursing home residents with advanced dementia.* J Am Geriatr Soc, 2010. **58**(5): p. 880-8.
106. Brunet, N.M., et al., *Optimizing drug therapy in patients with advanced dementia:A patient-centered approch.* Eur Geriatr Med, 2014. **5**(1): p. 66-71.
107. Leung, J.G., S. Nelson, and M. Leloux, *Pharmacotherapy during the end of life: caring for the actively dying patient.* AACN Adv Crit Care, 2014. **25**(2): p. 79-88; quiz 89-90.
108. Parsons, C., et al., *Potentially inappropriate prescribing in older people with dementia in care homes: a retrospective analysis.* Drugs Aging, 2012. **29**(2): p. 143-55.
109. Mitchell, S.L., et al., *Advanced dementia research in the nursing home: the CASCADE study.* Alzheimer Dis Assoc Disord, 2006. **20**(3): p. 166-75.
110. Koller, K. and K. Rockwood, *Frailty in older adults: implications for end-of-life care.* Cleve Clin J Med, 2013. **80**(3): p. 168-74.
111. Hall, S., *Palliative care for older people:better practice*, in *World Health Organization. Regional office for Europe*. 2011, International Palliative Care Initiative: New York, NY, USA.
112. Maltoni, M., et al., *Palliative sedation in end-of-life care and survival: a systematic review.* J Clin Oncol, 2012. **30**(12): p. 1378-83.

113. Qaseem, A., et al., *Evidence-based interventions to improve the palliative care of pain, dyspnea, and depression at the end of life: a clinical practice guideline from the American College of Physicians.* Ann Intern Med, 2008. **148**(2): p. 141-6.
114. Fick, D.M., et al., *Updating the Beers criteria for potentially inappropriate medication use in older adults: results of a US consensus panel of experts.* Arch Intern Med, 2003. **163**(22): p. 2716-24.
115. Holmes, H.M., et al., *Reconsidering medication appropriateness for patients late in life.* Arch Intern Med, 2006. **166**(6): p. 605-9.
116. Schiff, G.D., et al., *Principles of conservative prescribing.* Arch Intern Med, 2011. **171**(16): p. 1433-40.
117. Frank, C., *Deprescribing: a new word to guide medication review.* CMAJ, 2014. **186**(6): p. 407-8.
118. Scott, I.A., et al., *Minimizing inappropriate medications in older populations: a 10-step conceptual framework.* Am J Med, 2012. **125**(6): p. 529-37 e4.
119. Steinman, M.A. and J.T. Hanlon, *Managing medications in clinically complex elders: "There's got to be a happy medium".* JAMA, 2010. **304**(14): p. 1592-601.
120. Hughes, C.M., *Medication non-adherence in the elderly: how big is the problem?* Drugs Aging, 2004. **21**(12): p. 793-811.
121. Shelton, P.S., M.A. Fritsch, and M.A. Scott, *Assessing medication appropriateness in the elderly: a review of available measures.* Drugs Aging, 2000. **16**(6): p. 437-50.
122. Elliott, R.A. and M.C. Woodward, *Assessment of risk associated with medication related problems in elderly outpatients.* J Pharm Pract Res, 2009. **39**(2): p. 109-13.
123. Hanlon, J.T., et al., *A method for assessing drug therapy appropriateness.* J Clin Epidemiol, 1992. **45**(10): p. 1045-51.
124. Elliott, R.A. and J.L. Marriott, *Standardised assessment of patients' capacity to manage medications: a systematic review of published instruments.* BMC Geriatr, 2009. **9**: p. 27.
125. Fitch, K., et al., *The RAND/UCLA Appropriateness Method User's Manual*. 2001, RAND: Santa Monica, CA.
126. Day, J. and M. Bobeva, *A generic toolkit for the successful management of Delphi studies*, in *EJBRM*. 2005, Business School, Institute of Business and Law: Bournemouth University, UK p. 103-116.
127. Beers, M.H., et al., *Explicit criteria for determining inappropriate medication use in nursing home residents. UCLA Division of Geriatric Medicine.* Arch Intern Med, 1991. **151**(9): p. 1825-32.
128. McLeod, P.J., R.H. Allen, and R.N. Tamblyn, *Defining inappropriate practices in prescribing for elderly people: a national consensus panel.* CMAJ, 1997. **157**(3): p. 385-91.
129. American Geriatrics Society Beers Criteria Update Expert, P., *American Geriatrics Society updated Beers Criteria for potentially inappropriate medication use in older adults.* J Am Geriatr Soc, 2012. **60**(4): p. 616-31.
130. Resnick, B. and J.T. Pacala, *2012 Beers Criteria.* J Am Geriatr Soc, 2012. **60**(4): p. 612-3.
131. Rancourt, C., et al., *Potentially inappropriate prescriptions for older patients in long-term care.* BMC Geriatr, 2004. **4**: p. 9.
132. O'Mahony, D., et al., *STOPP & START criteria:A new approach to detecting potentially inappropriate prescribing in old age.* 2010. **1**(1): p. 45-51.
133. Rognstad, S., et al., *The Norwegian General Practice (NORGEP) criteria for assessing potentially inappropriate prescriptions to elderly patients. A modified Delphi study.* Scand J Prim Health Care, 2009. **27**(3): p. 153-9.
134. Lau, D.T., et al., *Hospitalization and death associated with potentially inappropriate medication prescriptions among elderly nursing home residents.* Arch Intern Med, 2005. **165**(1): p. 68-74.
135. Zuckerman, I.H., et al., *Potentially inappropriate prescribing before and after nursing home admission among patients with and without dementia.* Am J Geriatr Pharmacother, 2005. **3**(4): p. 246-54.

136. Fick, D.M., et al., *Health outcomes associated with potentially inappropriate medication use in older adults.* Res Nurs Health, 2008. **31**(1): p. 42-51.
137. Gorzoni, M.L., R.M. Fabbri, and S.L. Pires, *[Beer-Fick criteria and generic drugs in Brazil]*. Rev Assoc Med Bras, 2008. **54**(4): p. 353-6.
138. Onder, G., et al., *Impact of inappropriate drug use among hospitalized older adults.* Eur J Clin Pharmacol, 2005. **61**(5-6): p. 453-9.
139. Zhan, C., et al., *Potentially inappropriate medication use in the community-dwelling elderly: findings from the 1996 Medical Expenditure Panel Survey.* JAMA, 2001. **286**(22): p. 2823-9.
140. Naugler, C.T., et al., *Development and validation of an improving prescribing in the elderly tool.* Can J Clin Pharmacol, 2000. **7**(2): p. 103-7.
141. Kroger, E., et al., *Medication Use Among Nursing Home Residents With Severe Dementia: Identifying Categories of Appropriateness and Elements of a Successful Intervention.* J Am Med Dir Assoc, 2015. **16**(7): p. 629 e1-17.
142. Holmes, H.M., *Rational prescribing for patients with a reduced life expectancy.* Clin Pharmacol Ther, 2009. **85**(1): p. 103-7.
143. Schmader, K.E., et al., *Effects of geriatric evaluation and management on adverse drug reactions and suboptimal prescribing in the frail elderly.* Am J Med, 2004. **116**(6): p. 394-401.
144. Fahlman, C., et al., *Potentially inappropriate medication use by Medicaid+Choice beneficiaries in the last year of life.* J Palliat Med, 2007. **10**(3): p. 686-95.
145. Carey, I.M., et al., *What factors predict potentially inappropriate primary care prescribing in older people?Analysis of UK primary care patient record database.* Drug Aging, 2008. **25**(8): p. 693-706.
146. Stafford, L., et al., *Drug-related problems identified in post-discharge medication reviews for patients taking warfarin.* Int J Clin Pharm, 2011. **33**(4): p. 621-6.
147. Fick, D.M., et al., *Potentially inappropriate medication use in a Medicare managed care population: association with higher cost and utilization.* J Managed Care Pharm, 2001. **7**(5): p. 407-413.
148. Lang, P.O., et al., *Potentially inappropriate prescribing including under-use amongst older patients with cognitive or psychiatric co-morbidities.* Age Ageing, 2010. **39**(3): p. 373-81.
149. Niwata, S., Y. Yamada, and N. Ikegami, *Prevalence of inappropriate medication using Beers criteria in Japanese long-term care facilities.* BMC Geriatr, 2006. **6**: p. 1.
150. Dhalla, I.A., et al., *Inappropriate prescribing before and after nursing home admission.* J Am Geriatr Soc, 2002. **50**(6): p. 995-1000.
151. Reich, O., et al., *Potentially inappropriate medication use in older patients in Swiss managed care plans: prevalence, determinants and association with hospitalization.* PLoS One, 2014. **9**(8): p. e105425.
152. Onder, G., et al., *Adverse drug reactions and cognitive function among hospitalized older adults.* Eur J Clin Pharmacol, 2002. **58**(5): p. 371-7.
153. Giron, M.S., et al., *Psychotropic drug use in elderly people with and without dementia.* Int J Geriatr Psychiatry, 2001. **16**(9): p. 900-6.
154. Pitkala, K.H., T.E. Strandberg, and R.S. Tilvis, *Inappropriate drug prescribing in home-dwelling, elderly patients: a population-based survey.* Arch Intern Med, 2002. **162**(15): p. 1707-12.
155. Van der Hooft, C.S., et al., *Inappropriate drug prescribing in older adults: the updated 2002 Beers criteria--a population-based cohort study.* Br J Clin Pharmacol, 2005. **60**(2): p. 137-44.
156. Weschules, D.J., T.L. Maxwell, and J.W. Shega, *Acetylcholinesterase inhibitor and N-methyl-D-aspartic acid receptor antagonist use among hospice enrollees with a primary diagnosis of dementia.* J Palliat Med, 2008. **11**(5): p. 738-45.
157. Chan, V.T., et al., *Reduction of suboptimal prescribing and clinical outcome for dementia patients in a senior behavioral health inpatient unit.* Int Psychogeriatr, 2009. **21**(1): p. 195-9.

158. Nygaard, H.A., et al., *Nursing-home residents and their drug use: a comparison between mentally intact and mentally impaired residents. The Bergen district nursing home (BEDNURS) study.* Eur J Clin Pharmacol, 2003. **59**(5-6): p. 463-9.
159. Stegemann, S., et al., *Geriatric drug therapy: neglecting the inevitable majority.* Ageing Res Rev, 2010. **9**(4): p. 384-98.
160. Arcand, M. and R. Verreault, *Améliorer les soins de fin de vie en démence avancée.* Ger Psychol Neuropsychiatr Vieil, 2014. **12(supplément 1)**: p. 37.
161. Reisberg, B., *Functional assessment staging (FAST).* Psychopharmacol Bull, 1988. **24**(4): p. 653-9.
162. Garfinkel, D., S. Zur-Gil, and J. Ben-Israel, *The war against polypharmacy: a new cost-effective geriatric-palliative approach for improving drug therapy in disabled elderly people.* Isr Med Assoc J, 2007. **9**(6): p. 430-4.
163. Garfinkel, D. and D. Mangin, *Feasibility study of a systematic approach for discontinuation of multiple medications in older adults: addressing polypharmacy.* Arch Intern Med, 2010. **170**(18): p. 1648-54.
164. Tjia, J., et al., *Use of medications of questionable benefit in advanced dementia.* JAMDA, 2014. **174**(12): p. 1763-71.
165. Parsons, C., B.A. Briesacher, and J.L. Givens, *Cholinestrase inhibitor and memantine use in newly admitted nursing home residents with dementia.* J Am Geriatr Soc, 2011. **59**(7): p. 1253-9.
166. Seitz, D.P., A. Gruneir, and D.K. Conn, *Cholinesterase inhibitor use in US nursing homes:results from the National Nursing Home Survey.* J Am Geriatr Soc, 2009. **57**(12): p. 2269-74.
167. Gruber-Baldini, A.L., et al., *Treatment of dementia in community-dwelling and institutionalized medicare beneficiaries.* J Am Geriatr Soc, 2007. **55**(10): p. 1508-16.
168. Fossey, J., C. Ballard, and E. Juszczak, *Effect of enhanced psychosocial care on antipsychotic use in nursing home residents with severe dementia:cluster randomised trial.* Br Med J, 2006. **332**: p. 756-61.
169. Meador, K.G., J.A. Taylor, and P.B. Thapa, *Predictors of antipychotic withdrawal or dose reduction in a randomised controlled trial of provider education.* J Am Geriatr Soc, 1997. **45**(2): p. 207-10.
170. Avorn , J., S.B. Soumerai, and D.E. Everitt, *A randomized trial of a program to reduce the use of psychoactive drugs in nursing home.* N Eng J Med, 1992. **327**(3): p. 168-73.
171. Ray, W.A., J.A. Tylor, and K.G. Meador, *Reducing antipsychotic drug use in nursing homes: A controlled trial of provider education.* Arch Intern Med, 1993. **153**(6): p. 713-21.