USE OF DRUGS WITH ANTICHOLINERGIC PROPERTIES AND FACTORS AFFECTING COGNITION IN PATIENTS WITH MILD DEMENTIA

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PREFACE

This thesis is made as a completion of the master education in Health Science at University of Stavanger. Writing this thesis has been hard and challenging, but I have learned a lot in the process. Many people have contributed in this thesis and helped me in several ways, and I would like to take this opportunity to express my gratitude.

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I am grateful to my loving parents, family and friends, who put up with me and support me all along the way.

Finally, I would like to dedicate this thesis to my dear husband, Teddy, for his unfailing support, love and continuously belief in me. This thesis would not have been possible without his help. He is always there for me, and keeps me motivated if I ever feel down. As always, to my very wonderful children, Stefan and Konrad, who have shown great understanding during this work, and give me so much joy, love, support and terrific times. Thank you for being such huge blessings in my life.

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LIST OF ABBREVIATIONS

CDR : Clinical Dementia Rating

MMSE : Mini-Mental State Examination

ADE : Adverse Drug Event

START : Screening Tool to Alert doctors to the Right Treatment

STOPP : Screening Tool of Older Persons' potentially inappropriate Prescriptions

DLB : Dementia with Lewy-bodies

PDD : Parkinson's Disease Dementia

LBD : Lewy Body Dementia

AD : Alzheimer's Dementia

CIRS : Cumulative Illness Rating Scale

BBB : Blood-brain barrier

Abstract

Background: Elderly people, particularly those with dementia, are at high risk of adverse anticholinergic drug effects. Despite the well-recognized potential for cognitive decline with anticholinergic agents, their use continues even among patients with dementia. *Objectives:* to estimate the prevalence of drugs with anticholinergic drug effects and its impact on cognitive decline over time in home-dwelling people with dementia in Norway. *Methods:* Referrals to five outpatient clinics in geriatric medicine, old age psychiatry and neurology in Western Norway during 2005-2013 were included. Cognitive decline was assessed for up to 5 years using Clinical Dementia Rating (CDR) and Mini-Mental State Examination (MMSE). Cox regression was applied to model the cognitive decline. *Results:* Nearly 60% patients received at least one drug with anticholinergic property whereas almost 12% were taking drugs with well-known anticholinergic activity. However, the findings did not support the hypothesis that use of drugs with anticholinergic properties increases the risk of worsening cognitive decline among home-dwelling people with dementia. Moreover, the study showed that patients with Lewy body dementia and lower cognition at baseline predicted faster cognitive decline.

The thesis is part of the Master Study in Health Sciences at University of Stavanger, Norway. The thesis is divided into two parts; the first part is supported by theoretical framework, and the second part is an article, which is to be sent for publication.

1. INTRODUCTION

1.1 Background

Improvements in health care in the past century have contributed to people living longer and healthier lives. As a result, there is an increase in the number of people with dementia. Cognitive impairment is one of the main health problems facing elderly people in the new era. Some studies suggest that delaying the deterioration of cognitive function in elderly for a few years would result in a significant improvement on physical and economical burden related to the condition (Derousen, 2002).

Dementia is a clinical syndrome characterized by an inevitable progressive cognitive decline, which affects memory, thinking, behavior and ability to perform everyday activities. It represents a major public health challenge for many high-income countries and one of the major causes of disability and dependency among older people worldwide. (Prince et al., 2012; World Health Organization, 2012).

The World Health Organization has calculated that more than 47 million people worldwide are living with dementia in 2015 and that the number is expected to grow at an alarming rate. It is estimated that the number will increase to 76.5 million and rise to more than triple by 2050 (World Health Organization, 2016). In Norway, the number of people with dementia is approximately 78,000 in 2015, and by 2060 it is expected to triple. The risk of dementia increases with age and the incidence of dementia is estimated to be around 10,000 new people with dementia per year (Engedal & Haugen, 2009; Vossius et al., 2015).

Older people have often multiple chronic diseases, which frequently lead to polypharmacy and therefore increase the risk of inappropriate medications. Inappropriate medications are an important aspect of suboptimal prescribing in the elderly. Certain medications may exacerbate the progression of

dementia, and can make treating dementia even more challenging (Bunn et al., 2014; Schubert et al., 2006). Age-related changes in pharmacokinetics and pharmacodynamics, together with comorbidity and polypharmacy, increase risk for adverse drug reactions in dementia patients, which sequentially are cause of significant health challenges and costs (Corsonello, Pedone, & Incalzi, 2010).

Anticholinergic drugs are used therapeutically to treat medical conditions such as urinary incontinence, irritable bowel syndrome, diarrhea, seasonal allergies and Parkinson's disease (Feinberg, 1993; Gray et al., 2015). Peripheral adverse effects include dry mouth, dry eyes, constipation, blurred vision, pupil dilatation, and increased heart rate. Central side effects include impaired concentration, confusion, hallucinations, delirium, memory impairment and falls (Bell et al., 2012; Gerretsen P, 2011; Ness, Hoth, Barnett, Shorr, & Kaboli, 2006).

Although drugs with anticholinergic effects are considered as potentially inappropriate medications, anticholinergic medications are frequently prescribed to older adults for diverse conditions (Beuscart, Dupont, Defebvre, & Puisieux, 2014; Sura, Carnahan, Chen, & Aparasu, 2013). The prevalence of anticholinergic drug use in older people varies enormously. Previous studies have reported that 40-60% of patients with dementia used at least one anticholinergic medication and that 10-20% used drugs with clinically significant anticholinergic effects (Bhattacharya R., 2011; Sura et al., 2013). The prevalence is even higher in nursing home (Chatterjee, Mehta, Sherer, & Aparasu, 2010; Sura et al., 2013). These utilization rates are concerning because patients with dementia are more sensitive to anticholinergic effect due to impaired cholinergic neurotransmission and an associated decrease in cognitive function (Bell et al., 2012; Carriere et al., 2009; Sura et al., 2013).

As anticholinergic drugs are widely used, patients may be subjected to a high anticholinergic load. High anticholinergic drug load have been suggested to result in adverse events such as cognitive impairment and delirium (Bell et al.,

2012; Gray et al., 2015; Mate et al., 2015), hospitalizations (Kalisch Ellett, Pratt, Ramsay, Barratt, & Roughead, 2014) and mortality (Fox et al., 2011). These adverse events can have consequences for daily functioning, quality of life, caregiver burden and health-related costs. Although health professionals are well aware of the potential adverse effects of drugs with marked anticholinergic activity, most did not consider the cumulative anticholinergic load when prescribing for the elderly (Bell et al., 2012; Tune, 2001).

Despite the potentially enormous public health implications, only few studies has evaluated the prevalence of anticholinergic use and its association with worsening cognitive decline over time in home-dwelling people with mild dementia in Norway. Such information is important for the management of people with dementia, as avoiding drugs that accelerate cognitive decline may improve the quality of life of these patients.

1.2 Previous Research

As the population is steadily growing older, comorbidity is frequently present. Consequently, many patients are exposed to polypharmacy, which is associated with frequent negative health outcomes caused by drug-related problems (Viktil, Blix, Moger, & Reikvam, 2007). The findings reported by Gandhi et al. (2003) found that adverse events related to drugs occur frequently in primary care, and many are preventable. Most of the preventable events were due to prescribing errors (an inappropriate choice of drugs, drug interaction, or drug allergy). In addition, the patients in their study had significantly higher number of medications. The most frequent type of adverse drug events and the most frequent preventable or ameliorable events were those related to the central nervous system, e.g. antidepressant (Gandhi et al., 2003).

It is well known that anticholinergic medications should be avoided in older adults due to increased sensitivity towards adverse effects. In spite of the recommendation, medications with anticholinergic properties are commonly used in the elderly, including patients with dementia. It has been reported

previously that 40-60% of dementia patients use at least one anticholinergic medication and the prevalence was even higher in nursing homes (Bhattacharya R., 2011; Chatterjee et al., 2010; Mate et al., 2015; Sura et al., 2013). Over one in ten patients with dementia received medications with high anticholinergic potency. Nevertheless, the largest use of anticholinergic medications (>60%) was made by low potency anticholinergic drugs (Chatterjee et al., 2010; Mate et al., 2015; Sura et al., 2013).

Numerous studies have observed an association between anticholinergic drug load and the risk of developing cognitive impairment, but their results are conflicting (Cai, Campbell, Khan, Callahan, & Boustani, 2013; Carriere et al., 2009; Ehrt, Broich, Larsen, Ballard, & Aarsland, 2010; Gray et al., 2015). A recent longitudinal study found that higher cumulative anticholinergic use was associated with an increased risk of dementia. However, this study focused only on high potency anticholinergic drugs based on pharmacologic properties, and the results may be specific to drugs that are commonly used in the USA (Gray et al., 2015).

A cohort study from France observed an association between anticholinergic drug use and an increased risk of developing dementia and cognitive decline. Discontinuing anticholinergic drug treatment was associated with reduced risk of developing dementia (Carriere et al., 2009). In line with other studies, Cai et al. (2013) found an association between anticholinergic load and the risk of developing cognitive impairment. Such an association required both high anticholinergic load and 2 to 3 months of continuous exposure to a high burden. However, such a high exposure of anticholinergic load did not increase the probability of dementia diagnosis (Cai et al., 2013). Detailed assessment of the anticholinergic drug load in these studies examined only the well-known anticholinergic effects, but did not include other drugs associated with such effects (Cai et al., 2013; Carriere et al., 2009; Gray et al., 2015).

A community-based cohort study from Norway found that drugs with anticholinergic properties affected the rate of cognitive decline in patients with

Parkinson's disease. However, this study has some limitations. There was a high attrition due to death because of the long test-retest interval, and some survival could not provide adequate scores on test such as Mini Mental State Examination (MMSE). Moreover, MMSE is not a very sensitive measure of cognitive impairment in Parkinson's disease (Ehrt et al., 2010).

To my knowledge, just few longitudinal studies have shown no significant association between anticholinergic drug use and cognitive impairment in dementia. Bottiggi et al. (2006) discovered no significant differences between anticholinergic drug users and the non-users, after adjusting for age and education. Yet the results did lead to an accelerated rate of decline in scanning, visuomotor tracking, and components of exclusive functioning. However, the authors themselves considered their results as being preliminary, because their study was a non-randomized prospective study with unequal groups. In addition, the study did not have access to determine the continuous exposure to anticholinergic drugs (Bottiggi et al., 2006).

Ancelin et al. (2006) found that anticholinergic drug intake was associated with a non-degenerative cognitive impairment but suggested that it was unlikely linked to an increased risk of dementia. The results may due to the small sample size and because most of the drug users were classified as mild cognitive impairment. (Ancelin et al., 2006).

In addition, evidences suggest that taking more anticholinergic medications is associated with greater risk of hospitalization for confusion or dementia (Kalisch Ellett et al., 2014) and increased mortality (Fox et al., 2011).

1.3 Objectives of the study

The aim of the study was to estimate the prevalence of anticholinergic drug use and its impact on cognitive decline over time in home-dwelling people with mild dementia in Norway.

1.4 Research Questions and Hypotheses

1.4.1. Main question

How is the use of drugs with anticholinergic properties and its impact on cognitive decline over time in home-dwelling patients with mild dementia in Western Norway?

1.4.2. Additional questions

1. What is the prevalence of anticholinergic drugs use in home-dwelling patients with mild dementia in Western Norway?
2. What are the association between use of drugs with anticholinergic properties and the decline of cognition among home-dwelling people with mild dementia?
3. Does use of anticholinergic drugs increase the risk of increased cognitive impairment?

1.4.3. Hypothesis

The hypothesis is that use of drugs with anticholinergic properties is associated with increased risk of worse cognitive decline among home-dwelling patients with mild dementia in Western Norway.

1.5. Limitations

As a consequence of the defined study objectives, the following limitations apply:

- The term and definitions presented in chapter 2 of this thesis are limited to what is considered necessary in order to analyze and discuss the selected adverse events. The selection is not intended to be completed.
- The thesis is limited to the impact of use of drugs with anticholinergic properties to cognitive decline in home-dwelling patients.

2. THEORETICAL PERSPECTIVES

This chapter provides relevant theoretical backgrounds of dementia, anticholinergic drugs and age-related changes in elderly. Thus, it presents concept of patient safety and relation between adverse drug events and inappropriate prescribing.

2.1. Dementia

Dementia is a clinical syndrome of acquired cognitive impairment produced by brain dysfunction and although dementia is more common in older adults, it is not a normal consequence of aging (Engedal & Haugen, 2009; Quinn, 2013). Dementia leads to impairment in short- and long term memory, associated with impairment in abstract thinking, impaired judgment, and other disturbances of higher cortical function, or personality changes. They will often have psychological changes as well, for example, become frustrated or irritable, depression, anxious, inappropriate behavior, paranoid, agitation and hallucinations. The disturbance is severe enough to interfere significantly with work or usual social activities or relationships with others (Engedal & Haugen, 2009; McKeel, Burns, Meuser, & Morris, 2007).

The most common causes of dementia are Alzheimer's disease, vascular dementia, dementia with Lewy bodies, and frontotemporal dementia (Engedal & Haugen, 2009; Quinn, 2013). Some neurological diseases, such as Parkinson disease and Huntington disease, can cause dementia because of their effects on brain tissue. Dementia may also cause by vitamin deficiencies, long-term alcohol abuse and AIDS. Although many form of dementias, such as vitamin deficiencies and drugs-related dementia are reversible, but most forms are irreversible (Engedal & Haugen, 2009).

2.2. Anticholinergic Drugs

Anticholinergics drugs are a class of drugs that binds to muscarinic receptors in the parasympathetic system and thereby blocking the action of the neurotransmitter acetylcholine in the brain. Acetylcholine plays an important role in cognition, such as short-term memory and learning. Acetylcholine-producing cells in the basal forebrain are damaged in the early stages of dementia, which may contribute to the memory impairment, which is an early symptom of the disease (Becker, 2012; Micheau & Marighetto, 2011).

Some anticholinergic drugs are used therapeutically to treat medical conditions such as urinary incontinence, irritable bowel syndrome, diarrhea, seasonal allergies and Parkinson's disease. Others, such as antihistamines, antidepressants and antipsychotics, have significant unintended anticholinergic effects that are not the primary therapeutic activity (Feinberg, 1993; Gray et al., 2015).

Anticholinergic adverse effects can cause both peripheral and central side effects. Peripheral adverse effects include dry mouth, dry eyes, constipation, blurred vision, pupil dilatation, and increased heart rate. These peripheral adverse effects can lead to a plethora of medical complications, such as respiratory problems to myocardial infarction. Central side effects include impaired concentration, confusion, hallucinations, delirium, memory impairment and falls (Bell et al., 2012; Gerretsen P, 2011; Ness et al., 2006). Hence, drugs with anticholinergic effects are often considered as potentially inappropriate medications (Beuscart et al., 2014; Sura et al., 2013). The adverse effects may be marginalized as temporary, minor side effects of a medication or a result of patient's preexisting condition. Eliminating or reducing the doses of medications known to have anticholinergic potencies, may sometimes improve the anticholinergic adverse effects (Lieberman, 2004).

2.3. Age-related pharmacokinetics and pharmacodynamics changes

A wide spectrum of changes occurs in the human body with age, which can affect how the body reacts to drugs. That is why drug therapy in elderly may produce different and unexpected responses, compared with younger patients (Greenblatt, Harmatz, & Shader, 1991; Hämmerlein, Derendorf, & Lowenthal, 1998).

Age-related changes in pharmacokinetics mainly affect distribution, metabolism and excretion of the drug and to a lesser extent the drug absorption. The changes are mainly due to the loss of functional capacity of several organs and the reduced efficacy of homeostatic mechanisms. Principally hepatic drug clearance of several drugs decreases with aging due to reduced blood flow and hepatocyte mass. Renal function also decreases with aging, mainly because of sclerotic changes in the glomeruli. Moreover, as a result of decreased muscle mass, older patients frequently have reduced glomerular filtration rate despite normal serum creatinine, and such an obscured renal insufficiency may impact significantly the clearance of hydrosoluble drugs (Corsonello et al., 2010).

Pharmacodynamics describes how the drugs affects the body and gives knowledge on how the drug and its receptor interact. Changed receptor density, the homeostatic regulation, as well as age, gender, genetics and diseases are all variables that can affect the pharmacodynamics. There is a general trend of greater pharmacodynamics sensitivity in the elderly; however, this is not universal, and these age-related changes must be investigated separately for each individual drug, or at least relatively homogeneous groups of drugs (Bowie & Slattum, 2007).

Changes in pharmacodynamics are well documented in the central nervous system (CNS). Furthermore, older people frequently show an exaggerated response to CNS-active drugs. This is in part due to an underlying age-related

decline in CNS function and in part due to increased sensitivity for some CNS-drugs such as benzodiazepines, anesthetics, and opioids because of altered neurotransmitters and receptors density (Corsonello et al., 2010).

As age increased, the permeability of the blood-brain barrier (BBB) may also increase. Alterations in BBB permeability leading to higher brain concentrations and may result in poor tolerability by aged persons. Therefore, drugs with anticholinergic effects normally not passing the BBB now may penetrate it. As a result, BBB disruption may contribute to an acute worsening of global cognitive functioning with decreased attention and tend to be more severe for a given dose of drugs (Zeevi, Pachter, McCullough, Wolfson, & Kuchel, 2010).

2.4. Patient Safety

2.4.1. Definition

World Health Organization (2015) defined patient safety as

> *Freedom from accidental injuries during the course of medical care; activities to avoid, prevent, or correct adverse outcomes, which may result from the delivery of health care.*
>
> *The identification, analysis and management of patient-related risks and incidents, in order to make patient care safer and minimize harm to patients*.

Adverse events are defined as an undesirable clinical outcome resulted from some aspect of diagnosis or therapy, not underlying disease process, that leads to disability, prolonged hospital stay or function decline (Aase, 2010, 2015; Brennan et al., 1991). Several studies revealed that adverse events were the most prevalent preventable harms.

> *Adverse drug event is any injury, large or small, occurring during the patient's drug therapy and resulting either from appropriate care, or from*

unsuitable or suboptimal care. It includes the adverse drug reactions during normal use of the medicine, and any harm secondary to a medication error, both errors of omission or commission (Council of Europe, 2005).

There are two types of adverse drug events: those caused by errors and those that occur despite proper usage. Adverse drug reactions include all non-preventable adverse drug events that contribute to injury, but no error (Council of Europe, 2005).

2.4.2. Adverse Drug Events (ADEs)

As part of the Hippocratic Oath, *"Primum non nocere",* the Latin phrase that means "First, do no harm" is a basis for ethics taught in medical school. However, errors and adverse outcomes are still frequent in clinical practice in spite of increased attention to quality. To improve patient safety, preventing harms associated with the delivery of healthcare is a key component of overall quality of care (Nabhan et al., 2012). Several streams have been emerged to implement safe practices, to achieve a high level of safety in our health care organizations. One of the method is the need for monitoring, assessing, and improving physician performance (Leape & Fromson, 2006).

The Hallas criteria classify ADEs as preventable, probably preventable, probably not preventable or definitely not preventable. Preventable ADEs includes those arising from the prescription of potentially inappropriate medicines and suboptimal monitoring and dose adjustment that could have been entirely avoided. Non-preventable ADEs includes allergic or idiosyncratic reactions (Hallas et al., 1990).

Inappropriate prescribing includes the use of medicines where the risk of ADEs exceeds the expected clinical benefit in patients, especially where safer alternatives exist. Inappropriate prescribing also includes incorrect use of medicines (inappropriate dose or duration), prescription of medicines with clinically significant drug-drug or drug-disease interactions, and importantly,

the under-use of potentially beneficial medications (Hamilton, Gallagher, & O'Mahony, 2009).

Polypharmacy is the main risk factors of ADEs in older people. In practice, polypharmacy can be defined as "using more than a certain number of drugs, irrespective of the appropriateness of their use". All pharmaceutical agents have the potential for side effects; therefore, it is obvious that taking more than one drug increase the possibility to obtain more side effects (Masoodi, 2008). Another factor is the frailty of older people, means that older people take much longer time to recover than younger people (Vincent, 2010).

Inappropriate prescribing may be identified using lists of medications that are considered potentially inappropriate for older adults such as Beers' criteria. Beer's criteria consist of lists of medications to be avoided in elderly patients based on diagnosis, and do not address under-prescribing, drug-drug interactions or drug class duplication (Beers, 1997). In Europe, the STOPP (Screening Tool of Older Persons' potentially inappropriate Prescriptions) criteria were validated. STOPP criteria are uniquely designed for use alongside the START (Screening Tool to Alert doctors to the Right Treatment) criteria, which highlight under-prescription or omission of clinically indicated, evidence-based medications, thereby addressing more domains of prescribing appropriateness than Beers' criteria alone (Gallagher & O'Mahony, 2008). Both in Beer's and START-STOPP criteria, anticholinergic drugs are considered as potentially inappropriate medications and therefore should be avoided in elderly patients.

2.4.3. Models of Adverse Events

Person approach

The person approach focuses on errors from individual perspective. People are viewed as free agents that are responsible for causing error. To reduce error, efforts are targeted as individuals and involve advices "to do better", retraining, or adding new rules and procedures. Legal perspectives on error

and medical negligence are based on the concepts of personal responsibility, fault, blame and amends. Since this approach focuses on the individual that cause error, it isolates errors from their system context and ignores the circumstances and situations surrounding the errors. As a result, it may impede the pursuit of greater safety (Reason, 2000; Vincent, 2010).

System approach

The system approach focuses on fallibility as a part of the human condition and errors are to be expected, even in the best organizations. It concentrates on the conditions and underlying problems in the working environment and tries to build system defenses of barriers and safeguards to reduce errors. When an adverse event occurs, the focus is not on blaming the person who caused the error, but on how and why the defenses system failed (Reason, 2000; Vincent, 2010). High-reliability organizations, for instance aerospace, are the prime examples of the system approach. They have fewer accidents, recognize that human variability is the approach to prevent errors, but they work hard to focus on human variability and are preoccupied with the possibility of failure. They expect to make error and train their workforce to recognize and recover them (Reason, 2000).

2.4.4. Safety – II Approach

The publication of the Institute of Medicine (IOM) report To Err is Human in 2000 served as a catalyst for a growing interest in improving the safety of health care. Most people think of safety as the absence of accidents and incidents (or as an acceptable level of risk). Healthcare system consists of highly complex sociotechnical systems and thus differs from other high-risk sectors. Therefore, existing safety management methods should be supplied with new approaches to prevent patient harm (Hudson, 2003; Reason, 2000).

In this perspective, Hollnagel, Wears, and Braithwaite (2015) developed an approach to improve safety management. Safety-II is concentrating on the positive 'things that go right' in daily operations. The principle is to anticipate

rather than experience hazards, and adapt to situations rather than respond to unwanted events. Variations in human performance are not only causes of errors. They also provide an ability to adjust the activities. A Safety-II view requires some new practices as following, to look for what goes right, to focus on frequent events, to remain sensitive to the possibility of failure, to be thorough as well as efficient and to consider investing in safety as an investment in productivity (Hollnagel et al., 2015).

The illustration is adapted from World Health Organization's research cycle. It describes a process of identifying error to reduce or avoid unwanted events (fig. 1)

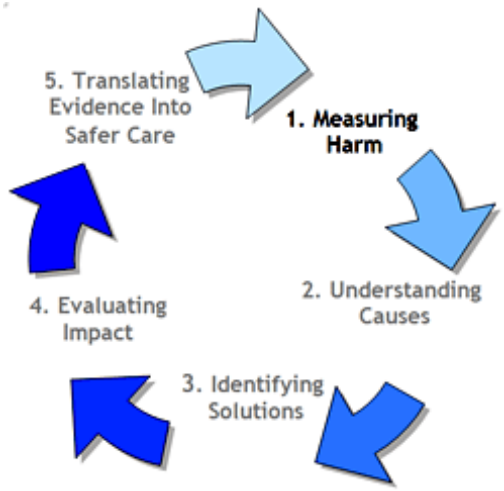


Figure 1. Based on the World Health Organization's research cycle (2015)

3. METHODS

This study used quantitative methods as research method. Quantitative research is particularly suited for:

- Finding answers to a research question that demands a quantitative answer.
- Explaining phenomena and testing of hypotheses.
- Determining how common a phenomenon is.
- Detecting associations between measured variables and make generalizations.

3.1. Research Design

This study was conducted as a longitudinal cohort study in home-dwelling patients with mild dementia in Western Norway. A longitudinal cohort study is a study where a group sharing common characteristics is followed over time to determine the proportion that develops an outcome. These will be classified as one group who are "exposed" and another group "not exposed" to possible risk factors (Cook, Netuveli, & Sheikh, 2003).

3.2. Data Collection

In the Dementia Study of Western Norway (DemVest study), all referrals to five outpatient clinics in geriatric medicine and old age psychiatry with a first time diagnosis of mild dementia (MMSE ≥20), in Rogaland counties (Stavanger and Haugesund) and Hordaland (Bergen) were included. In addition, the three neurology clinics in the region were invited to refer patients with suspected dementia to one of the participating centers. The main inclusion period was from March 2005 to March 2007. After this, only patients with dementia with Lewy bodies (DLB) or Parkinson's disease dementia (PDD) were included until 2013.

A research clinician performed a structured clinical interview of patients and caregivers regarding demographics, previous diseases and drug history. The comprehensive assessment procedure included a detailed disease history, clinical examination including physical, neurological, psychiatric and neuropsychological examinations, and routine blood tests.

After a comprehensive baseline assessment, patients were followed longitudinally and reassessed annually for 5 years. During the clinical follow-up, the diagnosis was reevaluated and the final diagnosis was made as a consensus between two experienced clinical dementia researchers in geriatric psychiatry. In total there were 266 patients having dementia in inclusion, but 12 patients were excluded because the MMSE score was too low, leaving 254 patients for this study. Everyone lived at home with their spouse or other caregivers at the time of inclusion. Of these, 28 patients died before first follow-up, but there were no dropouts for other reasons.

3.3. Inclusion Criteria

All patients diagnosed with mild dementia for the first time, i.e. having a Mini Mental State Examination (MMSE) score of at least 20 (Folstein, Folstein, & McHugh, 1975), and living at home with their spouse or other caregivers were included.

3.4. Exclusion Criteria

Patients were excluded if they did not have a dementia diagnosis or had acute delirium or confusion, had a terminal illness or recently were diagnosed with a major somatic illness or if they had bipolar disorder or other psychotic disorders.

3.5. Assessments

3.5.1. Dementia Diagnosis

The diagnosis of dementia was made according to the Diagnosis and Statistical Manual for Mental Disorders, 4th edition (DSM-IV), and classification of dementia according to consensus criteria (Emre et al., 2007; McKeith et al., 2005; McKhann et al., 1984). The diagnosis of Alzheimer's dementia was made according to The National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's disease and Related Disorders Association (McKhann et al., 1984). The diagnosis of dementia with Lewy body was made according to the revised consensus criteria (McKeith et al., 2005), and Parkinson's disease with dementia according to the recommendation from the Movement Disorder Society Task Force (Emre et al., 2007). The determination of diagnosis of other forms of dementia has been described in details in another study (Aarsland et al., 2008). The diagnostic criteria were independently applied by two of the authors in a previous cohort study. In case of disagreement, the final ascertainment was made based on consensus.

Since DLB and PDD share clinical and pathological features (Tsuboi & Dickson, 2005), they were combined and will from now collectively be referred to as the Lewy body dementia (LBD) group in this study. Vascular dementia, frontotemporal dementia and alcoholic dementia were grouped together and are referred to as other forms of dementia, due to small sample size.

3.5.2. Clinical Assessment

The clinical assessment was performed at each follow-up. Cognition was assessed with the Mini-Mental State Examination (MMSE) (Folstein et al., 1975) and Clinical Dementia Rating (CDR) (Berg, 1988). A trained research nurse scored the MMSE and the CDR was scored by a trained research physician. The scoring was made independent of the other cognitive tests, by the same clinician at every occasion to the extent possible.

The MMSE is the most commonly used cognitive screening test in primary level of care. The MMSE consist of several cognitive functions area, such as orientation, registration, recall, attention and calculation, language and complex commands. The results are summarized into a score that ranges from 30 (best) to 0 (worst), spanning the spectrum from normal cognition to severe dementia. A score of 24 or lower is indicative of cognitive impairment (Wyller, 2011).

A study by Perneczky et al. (2006) found that MMSE scores of 29-26, 25-21, 20-11, and 10-0 matched the CDR scores of 0.5, 1, 2 and 3, as questionable dementia, mild dementia, moderate and severe dementia, respectively. Therefore, in this study, the stage of severe dementia is defined as MMSE scores of 10 or lower and CDR score equal to 3.

CDR was used to assess severity of dementia staging by evaluating the degree of impairment in six domains of functioning at baseline and follow-up assessment. The CDR, first published in 1982, rated the patient's impairment in six domains (memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care). Subsequently, an algorithm is used to integrate the six domain scores into a global score. The CDR global scores are: 0 (no dementia), 0.5 (questionable dementia), 1 (mild dementia), 2 (moderate dementia), and 3 (severe dementia). The CDR has become an international standard for the staging of dementia with high validity and reliability (Perneczky et al., 2006).

Cumulative Illness Rating Scale (CIRS) was used to describe the total burden of medical illness, which measures the severity of chronic disease (Linn, Linn, & Gurel, 1968). The total score on the CIRS ranges from 0 to 56; however, a score above 25–30 implies severe pathology in several systems (Hudon, Fortin, & Vanasse, 2005).

3.5.3. Measurement of Anticholinergic Potency and Anticholinergic Load

The anticholinergic activity of drugs used at baseline was estimated using the anticholinergic risk scale developed by Durán, Azermai, and Vander Stichele (2013). This scale is modulated by systematically reviewing existing anticholinergic risk scales. In this study, the scale was classified in three categorical score, 0 (no anticholinergic activity), 1 (low anticholinergic activity) and 3 (high anticholinergic activity) in accordance with Beuscart et al. (2014). For drugs that were not included in Durán's study or in case of discrepancies between score, anticholinergic activity were specified by authors (JJ and RO) using Martindale, the complete drug reference, which is considered a reputed reference source (Brayfield, 2014), to take the final decision about the anticholinergic activity of the drug.

Anticholinergic drug load was defined as the cumulative effect of taking one or more drugs with anticholinergic activities. The anticholinergic activity score from every agent used by each patient were summed up, and the sum score was defined as the total anticholinergic drug load. Moreover, the total score was categorized into total score 0 (no anticholinergic drug load), ≤ 2 (low anticholinergic drug load) and ≥ 3 (high anticholinergic drug load).

3.6. Statistical Analysis

Statistical analyses of the data were performed using SPSS Statistics version 21.0 from IBM. Independent sample t-test was used to compare means of continuous parametric variables. Mann-Whitney U test was used in cases with two nonparametric continuous variables. The χ^2-test was used to explore the relation between categorical variables.

The Kaplan-Meier survival analysis was used to estimate the median time to severe dementia and the log rank test was performed to compare median time to severe dementia with respect to diagnosis, number of medications, use of anti-dementia, baseline MMSE total score, CIRS total score and CDR global

score at baseline. To analyze time to severe dementia, defined by CDR=3 and MMSE 0-10 (Perneczky et al., 2006) and to explore potential predictors associated with severe dementia, a Cox regression analysis was conducted. The independent factors are age, gender, education, dementia diagnosis, number of drugs used at baseline, use of anti-dementia medication, baseline MMSE total score and CDR global score, comorbidity as measured by CIRS and total anticholinergic load. The dependent factors are use of anticholinergic drugs. The primary outcome variable is the rate of cognitive decline, that is, the MMSE and CDR scores. Subsequently, variables that were significant were included in a multivariable stepwise regression model with backward elimination (likelihood ratio).

The Cox proportional hazards model investigates the relationship of predictors and the time to event through the hazard function. It assumes that the predictors have a multiplicative effect on the hazard and that this effect is constant over time. The hazard ratios (HR), defined as the ratio of the predicted hazard function lower than two different values of a predictor variable. A hazard ratio greater than 1 means the event is more likely to occur, and a ratio less than one means an event is less likely to occur. A hazard ratio of 1 means the predictor has no effect on the hazard of the event. Also, due to the regression framework of the model, one can get hazard ratio estimates that are controlled for other covariates in the model such as age, sex, and race (George, Seals, & Aban, 2014).

Furthermore, log minus log probability plot was performed to check the proportionality of the hazards model and the curves was approximately parallel and did not intersect after time apart. Two-sided p-values lower than 0.05 was considered as statistically significant. Results are presented as means, stated with their standard deviation (±SD), median with interquartile range (IQR) or 95% confidence interval (CI).

3.5 Ethical Considerations

The study was approved by the Regional Committee for Medical and Health Research Ethics (REK) in Western Norway (Ref.nr: 2016/29/REK vest). Written informed consent was obtained from all subjects after the study procedures had been explained to them and caregivers.

4. RESULTS

4.1. Baseline Characteristics

A total 254 patients were included at baseline with an average age of 75.7 years (SD 7.6). The majority of the patients were diagnosed with Alzheimer disease (48.8%). The demographic and clinical baseline characteristics are summarized in table 1.

Tabel 1. Demographic and characteristic of the study population

	Total sample	Using Anticholinergic Drugs	
		Yes	No
Number of participant, n(%)	254 (100)	145 (57.1)	109 (42.9)
Age at baseline, years (means ± SD)[a]	75.7 ± 7.6	76.3 ± 7.7	74.9 ± 7.3
Female (n,%)[b]	147 (57.9)	85 (33.5)	62 (24.4)
Years of education[c]	9 (7-11)	9 (7-11)	9 (7-12)
Diagnosis (n,%)[d]			
Alzheimer dementia	124 (48.8)	64 (25.2)	60 (23.6)
Lewy Body Dementia	78 (30.7)	44 (17.3)	34 (13.4)
Other forms of dementia	52 (20.5)	37 (14.6)	15 (5.9)
MMSE score[e]	24 (22-26)	23 (22-25)	24 (22-26)
CDR score ≤ 1 (n,%)[f]	220 (92.8)	120 (54.5)	100 (45.5)
CIRS score[g]	6 (4-8)	6 (4-9)	5 (3-7)
Number of drugs[h]	4 (2-6)	5 (4-7)	3 (1-4)
Anti dementia medication (n,%)[i]	114 (44.9)	59 (23.2)	55 (21.7)

Values are median and interquartile range (IQR), except where otherwise indicated.
The groups using and not using anticholinergic drugs were compared using the independent samples t-test (age), Mann-Whitney test (education, MMSE, CIRS and number of drugs) and chi-square test (sex, CDR, diagnose and use of anti dementia medication).

MMSE: Mini-Mental State Examination, CDR: Clinical Dementia Rating, CIRS: Cumulative Illness Rating Scale

a) p = 0.149, independent t-test
b) p = 0.781, Chi-square test
c) missing data for 6 cases, p = 0.995, Mann-Whitney test
d) p = 0.057, Chi-square test
e) p = 0.016, Mann-Whitney test
f) missing data for 17 cases, p = 0.650, Chi-square test
g) missing data for 19 cases, p < 0.005, Mann-Whitney test
h) p < 0.005, Mann-Whitney test
i) p = 0.121, Chi-square test

4.2. Use of anticholinergic drugs

Drugs with anticholinergic activity were used by 145 patients (57.1%). Of these, 59 (51.8%) were taking at least one anticholinergic medication. Moreover, 114 patients (44.9%) were taking anti dementia medications at baseline. Patients who used drugs with anticholinergic activity also had more comorbidity and a significantly higher number of medications compared to nonusers ($p<0.005$) (table 1).

Drugs with low anticholinergic activity were used by 138 patients (54.3%), whereby 53 patients (38.4%) of these took two or more anticholinergic drugs. Drugs with high anticholinergic activity were used by 30 participants (11.8%) and two of them used two drugs with high anticholinergic activity. A total of 44 patients (30.3%) had high cumulative anticholinergic load (total score of anticholinergic activities ≥ 3).

The most common drugs with low anticholinergic activity taken overall among the elderly dementia patients were escitalopram (19%), followed by oxazepam (14%). Among drugs with high anticholinergic activity, tolterodine (23%) and ipratropium (3%) were most frequently used.

The mean of total anticholinergic drug load was 1.23 ± 1.60 (range 0-8). Our findings revealed that higher total scores of anticholinergic load were due to the summative effect of multiple low potency anticholinergic medications (up to six medications), rather than a single drug with high anticholinergic properties.

Follow-up data on cognition were available for 226 patients (96 males and 130 females) of whom 115 (50.9%) had AD, 66 (29.2%) had LBD and 45 (19.9%) had other form of dementia diagnosis. Of these, 129 patients (57.1%) and 107 (47.3%) were taking anticholinergic medication and anti-dementia medicines at baseline, respectively. Among these patients, 188 patients (83%) had low anticholinergic load and 38 (17%) with high anticholinergic load.

During the observational period 172 patients died, but there were no dropouts for other reasons. The time to severe dementia was significantly higher in AD (3.9 years) compare to LBD (3.2 years) and other forms of dementia (2.5 years). However, there was no significant difference in age, sex, education and use of anti dementia medicines ($p > 0.05$ for all comparisons).

4.3. Predictors of cognitive decline

The median time to severe dementia, defined as MMSE $\leq$ 10 and CDR = 3, was 1894 days and 1915 days in patients that use anticholinergic drugs, and 1863 days and 1933 days in nonusers, ($p=0.744$ and $p=0.652$), respectively. Multivariable Cox regression analysis was run to determine the effect of baseline covariates on time to worsening of cognitive decline and severe dementia.

Having a diagnosis of LBD or other forms of dementia and having a high CDR global score at baseline was associated with shorter time to MMSE score decline over time (table 2). These factors remained statistically significant predictors for the progression of MMSE decline even after adjusting for relevant confounders Conversely, having a high MMSE total score or a high CIRS total score at baseline decreased the risk for MMSE decline significantly (adjusted HR 0.9 and 0.83, $p<0.005$, respectively, table 2).

The study revealed no significant interactions with anticholinergic drugs use ($p=0.744$). Time to severe dementia (MMSE $\leq$10) was slightly more rapid for

those who used anticholinergic drugs in the early years, but remained almost the same after five years (figure 2).

Table 2. Factor associated with the rate of decline on MMSE

	Unadjusted HRs (95% CI)	p Value	Adjusted HRs (95% CI)	p Value
Age, years	0.98 (0.95 – 1.01)	0.333		
Sex, female	0.89 (0.57 – 1.42)	0.636		
Education, years	1.02 (0.95 – 1.11)	0.555		
Diagnosis				
LBD	1.74 (1.03 – 2.95)	0.005	1.97 (1.11 – 3.49)	0.025
Other dementia	0.45 (0.19 – 1.05)	0.005	0.64 (0.26 – 1.55)	0.025
No. of drugs	0.87 (0.79 – 0.97)	0.007	0.93 (0.81 – 1.06)	0.267
CDR-GS ≤ 1 at baseline	1.43 (0.89 – 2.27)	0.132	1.68 (1.03 – 2.74)	0.036
MMSE total scores	0.90 (0.82 – 0.99)	0.034	0.9 (0.82 – 0.99)	0.038
CIRS total scores	0.87 (0.78 – 0.96)	0.004	0.83 (0.75 – 0.93)	0.001
Antidementia drugs use	1.70 (1.07 – 2.72)	0.024	1.33 (0.8 – 2.20)	0.272
Anticholinergic medicines	0.93 (0.59 – 1.46)	0.744		
Total ACH load	0.94 (0.8 – 1.12)	0.490		

Cox regression, time until MMSE 0-10, HRs presented with 95% CI.
Abbreviations: HR: Hazard Ratio, CI: Confidence Interval, LBD: Lewy-body dementia, CDR-GS: Clinical Dementia Rating Global Scores, MMSE: Mini-Mental State Examination, CIRS: Cumulative Illness Rating Scale, ACH: anticholinergic drug

Factor associated with time to severe dementia (CDR-GS = 3) is shown in table 3. Having LBD and other forms of dementia (adjusted HR 2.14 and 0.5, p=0.003) and higher CDR-GS at baseline (adjusted HR 1.83, p=0.019) remained significant predictors of a time to reach severe dementia. Higher baseline MMSE and CIRS score was considered as protective factors to severe dementia (p<0.005). We also conducted multivariable Cox regression analysis including anti dementia drug use in the model, which predicted shorter time to MMSE decline and severe dementia, but it was not statistically significant.

Figure 2. Time to decline on MMSE score with use of anticholinergic drugs and nonusers

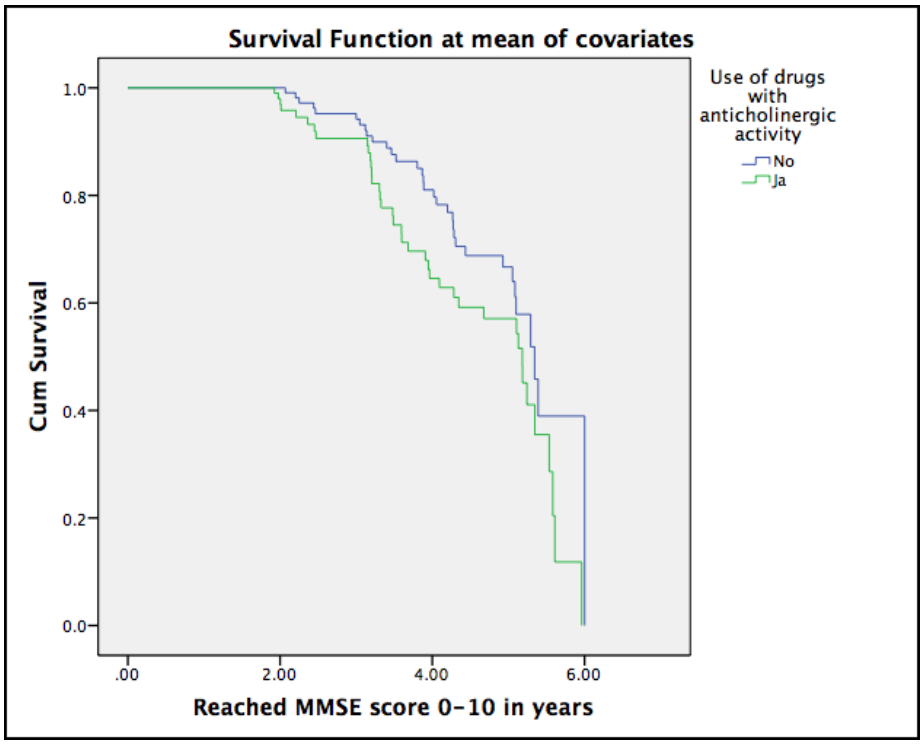


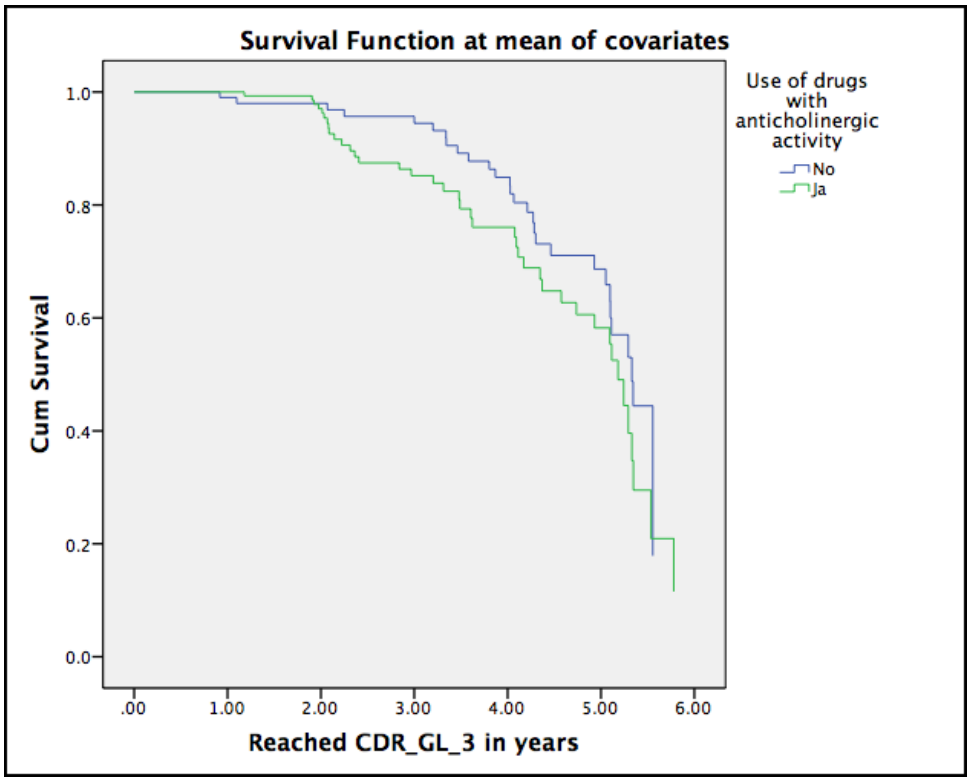
Table 3. Factor associated with time to reach severe dementia (CDR = 3)

	Unadjusted HRs (95% CI)	p Value	Adjusted HRs (95% CI)	p Value
Age, years	0.99 (0.96 – 1.02)	0.591		
Sex, female	1.01 (0.63 – 1.64)	0.959		
Education, years	1.04 (0.97 – 1.12)	0.319		
Diagnosis				
LBD	2.22 (1.31 – 3.77)	0.001	2.14 (1.21 – 3.78)	0.003
Other dementia	0.52 (0.22 – 1.23)	0.001	0.5 (0.21 – 1.2)	0.003
No. of drugs	0.96 (0.87 – 1.06)	0.405	1 (0.89 – 1.14)	0.968
CDR-GS ≤ 1 at baseline	1.75 (1.08 – 2.83)	0.021	1.83 (1.01 – 3.05)	0.019
MMSE total scores	0.84 (0.75 – 0.93)	0.001	0.84 (0.75 – 0.94)	0.002
CIRS total scores	0.96 (0.88 – 1.05)	0.379	0.91 (0.83 – 1)	0.040
Antidementia drugs use	1.33 (0.83 – 2.13)	0.232	1.45 (0.91 – 2.32)	0.121
Anticholinergic drugs	1.11 (0.7 – 1.78)	0.652		
Total ACH load	1.02 (0.87 – 1.2)	0.854		

Cox regression, time until CDR = 3. Abbreviations: HR: Hazard Ratio, LBD: Lewy-body dementia, CDR-GS: Clinical Dementia Rating Global Scores, MMSE: Mini-Mental State Examination, CIRS: Cumulative Illness Rating Scale, ACH: anticholinergic drug

Patients that use anticholinergic drugs had a shorter time to reach the severe dementia stage over time compared to nonusers, but they did not differ statistically significant (figure 3).

Figure 3. Observation time until severe dementia with anticholinergic drugs use and nonuser



Furthermore, log minus log probability plot was performed to check the proportionality of the hazards model (see figure 4 and figure 5 in attachments).

5. DISCUSSION

5.1. Main finding

The use of drugs with anticholinergic properties was common in these patients with dementia. Our longitudinal study found that 57% of home-dwelling elderly persons with dementia were taking drugs with anticholinergic activities, and nearly 12% were taking one or more anticholinergic medications with high activity. These findings are consistent with the reported prevalence in previous studies (Bhattacharya R., 2011; Mate et al., 2015; Sura et al., 2013).

Almost 40% patients in this current study were taking more than one (up to a value of six) anticholinergic medications with low activity. Our findings revealed that higher total scores of anticholinergic load were due to the summative effect of multiple low activity anticholinergic medications (up to six medications), rather than a single drug with high anticholinergic activities. The results are in line with previous research by Mate et al. (2015). This rate is concerning because previous studies reported that adverse drug events are often the result of cumulative anticholinergic drug load of multiple medications rather than of a single compound (Gerretsen & Pollock, 2013; Pasina et al., 2013; Tune, 2001).

A number of studies have reported that medicines with low anticholinergic activities, including nonprescription medicines, may contribute to older person's anticholinergic drug load and as consequent cause adverse events, such as negative cognitive effects. However, it was assumed to be reversible and transient (Ancelin et al., 2006; Boustani, 2008). Reducing the number and dose of medicines with anticholinergic potencies may decrease anticholinergic drug load (Bell et al., 2012). Hence, to diminish adverse effects on the dementia patients and those with cognitive impairment, clinicians should consider using alternative medications with no-to-minimal anticholinergic properties.

Participants that use drugs with anticholinergic properties had more often comorbid disease, lower MMSE at baseline and used more drugs than the non-users. Our findings support the recent studies that reported by Luukkanen et al. (2011) and Mate et al. (2015).

Patients with dementia often have additional multiple chronic diseases e.g. cardiovascular disease, requiring use of multiple drugs (Schubert et al., 2006). However, it is important to recognize that many drugs in daily long-term use have anticholinergic properties and that the use of these drugs cannot be fully avoided (Luukkanen et al., 2011).

The most frequently used drug classes with anticholinergic effects in our study were escitalopram (19%) and oxazepam (14%) for low anticholinergic activities. Escitalopram is an antidepressant of selective serotonin reuptake inhibitors class. Depressive symptoms have been reported in up to 40% of patients with Alzheimer disease, which is reflected in the high prevalence of antidepressant use in this population. However, a previous study found that the most frequently medication associated with ADEs is selective serotonin reuptake inhibitors (Gandhi et al., 2003). For that reason, use of antidepressant may be considered as inappropriate due to the increased risk of adverse events (Bell et al., 2012).

Tolterodine (23%) and ipratropium (2.8%) were the most common drugs with significant anticholinergic effects taken in the current study. Tolterodine is used for symptomatic treatment of urinary incontinence. These results are in line with a previous study which found that patients with dementia having urinary incontinence were more likely to use drugs with clinically significant anticholinergic potencies (Sura et al., 2013).

Urinary incontinence is often multifactorial in elderly patients with dementia and may be drug induced. Use of medicines with sedative properties (e.g. benzodiazepines and tricyclic antidepressants) and cholinesterase inhibitors (primarily used to treat the cognitive symptoms of dementia) have also been

associated with urinary incontinence. Anticholinergic medicines (e.g. tolterodine) are often not needed to treat urinary incontinence, especially if potential adverse events are taken into consideration (Bell et al., 2012). Tolterodine have associated with memory deficits and delirium, and therefore non-pharmacologic alternatives are preferred treatments to treat urinary incontinence in people with dementia (Edwards & O' Connor, 2002; Sura et al., 2013).

The study findings raise concern regarding inappropriate prescribing practices in dementia patients. Clinicians should consider the benefit-risk ratio of anticholinergic drugs and base their decision on individual patient characteristics and available evidence-based guidelines in order to avoid adverse events and enhance patient safety. This measure is in accordance with the concept of Safety-II (Hollnagel et al., 2015), which is to anticipate rather than experience hazards, and adapt to situations rather than respond to unwanted events.

Given the potential risk of anticholinergic drug use in elderly, a better understanding of the causes of frequent prescription is needed. Adverse drug-related events are frequent in primary care, and many are preventable or ameliorable. Ameliorable adverse drug events, which were much more common than preventable events, occurred when physicians failed to respond to medication-related symptoms and when patients failed to inform physicians about such symptoms. Therefore, improvements in monitoring for and responding to symptoms appear to be especially important for the prevention of adverse drug events in patients with dementia (Gandhi et al., 2003). This recurrent process of understanding causes and identifying solution on preventing unwanted outcome is in line with World Health Organization's adapted research cycle that is illustrated in figure 1. Moreover, avoiding drugs that accelerate cognitive decline in dementia patients may improve the quality of life of these patients.

5.2. Cognitive decline

In contrast to previous studies (Cai et al., 2013; Carriere et al., 2009; Ehrt et al., 2010; Gray et al., 2015), our results showed that use of anticholinergic drugs did not affect the prognosis of worsening cognitive decline over time in home-dwelling people with mild dementia. The results did not support our hypotheses, but the findings were somewhat similar to a longitudinal study by Bottiggi et al. (2006). Their study found that anticholinergic use did not lead an accelerated rate of global cognitive status decline.

The difference between our findings and previous results may be due to our focus on drugs with anticholinergic potencies in mild dementia patients. A recent study focused only on high potency anticholinergic drugs based on pharmacologic properties (Gray et al., 2015) and another study was based on anticholinergic drug lists, which is used for routine clinical practice (Carriere et al., 2009). Detailed assessment of the anticholinergic load in these studies included only the well-known anticholinergic effects, but did not include other drugs associated with such effects (Cai et al., 2013; Carriere et al., 2009; Gray et al., 2015). The only study that included other drugs with anticholinergic properties measured the cognitive decline in patients with Parkinson's disease (Ehrt et al., 2010). In addition, we did not take into account whether patients actually received the anticholinergic medications. Some medications could have been prescribed pro re nata and may never have been used.

In the adjusted model, our results showed that having LBD diagnosis and higher CDR-GS at baseline increased the time and risk to cognitive decline and severe dementia, whereas higher baseline MMSE score and higher baseline CIRS total score were associated with delayed cognitive decline. These findings are consistent with a previous study that patients with DLB have a more rapid cognitive decline than in AD (Rongve et al., 2016).

Possible explanations for these findings are severe parkinsonism, fluctuations in cognitive impairment, visual hallucinations and depression are more

common in LBD compared to AD. These symptoms may be treated with neuroleptic and antidepressant drugs, whereas having LBD increases the sensitivity to drug reactions, especially neuroleptic medication (McKeith, 2002). It is known that neuroleptic medicines and antidepressant have varying degrees of anticholinergic effects, which may explain the deterioration of cognitive decline in these patients. However, we did not find that patients with LBD used more anticholinergic drugs compared to AD. This could be due to lower number of cases with LBD compared to AD.

In the present study, use of anticholinergic drugs was not discontinued before initiating anti dementia medicines. Use of anti-dementia medicines predicted shorter time to MMSE decline and severe dementia in the unadjusted model, but was not significant after adjustment for various covariates. These effects may be because the anticholinergic action of drugs may reduce or eliminate the cognitive benefits of anti dementia medicines (Carnahan, Lund, Perry, & Chrischilles, 2004). Given that the aim of anti dementia medicines is to improve cognition, anticholinergic drugs could be in the absurd situation of receiving pro-cholinergic drugs to counteract the effects of anticholinergic agents (Ancelin et al., 2006). Therefore, it is important that clinicians review the anticholinergic load of their current medicine regiment before initiating anti dementia medicines, with the aim of minimizing or ceasing medicines with anticholinergic properties.

5.3. Interventions to improve patient safety in practice

Prescribing drugs with anticholinergic properties to dementia patients is generally considered inappropriate due to their adverse effects even though the current study failed to show an association between use of drugs with anticholinergic activities and cognitive decline in people with dementia. Inappropriate prescribing is included in preventable ADEs and preventing ADEs will improve patient safety and at the same time may enhance quality of life of patients.

As discussed previously, age-related changes on drug metabolism and polypharmacy make prescribing for older people are more challenging, and as a result, more vulnerable to ADEs (Masoodi, 2008; Vincent, 2010). In accordance to the principle of Safety-II and adapted research cycle model from WHO (2015), several strategies may be implemented to prevent and reduce ADEs in anticholinergic drugs to improve patient safety. These strategies can generally be categorized as person- or system based interventions, based on model adverse events as described previously. These interventions should be use together to optimally prevent ADEs.

Person approach

One of the method to implement safe practice is the need for improving physician performance (Leape & Fromson, 2006). Given that the risk of ADEs increases with number of medication taken, physicians should ideally review the medication list at each patient encounter. Physicians should know a patient's medical history before beginning a treatment to handle potential problems. Moreover, physicians should consider dose and adverse effects when prescribing anticholinergic medicine in elderly. Education about commonly prescribed anticholinergic drugs and increased monitoring for side effects could benefit physicians and patients (Gandhi et al., 2003).

Furthermore, reducing the number and dose of medicines with anticholinergic properties, particularly patients with dementia, can lead to fewer ADEs. Therefore, physicians should review the anticholinergic drug load of medicines before initiating other medicines. Moreover, physicians should consider that even medicines with minor anticholinergic activities might contribute to unwanted central and peripheral adverse events if used in combination with other agents with anticholinergic effects (Mate et al., 2015). Thus, attempts should be made to reduce inappropriate drug prescription by using available tools, such as Beer's criteria and START-STOPP criteria.

The risk of an ADE due to drug interactions is substantially higher when more medications are being prescribed. Physicians should consider drug-drug

interactions of anticholinergic drugs, i.e. before initiating cholinesterase inhibitors or memantine. As discussed previously, the addition of an anticholinergic drug such as tolterodine to patients that use cholinesterase inhibitors can be debilitating. Their opposing effect may result in diminish therapeutic effect (Bell et al., 2012).

To prevent ADEs, interactions may be determined using the drug interactions tool i.e. Lexi-Interact Online, etc. (Zhu & Weingart, 2015). Some institutions have also developed websites that provide information about drug interactions and make it possible for physicians to detect potential adverse effects caused by drug interactions. In addition, changing anticholinergic drugs with alternative medications without or minimal anticholinergic properties may reduce ADEs due to use of anticholinergic drugs.

Some anticholinergic drugs, such as cetirizine (Zyrtec), ranitidine (Zantac), loratadine (Clarytin) and loperamide (Imodium), are available as over-the-counter products. Therefore informing older adults about potentially modifiable risk would allow them to choose alternative products and collaborate with health care professionals to minimize overall anticholinergic use. Consequently, there is a strong need to increase awareness among health care professionals and older people about the potential anticholinergic medication-related risk.

System approach

Poorly designed systems trigger errors or make them difficult to detect and may cause medication errors and ADEs. A properly designed system focuses on creating efficient barriers in the working environment that will prevent errors in the future (Reason, 2000). It performs reliably because people are flexible and adaptive and human's performance variability is no longer seen as a threat. In line with the concept of Safety-II, in a good system, clinicians are able to adjust their work to conditions rather than because they work as imagined (Hollnagel et al., 2015).

Advanced systems of computerized medication ordering, such as those that check the dose of the drug, interactions with other drugs, and allergy to the drug, could have prevented 35% of preventable ADEs caused by illegible handwriting, inappropriate doses, drug interactions, and allergies (Gandhi et al., 2003). These systems may improve medication safety by providing standardization of practice, improving the completeness and legibility of prescriptions, alerting clinicians to drug allergies, drug-drug interactions, and cumulative dose-limits, updating clinicians with the most current medication information and providing dosage adjustment calculations based on clinical features such as weight or renal functions (Agrawal, 2009).

To reduce ADEs, use of electronic medical records to administer medications might be useful. Medication orders that are manually transcribed to a paper medication administration record and used by nurses to administer medications are prone to causing errors and ADEs. Using electronic medical records may help to prescribe appropriate medication and manage medication administration schedules and hence adopted by various medical group and hospital practices (Agrawal, 2009; Masoodi, 2008).

Likewise, pharmacist and clinicians should collaborate to improve pharmacotherapy. A study found that the use of an order-entry system for physicians, which sent electronic prescriptions to a pharmacy, decreased the time pharmacist spent recording prescription data and expanded the time they spent counseling patient (Tierney, 2003).

5.4. Strengths and Limitations of the Study

The strengths of current study included the use of the most recent clinical diagnosis of DLB and the specific and standardized clinical assessment program. Furthermore, the annual assessment was done by the same clinicians and continually updated, which increases the accuracy of diagnosis. Additionally, it is a rather homogeneous study sample with mild dementia at inclusion and low dropout rate. As described above, our study has taken into

consideration drugs with anticholinergic activities, whereas previous studies included only well-known anticholinergic effects. The scale was slightly modified by also including drugs that were not included previously, after independent assessment by the authors. A limitation with this method was that dosage and duration of treatment are not taken into account.

There are some limitations in our study. First, we used the anticholinergic drug scale adapted according to the recent study of Durán et al. (2013), which compared seven different scales. There was a big variation in the scales and the grades given to them. The distinction between low and high activity of anticholinergic drugs in the study might be considered as rather crude. However, that was the only way to achieve a consistent score from the various lists (Durán et al., 2013). Second, the use of drugs with anticholinergic properties was recorded only at baseline and possible changes in medications during the follow-up period were not taken into account, which might have influenced the finding. Since an association between cognitive impairment and drugs with anticholinergic properties has been discussed for many years, clinicians may also have reduced or discontinued anticholinergic therapy during the follow-up. Finally, we might have some interval-censored data that may have lead to a potential bias; therefore, another program will optimize data analysis. However, Cox regression is also adequate to evaluate the progression of cognitive decline in this study.

5.5. Future Research

Anticholinergic drugs are linked with many other poor outcomes in older people, including cognitive decline, constipation and an increased risk for falls. Although this current study did not confirm deleterious effects upon cognition, future research is needed to confirm these findings and to understand the underlying mechanisms. Longitudinal studies are required to determine the effects of increased and decreased anticholinergic load on cognitive function and other clinical outcomes for people with dementia. Furthermore, it would have been interested to investigate the true prevalence of adverse drug events

related to use of anticholinergic drugs among home-dwelling patients with dementia and what we can do to reduce their frequency, severity and consequences.

6. CONCLUSION

The study reported the prevalence of use of drugs with anticholinergic properties and its impact on cognitive decline over time in home-dwelling people with mild dementia. The study found that almost 60% home-dwelling patients with mild dementia stage used drugs with anticholinergic properties. Patients that used drugs with anticholinergic activities were likely having Alzheimer disease, lower baseline MMSE score, comorbidity, polypharmacy and taking anti-dementia medications at baseline. In line with previous studies, the major contributors to anticholinergic load were low level of anticholinergic potencies. The most frequently drugs with low anticholinergic properties that use in this population were escitalopram and oxazepam. Tolterodine and ipratropium were the most commonly used drugs with significant anticholinergic properties. The results showed that use of drugs with anticholinergic properties did not associate with cognitive decline among mild dementia patients. Although this study failed to show that use of drugs with anticholinergic properties increase risk to aggravate cognitive impairment in mild dementia patients, yet, prescribing drugs with anticholinergic properties to dementia patients is generally considered inappropriate due to their adverse effects.

Consequently, there is a strong need to improve the prescribing practices in the elderly, and particularly in those with dementia. To prevent ADEs, it is important to monitor, assess and improve physician's knowledge and performance in order to prevent inappropriate prescribing. These findings also have public health implications for the education of older people about potential safety risks because some anticholinergic are available as over-the-counter products. To prevent harm to patients, safety management should be supplied with new approaches.

This thesis emphasized the importance to consider how overall drug load may contribute adverse events. A reduction in anticholinergic drug load may result in improved short-term memory, confusion, behavior and delirium, together

with an enhanced quality of life and daily functioning of older people (Feinberg, 1993). Several strategies were suggested to improve prescribing practices and to reduce ADEs in anticholinergic drugs use in order to enhance patient safety. Future researches are needed to confirm these findings and to understand the underlying mechanisms.

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FIGURES

Figure 4. Log minus log plot on MMSE decline

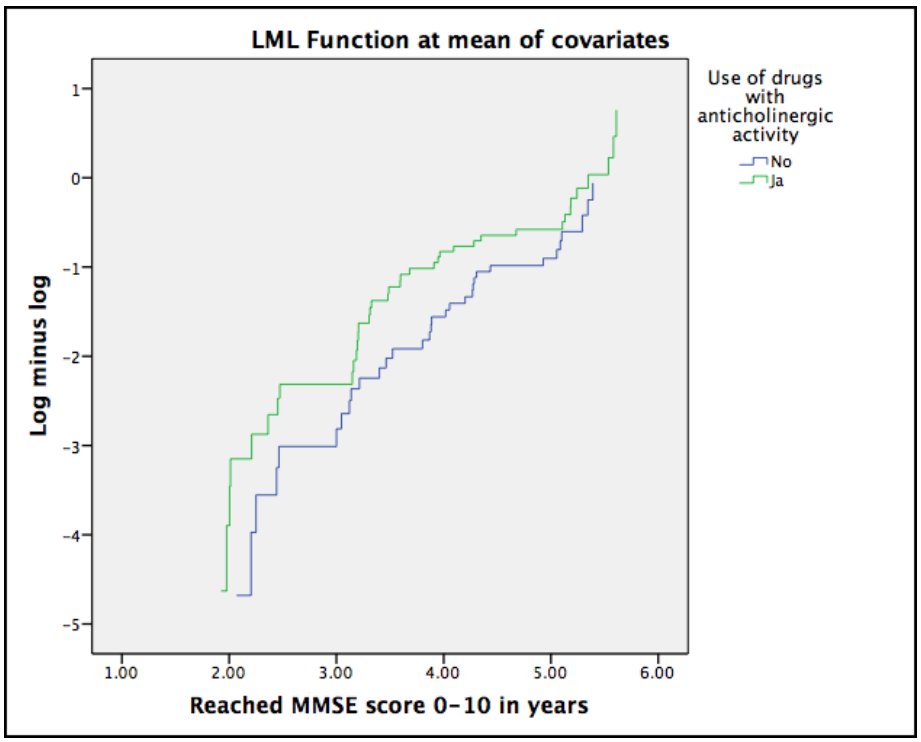


Figure 5. Log minus log plot on survival until severe dementia

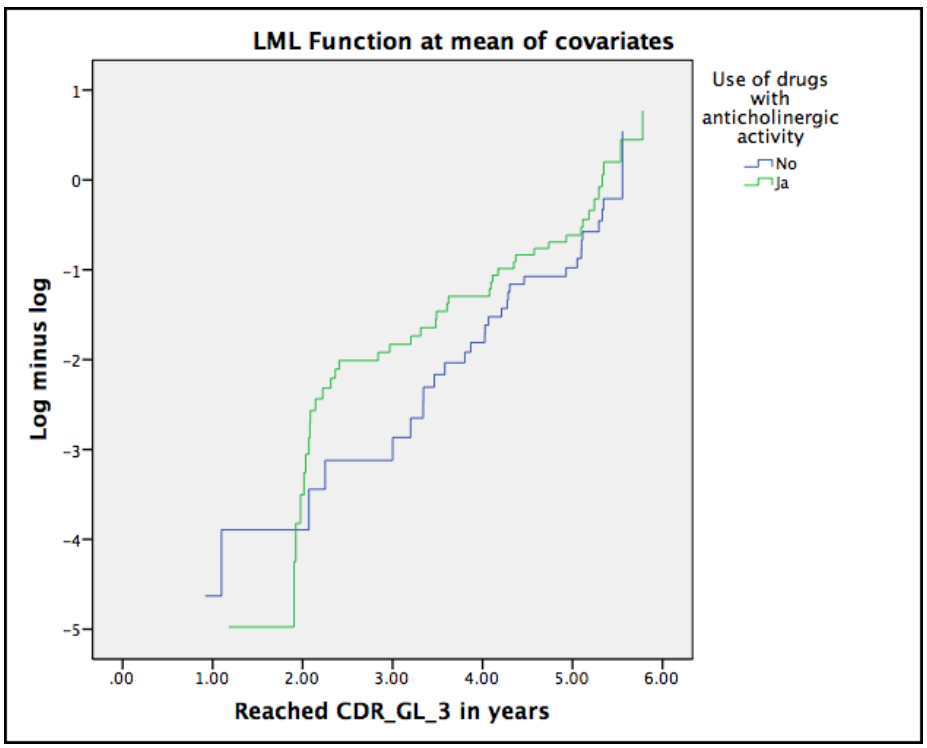


Figure 6. Time to decline on MMSE score

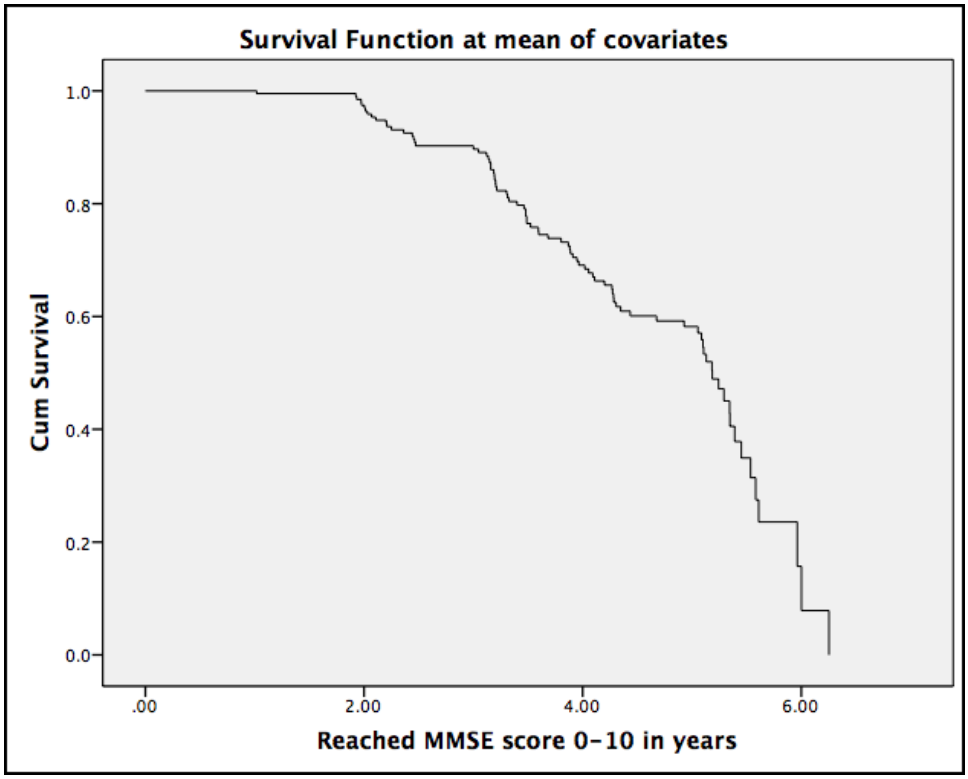
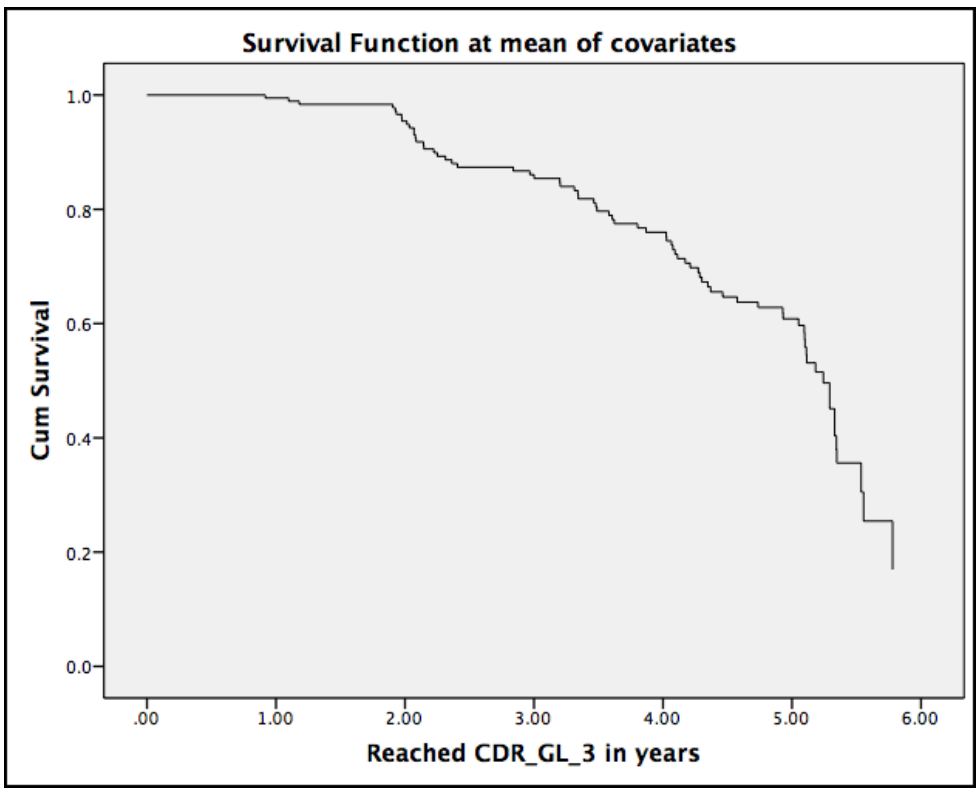


Figure 7. Time to severe dementia



Part 2

Article

Abstract

Background: From previous studies it is known that use of drugs with anticholinergic effects is not favorable, due to their association to adverse drug events such as worsening of cognitive impairment, especially in elderly patients. However, despite the well-recognized potential for cognitive decline, use of anticholinergic agents continues, even among patients with dementia.

Objectives: To estimate the prevalence of anticholinergic drug use and its impact on cognitive decline over time in home-dwelling people with mild dementia in Norway.

Methods: Referrals to five outpatient clinics in geriatric medicine, old age psychiatry and neurology in Western Norway during 2005-2013 were included. Standardized clinical measurements and diagnostic criteria were employed. Cognitive decline, using Clinical Dementia Rating (CDR) and Mini-Mental State Examination (MMSE), was assessed for up to 5 years. Cox regression analysis was used to analyze the decline on MMSE and CDR.

Results: One or more drugs with anticholinergic properties were used by 145 participants (57%). Of these, 30 participants (11.8%) were taking drugs with high anticholinergic potency. In multiple Cox regression analyses, Lewy body dementia (LBD) and a high CDR global score at baseline were associated with the increased progression of cognitive decline and severe dementia. However, there was no significant association between use of drugs with anticholinergic activities or anticholinergic drug load and impairment in cognitive outcome or severe dementia.

Conclusion: Use of drugs with anticholinergic drugs did not increase the time or risk of cognitive decline among home-dwelling people with dementia.

Keywords: anticholinergic drugs, dementia, home-dwelling, cognitive impairment

Introduction

Anticholinergic medications are frequently prescribed to older people for diverse conditions, such as urinary incontinence, irritable bowel syndrome, and Parkinson's disease. Other drugs, such as antihistamines, antidepressants and antipsychotics, have significant unintended anticholinergic effects (1, 2). Peripheral adverse effects include dry mouth and increased heart rate. Central side effects include impaired concentration, confusion, memory impairment and falls (3-5).

Age-related changes make the elderly susceptible to adverse drug effects, especially those with chronic conditions, such as dementia (6), due to increase permeability of the blood-brain barrier and changes in pharmacokinetics and pharmacodynamics. Therefore drugs with anticholinergic effects normally not passing the blood-brain barrier may now penetrate it (6, 7).

Dementia causes impaired cholinergic neurotransmission and subsequently a decrease in cognitive function (3, 8, 9). Numerous studies have observed an association between anticholinergic drug load and the risk of developing cognitive impairment, but their results were conflicting (1, 8, 10, 11). These studies did not include patients with mild dementia, and focused only on drugs with well-known anticholinergic effects.

The prevalence of anticholinergic drug use in older people varies enormously (1, 12). Previous studies have reported that 40-60% of patients with dementia use at least one anticholinergic medication and that 10-20% use drugs with well-known anticholinergic effects (9, 13). The prevalence is even higher in nursing home (9, 14).

As anticholinergic drugs are widely used, many patients are subjected to a high anticholinergic load, which may result in cognitive impairment and delirium (1, 3, 15). Anticholinergic toxicity usually occurs due to the cumulative effects of multiple drugs instead of an overdose of a single dose (16).

To our knowledge, no study has evaluated the prevalence of anticholinergic use and its association with worsening cognitive decline over time in home-dwelling people with mild dementia in Norway. Such information is important for the management of patients with dementia, as avoiding drugs that accelerate cognitive decline may improve the quality of life of these patients.

Methods

Subjects

Referrals to five outpatient clinics in geriatric medicine and old age psychiatry with a first time diagnosis of mild dementia, defined as Mini Mental State Examination (MMSE) ≥ 20 (17) in Western Norway were included. The main inclusion period was from March 2005 to March 2007. After this, only patients with dementia with Lewy bodies (DLB) or Parkinson's disease dementia (PDD) were included until 2013. After a comprehensive baseline assessment, patients were followed longitudinally and reassessed annually for 5 years. During the clinical follow-up, the diagnosis was reevaluated and the final diagnosis was made as a consensus between two experienced clinical dementia researchers in geriatric psychiatry. In total there were 266 people having dementia in inclusion, but 12 people were excluded because the MMSE score was too low, leaving 254 people for this study. Everyone lived at home with their spouse or other caregivers at the time of inclusion. Patients were excluded if they did not have a dementia diagnosis or had acute delirium or confusion, had a terminal illness, recently were diagnosed with a major somatic illness or if they had bipolar disorder or other psychotic disorders. In Cox regression analysis, 28 patients (9 patients with Alzheimer's disease, 12 patients with DLB and PDD, and 7 patients with other forms of dementia) were excluded because of death before first follow-up, but there were no dropouts for other reason. Moreover, 29 patients with CDR-GS at baseline > 1 were also excluded in Cox regression analysis.

Ethical Issues

The study was approved by the Regional Committee for Medical and Health Research Ethics (REK) in Western Norway. Written informed consent was obtained from all subjects after the study procedures had been explained to them and caregiver.

Dementia Diagnosis

The diagnosis of dementia was made according to the Diagnosis and Statistical Manual for Mental Disorders, 4th edition (DSM-IV), and classification of dementia according to consensus criteria (18-20). Details on recruitment strategy and diagnostic procedures have been described elsewhere (21). Since DLB and PDD share clinical and pathological features (22), they were combined and will from now collectively be referred to as Lewy body dementia (LBD) in this study. Vascular dementia, FTD and alcoholic dementia were grouped together and are referred to as other forms of dementia due to the small sample size.

Clinical Assessment

The clinical assessment was performed at each follow-up. Cognition was assessed with the Mini-Mental State Examination (MMSE) (17) and Clinical Dementia Rating (CDR) (23) was used to assess severity of dementia staging by evaluating the degree of impairment in six domains of functioning at baseline and follow-up assessment. Subsequently, an algorithm is used to calculate the CDR global score (CDR-GS) by integrating the score from six domains into one overall score of severity (24). The final CDR-GS categories are: no dementia (0), questionable dementia (0.5), mild dementia (1), moderate dementia (2), and severe dementia (3) (25). Cumulative Illness Rating Scale (CIRS) was used to describe the total burden of medical illness, which measures the severity of chronic disease(26). A study by Perneczky et al. (2006) found that MMSE

scores of 29-26, 25-21, 20-11, and 10-0 matched CDR scores of 0.5, 1, 2 and 3, as questionable dementia, mild dementia, moderate and severe dementia, respectively. Therefore, in this study, the stage of severe dementia is defined as MMSE scores ≤ 10 and CDR = 3.

Measurement of Anticholinergic Drug Load

The anticholinergic effect of drugs use at baseline was estimated using the anticholinergic risk scale developed by Durán et al. (27). This scale is modulated by systematically reviewing existing anticholinergic risk scales. In our study, we transformed this scale into three categorical score, 0 (no anticholinergic activity), 1 (low anticholinergic activity) and 3 (high anticholinergic activity) in accordance with Beuscart et al. (28). For drugs that were not included in Duran's study or in case of discrepancies between score, anticholinergic activity were specified by authors (JJ and RO) using a reputed reference source (29) to take the final decision about the anticholinergic activity of the drug.

The total anticholinergic drug load per patient is calculated by summing the anticholinergic activities from every drug used by each patient. Moreover, the total score was categorized into total score 0 (no anticholinergic drug load), ≤ 2 (low anticholinergic drug load) and ≥ 3 (high anticholinergic load).

Statistical Analysis

Statistical analyses of the data were performed using SPSS Statistics version 21.0 from IBM. Independent sample t-test was used to compare means of continuous parametric variables. Mann-Whitney U test was used in case of two nonparametric continuous variables. The χ^2-test was used to explore the relation between categorical variables. The primary outcome variable is the rate of cognitive decline, that is, the MMSE and CDR scores. The Kaplan-Meier survival analysis was used to estimate the median time to severe dementia and the log rank test was performed to compare time to severe dementia with

respect to diagnosis, number of medications, use of anti-dementia medicines, MMSE total score, CIRS total score and CDR global score at baseline.

To analyze time to severe dementia, defined by CDR=3 and MMSE ≤10 (25) and to explore potential predictors associated with the severity of dementia, Cox regression analysis was conducted. Furthermore, log minus log probability plot was performed to check the proportionality of the hazards model and the curves was approximately parallel and did not intersect after time apart. Two-sided p-values lower than 0.05 were considered as statistically significant. Results are presented as means, stated with their standard deviation (±SD), median with interquartile range (IQR) or 95% confidence interval (CI).

Results

Study sample

A total 254 patients were included at baseline with an average age of 75.7 years (SD 7.6). The majority of the patients were diagnosed with Alzheimer disease (48.8%) while the rest had LBD (30.7%) or other forms of dementia (20.5%). The demographic and clinical baseline characteristics are summarized in table 1.

Use of anticholinergic drugs

Drugs with anticholinergic effects were used by 145 patients (57.1%). Of these, 59 (51.8%) were taking at least one anticholinergic medication. Patients who used drugs with anticholinergic activity also had more comorbidity, higher CDR score and a significantly higher number of medications compared to nonusers ($p<0.005$, see table 1).

At baseline, 138 patients (54.3%) were taking drugs with low anticholinergic activity, which 53 patients (38.4%) received more than one drug with low anticholinergic activity. Thirty participants (11.8%) were taking drugs with high anticholinergic activity and two of them received two drugs with high

anticholinergic activity. A total of 44 patients (30.3%) had high cumulative anticholinergic load (total score of anticholinergic activity ≥ 3).

The most frequently used drug classes with anticholinergic effects in our study were escitalopram (19%) and oxazepam (14%) for low anticholinergic activities, and tolterodine (23%) and ipratropium (2.8%) for drugs with significant anticholinergic effects.

Follow-up data were available for 226 patients (96 males and 130 females) of whom 115 (50.9%) had AD, 66 (29.2%) had LBD and 45 (19.9%) had other forms of dementia. Of these, 129 patients (57.1%) and 107 (47.3%) were taking anticholinergic medication and anti dementia medicines at baseline, respectively. However, there was no significant difference in age, sex, education and use of anti dementia medicines ($p > 0.05$ for all comparisons). During the observational period 172 patients died, but there were no dropouts for other reasons. The survival time was significantly higher in AD (3.9 years) compare to LBD (3.2 years) and other forms of dementia (2.5 years).

Predictors of cognitive decline

The median time to severe dementia, defined as MMSE ≤ 10 and CDR = 3, was 1894 days and 1863 days in patients that use anticholinergic drugs and 1915 days and 1933 days in nonusers ($p=0.744$ and $p=0.652$), respectively. Multivariable Cox regression analysis was run to determine the effect of baseline covariates on time to worsening of cognitive decline and degree of dementia. Age, sex, education, dementia diagnosis, comorbidity as measured by CIRS, baseline MMSE and CDR global score and total anticholinergic activity were used as covariates. Subsequently, variables that were significant were included in a multivariable stepwise regression model with backward elimination (likelihood ratio). (Table 2 and 3)

Factors associated with time to progression of cognitive decline and severe dementia is shown in table 2 and 3. Factors that remained significant

predictors of faster cognitive decline and severe dementia, measured with MMSE and CDR, were following: having LBD and a high CDR-GS at baseline. Conversely, having a high baseline CIRS total score and MMSE total score decreased the risk for MMSE decline significantly ($p<0.05$). Use of anti-dementia drug predicted shorter time to MMSE decline and severe dementia, but it was not statistically significant ($p=0.272$ and $p=0.121$, respectively).

The rate of cognitive decline over time showed the decrease was slightly more rapid in patients that used anticholinergic drugs compared to nonusers in the earlier years, but remained almost the same after 5 years (figure 1 and 2). In addition, there were no significant interactions with anticholinergic drugs use or total anticholinergic drug load ($p>0.05$).

Discussion

Main findings

The use of drugs with anticholinergic properties was common in these patients with dementia. The longitudinal study showed that 57% of home-dwelling elderly with dementia were taking drugs with anticholinergic activities, and nearly 12% were taking one or more anticholinergic medications with high activity. These findings are consistent with the reported prevalence in previous studies (9, 13, 15). Almost 40% of the patients were taking more than one (up to a value of six) anticholinergic medications with low activity.

Our findings revealed that higher total scores of anticholinergic load were due to the summative effect of multiple low potency anticholinergic medications (up to six medications), rather than a single drug with high anticholinergic properties. This is in line with previous studies that reported adverse drug events are often the result of cumulative anticholinergic load of multiple medications and metabolites rather than of a single compound (16, 30, 31). Although anticholinergic use is a significant concern in dementia patients, clinicians may be less aware of the cumulative load of multiple low potency

anticholinergic drugs than well-recognized anticholinergic properties when making prescriptions (3, 32). Hence, to diminish adverse effects on the dementia patients and those with cognitive impairment, clinicians should consider using alternative medications with no-to-minimal anticholinergic properties.

Participants that used drugs with anticholinergic properties had more often comorbid diseases, lower MMSE at baseline and used more drugs than the non-users. Our findings supports a recent study that reported polypharmacy (i.e. taking five or more medications) associated with higher anticholinergic load (15). Patients with dementia often have cardiovascular disease, such as coronary heart disease, stroke, diabetes mellitus and hypertension, requiring use of multiple drugs (33). However, it is important to recognize that many drugs in daily long-term use have anticholinergic properties and that the use of these drugs cannot be fully avoided (34). Consequently, there is a need to evaluate and monitor use of anticholinergic drugs as patient safety practice in elderly patients with dementia.

Cognitive decline

In contrast to previous studies (1, 8, 10, 11), our findings concluded that no significant difference in the rate of cognitive decline on MMSE and severe dementia in patients use anticholinergic drugs and non-users. The difference between our findings and previous literature results may be due to our focus on drugs with anticholinergic properties in mild dementia patients. A recent longitudinal study focused only on high activity anticholinergic drugs based on pharmacologic properties (1) and a previous cohort study was based on anticholinergic drug lists, which is used for routine clinical practice (8). Detailed assessment of the anticholinergic load in these studies included only the well-known anticholinergic effects, but did not include other drugs associated with such effects (1, 8, 10). The only study that included other drugs with anticholinergic properties measured the cognitive decline in patients with Parkinson's disease (11). In addition, we did not take into account whether patients actually received the anticholinergic medications (as some could have

been ordered/prescribed on an as needed basis and patients may never have received the medication).

In the adjusted model, our results showed that having LBD diagnosis and higher CDR-GS increased the time and risk to cognitive decline and severe dementia, whereas higher baseline MMSE scores and higher baseline CIRS total score were associated with delayed cognitive decline. These findings are consistent with a previous study that patients with DLB have a more rapid cognitive decline than in AD (35). Possible explanations for these findings are severe parkinsonism, fluctuations in cognitive impairment, visual hallucinations and depression are more common in LBD compared to AD. These symptoms may be treated with neuroleptic and antidepressant drugs, whereas having LBD increased sensitivity to drug reactions, especially neuroleptic medication (36). It is known that neuroleptic medicines and antidepressant have varying degrees of anticholinergic effects, which may explain the deterioration of cognitive decline in these patients. However, we did not find that patients with LBD used more anticholinergic drugs compared to AD. This could be due to lower number of cases with LBD compared to AD.

In the present study, use of anticholinergic drugs was not discontinued before initiating anti dementia medicines. Use of anti-dementia medicines predicted shorter time to MMSE decline and severe dementia in the unadjusted model, but was no longer significant after adjustment for various covariates. This effects may be because the anticholinergic action of drugs may reduce or eliminate the cognitive benefits of anti dementia medicines (37).

The strengths of the current study included the use of the most recent clinical diagnosis of DLB and the specific and standardized clinical assessment program. Furthermore, the annual assessment was done by the same clinicians and continually updated, which increases the accuracy of diagnosis. Moreover, we also used CDR as an outcome measure, to apply a more sophisticated statistical approach. CDR measures the full range of functional deficits due to cognition as judged by a trained clinician, and is more accurate and thorough

measurement. Additionally, it is a rather homogeneous patient group with mild dementia at inclusion and low dropout rate. As described above, our study has taken into consideration drugs with anticholinergic properties, whereas previous studies included only well-known anticholinergic effects. We slightly modified the scale by also including drugs that were not included previously, after independent assessment by two of the authors. A limitation with this method was that dosage and duration of treatment are not taken into account.

There are some limitations in our study. First, we used the adapted anticholinergic drug scale according to the recent study of Durán et al. (27), which compared seven different scales. There was a big variation in the scales and the grades given to them. The distinction between low and high activity of anticholinergic drugs in the study might be considered as rather crude. However, that was the only way to achieve a consistent score from the various lists (27). Second, the use of drugs with anticholinergic properties was recorded only at baseline and possible changes in medications during the follow-up period were not taken into account, which might have influenced the finding. An association between cognitive impairment and drugs with anticholinergic properties has been discussed for many years and clinicians may also have reduced or discontinued anticholinergic therapy during the follow-up. Finally, we might have some interval-censored data that may have lead to a potential bias; therefore, another program would maybe optimize the data analysis. However, Cox regression is also adequate to evaluate the progression of cognitive decline in this study.

In conclusion, the study revealed that almost 60% home-dwelling patients with mild dementia used drugs with anticholinergic activities. In many cases, it is the low-activity anticholinergic drugs that are the major contributors to anticholinergic load. However, we found no association between use of anticholinergic drugs or anticholinergic drug load and the progression of cognitive decline or severity of dementia stage. Future researches are needed to confirm these findings and to understand the underlying mechanisms.

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Conflicts of Interest

None declared.

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Attachment

Tables and Figures

Tabel 1. Demographic and characteristic of the study population

	Total sample	Using Anticholinergic Drugs	
		Yes	No
Number of participant, n(%)	254 (100)	145 (57.1)	109 (42.9)
Age at baseline, years (means ± SD)[a]	75.7 ± 7.6	76.3 ± 7.7	74.9 ± 7.3
Female (n,%)[b]	147 (57.9)	85 (33.5)	62 (24.4)
Years of education[c]	9 (7-11)	9 (7-11)	9 (7-12)
Diagnosis (n,%)[d]			
Alzheimer dementia	124 (48.8)	64 (25.2)	60 (23.6)
Lewy Body Dementia	78 (30.7)	44 (17.3)	34 (13.4)
Other forms of dementia	52 (20.5)	37 (14.6)	15 (5.9)
MMSE score[e]	24 (22-26)	23 (22-25)	24 (22-26)
CDR score ≤ 1 (n,%)[f]	220 (92.8)	120 (54.5)	100 (45.5)
CIRS score[g]	6 (4-8)	6 (4-9)	5 (3-7)
Number of drugs used[h]	4 (2-6)	5 (4-7)	3 (1-4)
Use of anti-dementia medications (n,%)[i]	114 (44.9)	59 (23.2)	55 (21.7)

Values are median and interquartile range (IQR), except where otherwise indicated.
The groups using and not using anticholinergic drugs were compared using the independent samples t-test (age), Mann-Whitney test (education, MMSE, CIRS and number of drugs) and chi-square test (sex, CDR, diagnose and use of anti dementia medication).

Abbreviations: MMSE: Mini-Mental State Examination, CDR: Clinical Dementia Rating, CIRS: Cumulative Illness Rating Scale

a) p = 0.149, independent t-test
b) p = 0.781, Chi-square test
c) missing data for 6 cases, p = 0.995, Mann-Whitney test
d) p = 0.057, Chi-square test
e) p = 0.016, Mann-Whitney test
f) missing data for 17 cases, p = 0.650, Chi-square test
g) missing data for 19 cases, p < 0.005, Mann-Whitney test
h) p < 0.005, Mann-Whitney test
i) p = 0.121, Chi-square test

Table 2. Factor associated with the rate of decline on MMSE

	Unadjusted HRs (95% CI)	p Value	Adjusted HRs (95% CI)	p Value
Age, years	0.98 (0.95 – 1.01)	0.333		
Sex, female	0.89 (0.57 – 1.42)	0.636		
Education, years	1.02 (0.95 – 1.11)	0.555		
Diagnosis				
LBD	1.74 (1.03 – 2.95)	0.005	1.97 (1.11 – 3.49)	0.025
Other dementia	0.45 (0.19 – 1.05)	0.005	0.64 (0.26 – 1.55)	0.025
No. of drugs	0.87 (0.79 – 0.97)	0.007	0.93 (0.81 – 1.06)	0.267
CDR-GS ≤ 1 at baseline	1.43 (0.89 – 2.27)	0.132	1.68 (1.03 – 2.74)	0.036
MMSE total scores	0.90 (0.82 – 0.99)	0.034	0.9 (0.82 – 0.99)	0.038
CIRS total scores	0.87 (0.78 – 0.96)	0.004	0.83 (0.75 – 0.93)	0.001
Antidementia drugs use	1.70 (1.07 – 2.72)	0.024	1.33 (0.8 – 2.20)	0.272
Anticholinergic drugs use	0.93 (0.59 – 1.46)	0.744		
Total ACH load	0.94 (0.8 – 1.12)	0.490		

Cox regression, time until MMSE 0-10.
Abbreviations: HR: Hazard Ratio, CI: Confidence Interval LBD: Lewy-body dementia CDR-GS: Clinical Dementia Rating Global Scores, MMSE: Mini-Mental State Examination, CIRS: Cumulative Illness Rating Scale, ACH: anticholinergic drug

Table 3. Factor associated with time to reach severe dementia

	Unadjusted HRs (95% CI)	p Value	Adjusted HRs (95% CI)	p Value
Age, years	0.99 (0.96 – 1.02)	0.591		
Sex, female	1.01 (0.63 – 1.64)	0.959		
Education, years	1.04 (0.97 – 1.12)	0.319		
Diagnosis				
LBD	2.22 (1.31 – 3.77)	0.001	2.14 (1.21 – 3.78)	0.003
Other dementia	0.52 (0.22 – 1.23)	0.001	0.5 (0.21 – 1.2)	0.003
No. of drugs	0.96 (0.87 – 1.06)	0.405	1 (0.89 – 1.14)	0.968
CDR-GS ≤ 1 at baseline	1.75 (1.08 – 2.83)	0.021	1.83 (1.01 – 3.05)	0.019
MMSE total scores	0.84 (0.75 – 0.93)	0.001	0.84 (0.75 – 0.94)	0.002
CIRS total scores	0.96 (0.88 – 1.05)	0.379	0.91 (0.83 – 1)	0.040
Antidementia drugs use	1.33 (0.83 – 2.13)	0.232	1.45 (0.91 – 2.32)	0.121
Anticholinergic drugs use	1.11 (0.7 – 1.78)	0.652		
Total ACH load	1.02 (0.87 – 1.2)	0.854		

Cox regression, time until CDR = 3. HR presented with 95% CI.

Abbreviations: HR: Hazard Ratio, CI: Confidence Interval, LBD: Lewy-body dementia, CDR-GS: Clinical Dementia Rating Global Scores, MMSE: Mini-Mental State Examination, CIRS: Cumulative Illness Rating Scale, ACH: anticholinergic drug

Figure 1. Time to decline on MMSE score with use of anticholinergic drugs and nonusers

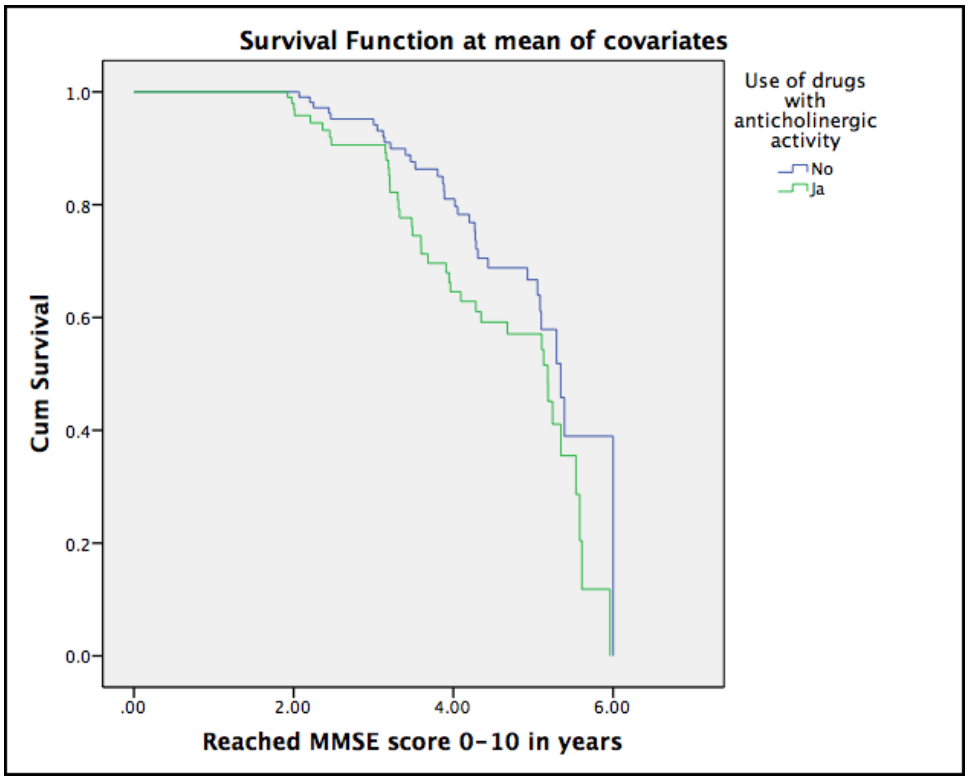
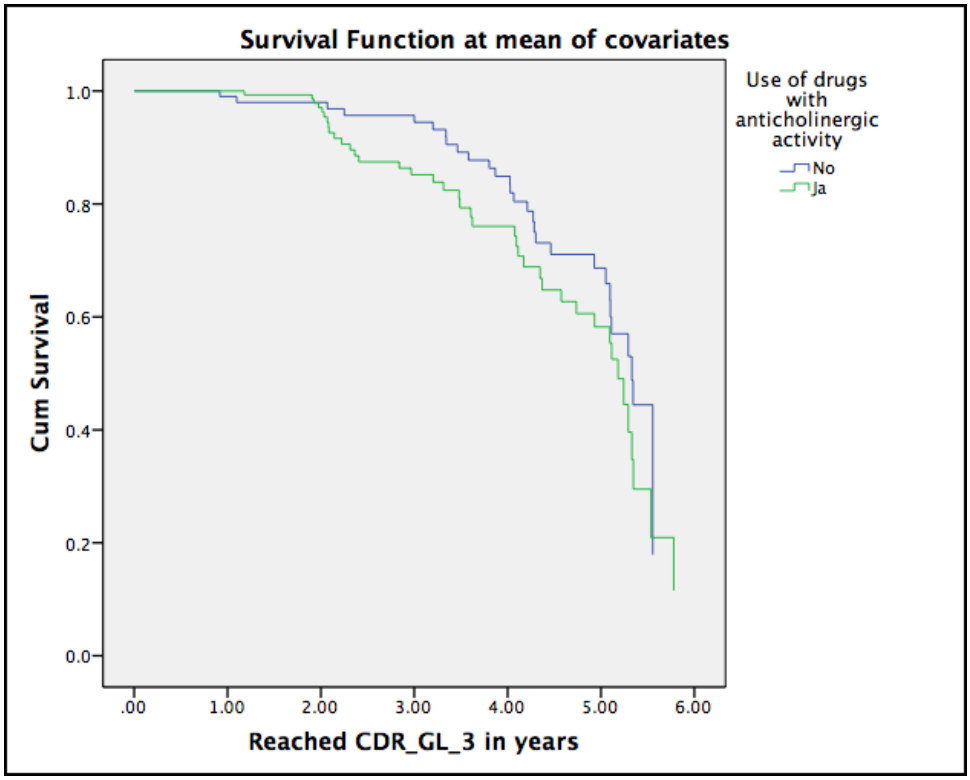


Figure 2. Observation time until severe dementia with anticholinergic drugs use and nonuser



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From time to time the Journal will publish themed issues, including review articles and related original research papers. Authors who want to suggest a

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Systematic reviews

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- **Introduction** This should mention the background (*e.g.* relevant clinical and pharmacological issues) and describe the scope and aim of the review. What was the reason for the review? The strengths and weaknesses of the existing literature should be briefly described, earlier reviews identified and the need for the present paper explained.
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- **Discussion** Compare the findings to existing knowledge; outline the limitations of the review.
- **Conclusion** Summarize the key findings and the implications for clinical pharmacology and/or practical drug therapy.

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Comments on previously published papers, items of topical interest, and brief original communications will be considered under this heading. The length, including references, should not exceed 800 words, plus one figure or table. The letter should NOT be divided into sections.

Case reports (must be submitted as Letter to the Editor)

The Journal generally does not publish case reports as full papers but will do so as letters to the Editor. As for other letters the length, including references,

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TERMINOLOGY Stereoisomers

When a drug can exist as stereoisomers or diastereomers (for example geometrical isomers), the form of compound studied must be designated as follows in the methods section.

In the case of racemates the prefix *rac*- should precede the drug name (for example *rac*-propranolol).

When possible the absolute configuration of enantiomers should be indicated (for example (*S*)-warfarin).

Similarly, geometrical isomerism should be indicated by the prefixes Z/E or *cis*/*trans*. When appropriate, the interpretation of data obtained using mixtures of isomers should take account of stereochemical aspects.

Drug names

Prescribed drugs should be designated by an International Non-proprietary Name (recommended, rINN, or proposed, pINN). If such a name is not available, a drug should be designated by its British Approved Name (BAN; for example hyoscyamine) or its chemical name (for example glyceryl trinitrate).

When a mixture of drugs has a combination BAN (for example co-trimoxazole, co-fluampicil), that should be used.

For brevity, a company's code name may be used, but in that case the full chemical name or a figure showing the structure of the drug should be given in the introduction or a reference provided that gives this information.

Some mediators with well established common names (*e.g*. prostacyclin) are also prescribed as licensed preparations with an rINN (*e*. *g*. epoprostenol). In

such cases the rINN should be used in the context of therapeutic use. Sometimes English and American usage varies, as with adrenaline / epinephrine and noradrenaline / norepinephrine. “Adrenaline / noradrenaline” relate clearly to terms such as “noradrenergic”, “adrenergic” and “adrenal gland” but we will accept the term preferred by authors.

Units

SI units (mass or molar units) should be used. If other units are used, a conversion factor should be included in the **Methods** section.

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STRUCTURE

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- a running head of no more than 75 characters, including spaces;
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The summary should be a maximum of 250 words; abstracting services truncate summaries that are longer. It should be couched in terms that will be understood by most readers of the Journal.

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Authors should include details of the precision, accuracy, sensitivity, and specificity of an analytical method used to measure drugs, metabolites or biomarkers or refer to other publications in which the information is given.

- **Precision** is a measure of random error, usually expressed as the coefficient of variation.
- **Accuracy** is a measure of systematic error, also called bias; it can be expressed as the percentage difference between the result for a test sample and the reference value for that compound.
- **Sensitivity** or lower limit of quantification.
- **Specificity** is the extent to which the method does not detect compounds other than those intended.

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Examples:

1 Johnson TN, Rostami-Hodjegan A, Tucker GT. A comparison of methods to predict drug clearance in neonates, infants and children. Br J Clin Pharmacol 2004; 57: 677-8.

2 Metters J (editor). Independent Steering Committee Report of an Independent Review of Access to the Yellow Card Scheme. London: The Stationery Office, 2004.

3 Hoffman BB, Lefkowitz RJ. Beta-adrenergic receptor antagonists. In: The Pharmacological Basis of Therapeutics, Eighth Edition, eds Gilman AG, Rail TW, Nies AS, New York: Pergamon Press, 1990: 229-43.

Accepted articles and Early view

References to papers published as Accepted Articles should be cited thus: Ferro A. Paediatric prescribing: why children are not small adults. *Br J Clin*

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Acknowledgements

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