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MARJAANA KOPONEN

ANTIPSYCHOTIC USE AND RISK OF HIP FRACTURE AND MORTALITY AMONG COMMUNITY DWELLERS WITH ALZHEIMER'S DISEASE

A nationwide register-based study

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Author's address: School of Pharmacy
University of Eastern Finland
KUOPIO
FINLAND

Supervisors: Professor Sirpa Hartikainen, M.D., Ph.D.
School of Pharmacy
University of Eastern Finland
KUOPIO
FINLAND

Professor Riitta Ahonen, Ph.D.
School of Pharmacy
University of Eastern Finland
KUOPIO
FINLAND

Associate Professor Anna-Maija Tolppanen, Ph.D.
School of Pharmacy
University of Eastern Finland
KUOPIO
FINLAND

Reviewers: Assistant Professor Helga Gardarsdottir, Ph.D.
Division of Pharmacoepidemiology and Clinical Pharmacology
Utrecht Institute for Pharmaceutical Sciences, Faculty of Science,
Utrecht University
UTRECHT
THE NETHERLANDS

Professor Maria Eriksdotter, M.D., Ph.D.
Department of Neurobiology, Care Sciences and Society
Karolinska Institutet
STOCKHOLM
SWEDEN

Opponent: Adjunct Professor Harriet Finne-Soveri, M.D., Ph.D.
Medical Faculty, University of Helsinki
Chief medical officer for elderly care services, Helsinki City
HELSINKI
FINLAND

Koponen, Marjaana
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ABSTRACT

As the population ages, there are more and more individuals with Alzheimer's disease (AD) in countries all around the world. In addition to the cognitive and functional declines, behavioral and psychological symptoms of dementia (BPSD) are common in all stages of AD. Antipsychotics are recommended only for short-term treatment of the most severe BPSD. Despite safety concerns, antipsychotics are frequently prescribed for patients with dementia.

The aims of this thesis were to describe the incidence of antipsychotic use in relation to the diagnosis of AD and to determine the duration of antipsychotic use and factors associated with long-term use among community dwellers with AD. Furthermore, the associations between antipsychotic use and the risk of hip fracture and mortality were investigated.

This study was based on data from two large Finnish register-based MEDALZ (Medication use and Alzheimer's disease) cohorts. Persons with clinically verified diagnoses of AD were identified from the Special Reimbursement Register. Data from several nationwide registers such as the Prescription Register (since 1995) and the Hospital Discharge Register (since 1972) have been linked to these cohorts. The MEDALZ-2005 cohort contained follow-up data until 2009 and included all residents of Finland who had been diagnosed with AD, and who were alive and community-dwelling at the end of 2005. The incidence and duration of antipsychotic use were studied among those diagnosed with AD in 2005 (n=7,217). In order to evaluate the risk of hip fracture and mortality, a larger MEDALZ cohort including all community dwellers who received an AD diagnosis between 2005 and 2011 was utilized (n=70,718). Periods of antipsychotic drug use were calculated with a novel PRE2DUP modeling method from the Prescription Register data. The analyses were restricted to new users of antipsychotics.

A distinct increase in antipsychotic initiations occurred around the time of AD diagnosis and the incidence remained at a high level thereafter. Long-term use was frequent among community-dwelling Finns with AD; this was associated with initiation of use after AD diagnosis and age at the time of initiation.

Antipsychotic use was associated with an increased risk of hip fracture and mortality. Both risks were increased from the first days of antipsychotic use and remained elevated in long-term use. Compared with nonuse, antipsychotic polypharmacy was associated with higher mortality than monotherapy.

In conclusion, the findings support the recommendations in the current treatment guidelines. It is important to restrict antipsychotic use for the treatment of the most severe BPSD, to monitor their use at regular intervals, to limit the duration of use and to avoid antipsychotic polypharmacy in patients with AD.

National Library of Medicine Classification: QV 56, QV 77.9, WA 900, WE 855, WT 155
Medical Subject Headings: Alzheimer Disease; Antipsychotic Agents; Incidence; Prevalence; Drug-Related Side Effects and Adverse Reactions; Risk; Hip Fractures; Mortality; Cohort Studies; Longitudinal Studies; Follow-Up Studies; Pharmacoepidemiology; Drug Utilization; Polypharmacy; Registries; Finland

Koponen, Marjaana
Psykoosilääkkeiden käyttö ja käytön yhteys lonkkamurtumiin ja kuolleisuuteen Alzheimerin tautia sairastavilla, valtakunnallinen rekisteritutkimus
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TIIVISTELMÄ

Väestön ikääntyessä Alzheimerin tautia sairastavien määrä kasvaa maailmanlaajuisesti. Kognition ja toimintakyvyn heikentymisen lisäksi käytösoireet ovat yleisiä taudin kaikissa vaiheissa. Psykoosilääkkeitä suositellaan käytettävän vain vaikeimpien käytösoireiden lyhytaikaisessa hoidossa, koska niiden käyttö voi lisätä erilaisten haittatapahtumien riskiä.

Tämän väitöskirjatutkimuksen tavoitteena oli kuvata psykoosilääkkeiden käytön ilmaantuvuutta suhteessa Alzheimerin taudin diagnoosiin sekä psykoosilääkkeiden käytön kestoa ja pitkäaikaiseen käyttöön liittyviä tekijöitä Alzheimerin tautia sairastavassa väestössä. Lisäksi tutkittiin psykoosilääkkeiden käytön yhteyttä lonkkamurtumien ilmaantuvuuteen sekä kuolleisuuteen.

Tutkimus perustui kahteen valtakunnalliseen rekisteripohjaiseen MEDALZ (Medication use and Alzheimer's disease) -kohorttiin. Kelan erityiskorvausrekisteristä tunnistettiin kaikki henkilöt, joille oli myönnetty Alzheimerin taudin lääkkeiden rajoitettu peruskorvausoikeus. Näiden henkilöiden lääke- ja terveystiedot koottiin yhteen useasta kansallisesta rekisteristä kuten Kelan reseptitiedostosta (1995 lähtien) ja Terveyden ja hyvinvoinnin laitoksen hoitoilmoitusrekisteristä (1972 lähtien). MEDALZ-2005 -kohortissa on seurantatietoa vuoteen 2009 saakka ja se sisältää kaikki henkilöt, joilla oli Alzheimerin taudin diagnoosi ja jotka olivat elossa ja laitoshoidon ulkopuolella vuoden 2005 lopussa. Psykoosilääkkeen käytön ilmaantuvuutta sekä käytön kestoa tutkittiin Alzheimerin taudin diagnoosin vuonna 2005 saaneilla (n=7 217). Lonkkamurtuma- ja kuolleisuusriskin tutkimista varten käytettiin laajempaa MEDALZ-kohorttia sisältäen henkilöt, jotka saivat ensimmäisen Alzheimerin taudin diagnoosin vuosina 2005–2011 (n=70 718). Psykoosilääkkeiden käyttöjaksot laskettiin uudenlaisella PRE2DUP-mallinnusmenetelmällä reseptitiedoston ostotiedoista. Analyysit rajattiin uusiin psykoosilääkkeiden käyttäjiin.

Psykoosilääkkeiden aloittajien määrä oli suurimmillaan Alzheimerin taudin diagnoosin läheisyydessä ja käytön ilmaantuvuus pysyi suurena diagnoosin jälkeenkin. Pitkäaikainen käyttö oli yleistä ja se oli yhteydessä psykoosilääkkeiden aloitukseen Alzheimerin taudin diagnoosin jälkeen sekä ikään aloitushetkellä.

Psykoosilääkkeiden käyttö oli yhteydessä lisääntyneeseen lonkkamurtuma- ja kuolleisuusriskiin. Molemmat riskit olivat suurentuneet käytön alusta lähtien ja säilyivät käytön jatkuessa. Kahden tai useamman psykoosilääkkeen päällekkäiskäyttöön liittyi korkeampi kuolleisuusriski kuin yhden psykoosilääkkeen käyttöön.

Tulokset tukevat nykyisiä hoitosuosituksia muistisairaiden käytösoireiden hoidosta. On tärkeää määrätä psykoosilääkkeitä vain vaikeimpien käytösoireiden hoitoon, seurata käytön vastetta ja haittoja säännöllisesti, pitää käyttö mahdollisimman lyhytaikaisena sekä välttää psykoosilääkkeiden päällekkäiskäyttöä.

Luokitus: QV 56, QV 77.9, WA 900, WE 855, WT 155
Yleinen suomalainen asiasanasto: Alzheimerin tauti; psykoosit; psyykenlääkkeet; haitat; riskit; ilmaantuvuus; esiintyvyys; luunmurtumat; lonkka; kuolleisuus; kohorttitutkimus; pitkittäistutkimus; seurantatutkimus; epidemiologia; lääkkeet; polyfarmasia; rekisterit; Suomi

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When I started my PhD studies I did not drink coffee at all but I learned to consume it soon after I started visiting the Social Pharmacy coffee room. I wish to thank all the current and past personnel of Social Pharmacy for all the enjoyable moments. Special thanks to Paula Räsänen for her readiness to help in all practical issues, Kati Sepponen for her company during several lunch breaks and Miia Tiihonen for fun and long after parties. Heartfelt thanks

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Kuopio, September 2017

Marjaana Koponen

List of the original publications

This dissertation is based on the following original publications:

I Koponen M, Tolppanen AM, Taipale H, Tanskanen A, Tiihonen J, Johnell K, Fastbom J, Ahonen R, Hartikainen S. Incidence of antipsychotic use in relation to diagnosis of Alzheimer's disease among community-dwelling persons. *The British Journal of Psychiatry 207(5): 444-449, 2015.*

II Koponen M, Taipale H, Tanskanen A, Tolppanen AM, Tiihonen J, Ahonen R, Hartikainen S. Long-term use of antipsychotics among community-dwelling persons with Alzheimer's disease: A nationwide register-based study. *European Neuropsychopharmacology 25(10): 1706-1713, 2015.*

III Koponen M, Taipale H, Lavikainen P, Tanskanen A, Tiihonen J, Tolppanen AM, Ahonen R, Hartikainen S. Antipsychotic use and the risk of hip fracture among community-dwelling persons with Alzheimer's disease. *The Journal of Clinical Psychiatry 78(3):e257-e263, 2017.*

IV Koponen M, Taipale H, Lavikainen P, Tanskanen A, Tiihonen J, Tolppanen AM, Ahonen R, Hartikainen S. Risk of mortality associated with antipsychotic monotherapy and polypharmacy among community-dwelling persons with Alzheimer's disease. *Journal of Alzheimer's Disease 56(1):107-118, 2017.*

Contents

Abbreviations

AAP	Atypical antipsychotic
AChEI	Acetylcholinesterase inhibitor
AD	Alzheimer's disease
AP	Antipsychotic drug
APA	American Psychiatric Association
ATC	Anatomical Therapeutic Chemical
BPSD	Behavioral and psychological symptoms of dementia
CAP	Conventional antipsychotic
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
DDD	Defined Daily Dose
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th edition
ECG	Electrocardiography
EMA	European Medicines Agency
EPS	Extrapyramidal symptoms
FDA	U.S. Food and Drug Administration
HR	Hazard ratio
ICD	International Classification of Diseases
IRR	Incidence rate ratio
IQR	Interquartile range
LTC	Long-term care residents
MCI	Mild Cognitive Impairment
MEDALZ	Medication use and Alzheimer's disease
NH	Nursing home
NICE	National Institute for Health and Care Excellence (UK)
NIHW	Finnish National Institute of Health and Welfare
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association

NOMESCO	Nordic Medico-Statistical Committee
OR	Odds ratio
PRE2DUP	Prescriptions to drug use periods
RR	Relative risk
SD	Standard deviation
SII	Finnish Social Insurance Institution
WHO	World Health Organization

1 Introduction

Observational pharmacoepidemiological studies are needed to extend our understanding of the effectiveness and safety of drugs among real-life users (Hilmer et al. 2012). Study participants in randomized controlled trials may poorly reflect the actual real-life users due to several inclusion and exclusion criteria (Leinonen et al. 2015). Real-life users are often older and use multiple drugs concomitantly for many comorbidities, making them more vulnerable to adverse effects (Hilmer et al. 2012). In addition, because of the small sample sizes and short duration, less common adverse events may not be detected in randomized controlled trials. For example, the increased risk of mortality among atypical antipsychotic users with dementia was initially detected from pooled data of several randomized controlled trials (FDA 2005, Schneider et al. 2005). Subsequently, observational studies provided additional evidence that the risk of mortality was likely similar or higher among conventional antipsychotic users (Gill et al. 2007, Schneeweiss et al. 2007). Although there is now more evidence about the safety aspects associated with antipsychotic use, several research gaps exist (Trifirò et al. 2014). There is a lack of data on safety of long-term antipsychotic use as well as uncertainty whether certain individual antipsychotic drugs are safer than others. Most studies have focused on older people in general rather than persons with dementia or with a specific type of dementia.

Nordic prescription registers represent a vast and reliable data source for pharmacoepidemiological research (Furu et al. 2010, Wettermark et al. 2013). These registers enable high-quality studies on both the beneficial and adverse effects of drug use in large unselected populations with long follow-up data. In addition, studying drug utilization in large representative cohorts provides valuable information on treatment practices, highlights possible ways for improvement and enables evaluating the impact of interventions on drug use.

This thesis is a part of a large nationwide register-based MEDALZ (Medication use and Alzheimer's disease) study including all community-dwelling residents of Finland who received a clinically verified diagnosis of AD between 2005 and 2011 (Tolppanen et al. 2016a, Gerho). One major aim of the MEDALZ study is to investigate the changes and appropriateness as well as the safety and effectiveness of medication use among persons with AD. Accordingly, the aims of this thesis were to study the incidence of antipsychotic use in relation to diagnosis of AD, duration of antipsychotic use and factors associated with long-term use as well as the associations between antipsychotic use and risk of hip fracture and mortality among community dwellers with AD.

2 Review of the Literature

2.1 ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is a neurodegenerative disease characterized by progressive deterioration in memory and other cognitive domains, a functional decline as well as behavioral and psychological symptoms (Alzheimer's Association 2016). AD is the most common cause of dementia, accounting for 60-80% of all dementia cases. Dementia is a syndrome in which the deterioration in cognitive function has led to a reduced ability to perform daily activities. Due to population aging, the number of people with dementia is increasing. According to the World Alzheimer Report (Prince et al. 2015), there were 46.8 million people living with dementia in 2015 worldwide and this is estimated to triple to 131.5 million by 2050. In Finland, approximately 100 000 persons were estimated to have mild dementia in 2013 with a further 93 000 persons displaying at least moderate dementia (Memory disorders: Current Care Guidelines 2017). Dementia is a major cause of disability and dependence among older people; in 2015, the worldwide cost of dementia was estimated at US$ 818 billion (Prince et al. 2015).

Age is the most important risk factor for dementia and the incidence of dementia increases with age (Prince et al. 2015, Alzheimer's Association 2016). With every 6.3 year increase in age, the incidence of dementia doubles (Prince et al. 2015). The incidence is estimated to be 3.9 per 1000 person years at age 60-64 and 104.8 per 1000 person-years at age 90 years and over. According to a recent systematic review, there is evidence that the incidence of dementia may have declined in high-income countries (Prince et al. 2016). This decline may have partly resulted from increasing levels of education and better control of cardiovascular risk factors. The review found conflicting results if there has been a corresponding decline in the prevalence of dementia. A more recent study reported that the prevalence of dementia in the US declined significantly between 2000 and 2012 (Langa et al. 2017). However, the Alzheimer's Association has noted that despite this possible decline in the age-specific dementia risk, the total number of persons with dementia as well as the social and economic burden are still expected to increase considerably due to population aging (Alzheimer's Association 2016). In 2015, it was estimated that approximately 60% of persons with dementia were living in low and middle income counties and most of the future increase is expected to take place in those countries (Prince et al. 2015).

The pathological brain changes that characterize AD are the progressive accumulation of extracellular β-amyloid plaques and intracellular neurofibrillary tangles formed by hyperphosphorylated tau (Jack et al. 2010). However, neurodegeneration manifested as atrophy, neuron loss, gliosis and synapse loss are most closely related to the emergence of clinical symptoms. The pathophysiological process of AD starts to evolve years, even decades, before the first clinical symptoms appear. Thus, the updated diagnostic criteria of AD distinguish the pathophysiological process and clinically observable syndromes by dividing the continuum of AD into three phases: asymptomatic preclinical phase of AD, mild cognitive impairment (MCI) due to AD, and dementia due to AD (Albert et al. 2011, Jack et al. 2011, McKhann et al. 2011, Sperling et al. 2011).

Individuals with MCI have impairment in at least one cognitive domain such as memory, executive function, attention, language and visuospatial skills (Albert et al. 2011). This impairment is greater than would be expected taking into account the person's age and educational background. Like dementia, MCI is a syndrome that can have many different etiologies. In individuals with MCI due to AD, the most common symptom is impairment in episodic memory i.e. difficulties in learning and remembering new information. MCI can cause slight problems performing complex tasks but does not significantly interfere with

everyday life or independent functioning. On the contrary, Dubois et al. (2010) proposed the term "prodromal AD" should refer to the early symptomatic predementia phase of AD. They proposed that the term MCI should be reserved for persons who have symptoms that are not characteristic of AD or when biomarkers do not support the presence of pathophysiological changes of AD (Dubois et al. 2010).

Since AD is a slowly progressive disorder with a gradual onset of symptoms, it can be difficult to identify exact points when a person has transitioned from the preclinical phase to the predementia phase or from the predementia phase to the onset of dementia (Albert et al. 2011, McKhann et al. 2011). A distinction between dementia and MCI can be made when the cognitive or behavioral symptoms of AD cause a significant impairment in the ability to function at work or to perform usual daily activities. The symptoms of AD gradually worsen over time (Alzheimer's Association, Memory disorders: Current Care Guidelines 2017). However, the rate of cognitive and functional decline varies across individuals. Dementia due to AD is commonly categorized into mild, moderate and severe stages. Table 1 describes the clinical symptoms in these different stages.

Table 1. Symptoms in different stages of Alzheimer's disease (Adapted from Memory disorders: Current Care Guidelines 2017 and Hughes et al. 1982)

	Mild AD	**Moderate AD**	**Severe AD**
Cognitive deficits	Moderate memory loss, especially of recent events Deterioration of executive functions Difficulties in planning and problem solving Difficulties in finding words Difficulties in calculation Decreased orientation to time Ability to concentrate declines	Severe memory loss, new information rapidly lost Impaired judgment and problem solving Difficulties in speaking Disoriented with respect to time and often to place Weak ability to concentrate Impaired visuospatial abilities Apraxia	Severe memory loss, only fragments remain Severe aphasia Disoriented to time and place Unable to concentrate Severe agnosia Severe apraxia
Impact on daily life	Problems in following complex conversations Difficulties in managing money and running errands Problems in taking care of medication Difficulties in driving Ability to work deteriorates Withdrawal from hobbies and social events	Problems in following and joining normal conversations Misplacing things Getting lost in familiar places Problems in recognizing family and friends Inability to perform IADL Needs reminding about ADL	Inability to communicate Unaware of recent events and surroundings Assistance needed in all ADL Incontinence Difficulties in walking, sitting and eventually swallowing
Common BPSD	Apathy Isolation Irritability Anxiety Depression Delusions	Delusions Hallucinations Apathy Agitation Wandering Sleep disturbances Depression	Agitation Aggression Aberrant motor behavior Sleep disturbances Apathy

ADL=Activities of daily living such as dressing, bathing, toilet hygiene, and eating; BPSD=behavioral and psychological symptoms of dementia; IADL=Instrumental activities of daily living such as preparing meals, managing money, taking medications, and shopping.

Behavioral and psychological symptoms of dementia (BPSD) include symptoms such as apathy, depression, anxiety, agitation, aggression, delusions, hallucinations, sleep disturbances, and disinhibition (Kales et al. 2015). Almost all individuals with AD experience one or more BPSD at some point during the course of the disease (Table 1). Behavioral and

psychological symptoms occur already in the prodromal phase of AD (Rosenberg et al. 2013). They are frequent in MCI and are associated with an increased risk of progression to dementia (Monastero et al. 2009, Rosenberg et al. 2013, Forrester et al. 2016). The prevalence of individual symptoms varies during the course of AD and symptoms fluctuate intermittently (Lyketsos et al. 2011, Kales et al. 2015). Depression and apathy are the most frequent symptoms in individuals with early AD (Lyketsos et al. 2011). When AD progresses, delusions, hallucinations and aggression become more common. Throughout the course of AD, apathy is the most persistent and frequent symptom. In addition, the incidence of agitation is high during all stages of AD. BPSD have been associated with poor outcomes including earlier progression to severe dementia, higher use of health care services, earlier institutionalization, increased care costs, and earlier death (Beeri et al. 2002, Herrmann et al. 2006, Peters et al. 2015, Farré et al. 2016, Toot et al. 2017). BPSD are also distressing to the caregiver, potentially impairing their well-being (Feast et al. 2016).

2.1.1 Treatment of behavioral and psychological symptoms of dementia

Several guidelines recommend non-pharmacological treatment options as first-line treatment approach for BPSD (NICE 2006, Zuidema et al. 2015, APA 2016, Memory disorders: Current Care Guidelines 2017). Persons with AD should be examined for potentially modifiable contributors to BPSD, some of which are described in Figure 1.

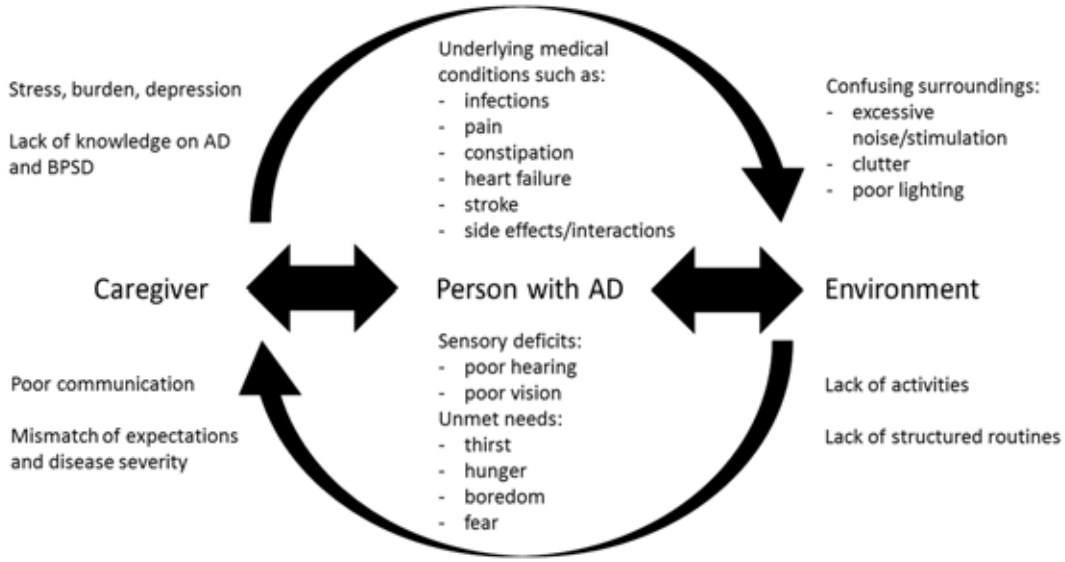

Figure 1. Some modifiable contributors to BPSD (adapted from Kales et al. 2015)

Non-pharmacological treatment interventions can target the person with AD, the caregiver and/or the environment (Kales et al. 2015). It is important that the patient should receive appropriate treatment of underlying medical conditions. In addition, non-pharmacological treatment can include strategies such as providing meaningful activities that match the patient's interest and capabilities, establishing daily routines, and simplifying the environment. Caregivers have a crucial role in recognizing situations that trigger BPSD and in implementing non-pharmacological treatment strategies. Interventions targeted to the caregiver could include providing education about BPSD and enhancing communication between the caregiver and the person with AD.

Acetylcholinesterase inhibitors (AChEIs) are the first-line treatment option for mild to moderate AD and memantine is recommended for the treatment of moderate to severe AD. (NICE 2011, Herrmann et al. 2013a, Rabins et al. 2014, Memory disorders: Current Care

Guidelines 2017). Guidelines differ on whether the combination of AChEIs and memantine is recommended for persons with moderate to severe AD due to unclear evidence of the efficacy of combination therapy. The pharmacotherapy of AD aims to stabilize or slow down the deterioration of cognitive function, enhance independence, maintain the ability to perform activities of daily living, and reduce BPSD (NICE 2011, Memory disorders: Current Care Guidelines 2017). However, the evidence of efficacy of AChEIs and memantine to treat BPSD is conflicting (Cummings et al. 2004, Howard et al. 2007, Gauthier et al. 2008, Fox et al. 2012, Herrmann et al. 2013b, Matsunaga et al. 2015). RCTs that primarily investigated the efficacy of AChEIs or memantine in the treatment of clinically significant agitation or aggression of AD found no improvement compared with placebo (Howard et al. 2007, Fox et al. 2012, Herrmann et al. 2013b). A 12-week open randomized trial compared the effects of galantamine and risperidone on BPSD and found that both treatments resulted in improved BPSD with no treatment differences being detected in several domains (Freund-Levi et al. 2014a). However, risperidone displayed a significant treatment advantage over galantamine on irritation and agitation (Freund-Levi et al. 2014a, 2014b). The authors concluded that due to its more favorable side effect profile, an AChEI such as galantamine could be used as a first-line pharmacological treatment for BPSD and modest agitation before the initiation of antipsychotic is considered (Freund-Levi et al. 2014a, 2014b). However, large randomized, double-blind, placebo-controlled trials are needed to elucidate and confirm these findings. Some guidelines have concluded that there is insufficient evidence to recommend routine use of AChEIs or/and memantine for the treatment of BPSD (Herrmann et al. 2013a, Rabins et al. 2014). On the other hand, the Finnish Current Care guideline on memory disorders states that appropriate treatment of AD with AChEIs or/and memantine is the first-line pharmacological treatment approach for BPSD (Memory disorders: Current Care Guidelines 2017).

In acute situations and when there is the risk of harm to the patient or others, psychotropic drugs may be considered (Kales et al. 2015). Psychotropics should not be used in the treatment of BPSD for which they are not efficacious i.e. wandering, hoarding, repetitive vocalizations, yelling, dressing/undressing and eating inedible objects (Kales et al. 2015, Memory disorders: Current Care Guidelines 2017). Considering all of the psychotropic drugs used in the treatment of BPSD, antipsychotics have the most convincing evidence in the treatment of agitation, aggression and psychosis (Kales et al. 2015), but even in these cases, their efficacy has been modest (Lonergan et al. 2002, Ballard et al. 2006, Maher et al. 2011). Randomized controlled trials have been criticized because the outcome measure has often been a change in overall behavioral rating scale and various different scales have been used in different trials making it difficult to evaluate the implication of the outcomes for clinical practice (Sink et al. 2005, Ballard et al. 2006). As the possible adverse effects may outweigh benefits of antipsychotic use, several guidelines recommend that antipsychotics should be used only in the treatment of severe psychotic symptoms and aggression when symptoms cause significant distress or harm to the patient or others (e.g. NICE 2006, Zuidema et al. 2015, APA 2016, Memory disorders: Current Care Guidelines 2017). Short-term use is highlighted as symptoms may resolve by themselves and on the other hand, antipsychotics may cause serious adverse events. Depending on the guidelines, it is recommended that use should be regularly reviewed every three to six months and withdrawal should be attempted after a period of behavioral stability. A guideline recently issued by the American Psychiatric Association (APA 2016) recommends that antipsychotics should be withdrawn if there is no clinically significant response after a 4-week treatment. If there is an adequate response, an attempt of withdrawal should be made within 4 months after initiation of use unless previous attempts have led to recurrence or worsening of symptoms. According to a Cochrane review, antipsychotics can be successfully withdrawn in many older persons with AD (Declercq et al. 2013). However, a relapse of symptoms may occur after withdrawal in some persons with more severe BPSD responding well to antipsychotics.

Management of BPSD is challenging and the evidence of benefits of different treatment options should be always weighed against the potential risk of harms (Kales et al. 2015). There is very limited evidence for either efficacy or safety of other psychotropic drugs as alternatives to antipsychotics (Rabins et al. 2014, Kales et al. 2015). Seitz et al. (2011) conducted a Cochrane review and found a few studies of antidepressants for the treatment of agitation and psychosis in persons with dementia. In two of the included studies, the selective serotonin re-uptake inhibitors (SSRIs) sertraline and citalopram were associated with a modest reduction in agitation when compared with placebo. It was concluded that more studies with larger sample sizes would be needed to determine whether antidepressants are safe and effective in the treatment of agitation and psychosis in dementia. Based on the study of Porsteinsson et al. (2014) citalopram may reduce agitation at a dose of 30 mg per day but QT prolongation and possible cognitive adverse effects may limit its usability. In fact, in 2011 the product information of citalopram was updated and the maximum recommended dose for older persons was reduced to 20 mg/day due to the risk of QT prolongation and citalopram is not recommended for patients with pre-existing risk factors for QT prolongation (EMA 2011, FDA 2012). High quality randomized controlled trials on efficacy of benzodiazepines and related drugs to treat BPSD are lacking (Rabins et al. 2014, Kales et al. 2015). Due to adverse events such as excessive sedation, dizziness, falls, possible worsening of cognition and target behavior, benzodiazepines are only recommended to be used in as-needed basis in acute situations (Rabins et al. 2014, Kales et al. 2015). Valproate has not been shown to be effective in the treatment of agitation and psychosis (APA 2007, Rabins et al. 2014). It has been reported that carbamazepine may have modest efficacy for agitation but it is not recommended for routine use due to weak evidence and risks of drug-drug interactions and poor tolerability in long-term use (Rabins et al. 2014).

2.2 ANTIPSYCHOTIC USE AMONG COMMUNITY DWELLERS WITH DEMENTIA

Persons with dementia are approximately 5 to 7 times more likely to use antipsychotics than persons without dementia (Laitinen et al. 2011, Schulze et al. 2013a, Gallini et al. 2014, Taipale et al. 2014a, Wastesson et al. 2015, Nørgaard et al. 2016). The annual prevalence of antipsychotic use among community dwellers with dementia has varied between studies from 18% to 26% depending on the study population, country, study period, data source and methods used to measure antipsychotic use (Laitinen et al. 2011, Franchi et al. 2012, Rattinger et al. 2013, Schulze et al. 2013a, Boucherie et al. 2017). Most studies have reported the prevalence of antipsychotic use among persons with any dementia without specifying the type of dementia. However, there is evidence that the prevalence of antipsychotic use differs according to the subtype of dementia (Calvó-Perxas et al. 2012, Johnell et al. 2013). In two previous studies, antipsychotic use was most common among those with dementia with Lewy bodies (Calvó-Perxas et al. 2012, Johnell et al. 2013). In addition, in a Swedish study, individuals with AD or mixed AD/vascular dementia were less likely to use antipsychotics at the time of diagnosis than persons with other subtypes of dementia (Johnell et al. 2013).

Several studies have assessed trends in the prevalence of antipsychotic use among persons with dementia; some of the results are described in Table 2. The results and magnitude of changes vary depending on the country, population, study period, and initial frequency of antipsychotic use. In Finland, there was a slight increase in the prevalence of overall antipsychotic use among community dwellers with incident AD (Taipale et al. 2014a). Among persons with prevalent dementia, a decline in the prevalence was observed in some studies for example in the UK (Sultana et al. 2016a, Donegan et al. 2017), the Netherlands (Sultana et al. 2016b), Denmark (Nørgaard et al. 2016), France (Gallini et al. 2014) and US (Kales et al. 2011). However, the declining trend was not necessarily consistent throughout the whole study period as there was temporal increases and decreases in antipsychotic use

(Guthrie et al. 2013, Sultana et al. 2016a). In a regional study from Italy, the prevalence of overall antipsychotic use declined during 2002-2008 (Franchi et al. 2012) whereas in a nationwide study prevalence substantially increased between 2000 and 2012 (Sultana et al. 2016a). On the contrary, in a German study, the prevalence remained stable (Schulze et al. 2013b).

Trends for use of atypical, conventional and individual antipsychotics differed in many studies from the trend for overall antipsychotic use (Table 2). In the UK and Italy, the first safety warnings led to a decline in the use of risperidone and olanzapine but an increased use of quetiapine and conventional antipsychotics was observed (Sultana et al. 2016a). In studies from Germany, France, Finland, and Denmark, the use of atypical antipsychotics increased whereas the use of conventional antipsychotics decreased over time (Schulze et al. 2013b, Gallini et al. 2014, Taipale et al. 2014a, Nørgaard et al. 2016).

At present, Martinez et al. (2013) is the only study that has described the prevalence of antipsychotic use up to ten years before and four years after the date of incident dementia diagnosis. They found that antipsychotic use increased from 2.2% 10 years prior to the dementia diagnosis up to 5.1% up until one year preceding diagnosis. On the date of dementia diagnosis, the prevalence of antipsychotic use was 11.1% and it increased further to 18.7% at four years after the diagnosis.

Table 2. Changes in prevalence of antipsychotic use among persons with dementia living in the community or mixed residential settings

Reference	Country	Residential setting	N	Definition and measures of antipsychotic use	Study year (measurement point)	Prevalence according to study years		
						Any AP	CAPs	AAPs
Nørgaard et al. 2016	Denmark	Mixed, 49% NH in 2012	19,062 (2000) 34,553 (2012)	Annual prevalence ≥1 AP dispensation	2000 2004 2012	31.3% 20.4%	21.2% 10.3% 4.5%	13.4% 22.0% 17.3%
Schulze et al. 2013b	Germany	Mixed	3,460 (2004) 8,042 (2009)	Annual prevalence ≥1 AP dispensation	2004 2009	35.5% 32.5%	27.2% 23.0%	17.1% 18.9%
Taipale et al. 2014a	Finland	Community-dwelling	69,080	Annual prevalence within a year after diagnosis of incident AD ≥1 AP dispensation	2005 2011	18.4% 19.7%	3.5% 1.5%	16.1% 19.0%
Franchi et al. 2012	Lombardy region, Italy	Community-dwelling	2,590 (2002) 4,621 (2008)	Annual prevalence ≥1 AP dispensation	2002 2008	24.2% 18.1%	3% 5%	21.0% 14.6%
Sultana et al. 2016a	Italy	Mixed	10,857	Quarterly prevalence ≥1 AP prescription	Q1 2000 Q1 2004 Q1 2009 Q4 2012	7% 11% 21% 32%	~6% ~6% ~9% ~14%	~3% ~5% ~11% ~18%
Sultana et al. 2016a	UK	Mixed	58,497	Quarterly prevalence ≥1 AP prescription	Q1 2000 Q1 2004 Q1 2009 Q4 2012	7% 10% 15% 11%	~6% ~3% ~5% ~3%	~2% ~8% ~11% ~9%
Donegan et al. 2017	UK	Mixed	19,635 (2005) 25,925 (2015)	Quarterly prevalence ≥1 AP prescription	2005 2015	22.1% 11.4%	9.4% 1.9%	13.6% 9.7%
Guthrie et al. 2013	Scotland	Mixed	1,912 (Q1 2001) 3,478 (Q1 2011)	Quarterly prevalence ≥1 AP prescription	Q1 2001 Q1 2009 Q1 2011	15.9% 18.4% 13.5%		
Sultana et al. 2016b	Netherlands	Community-dwelling	14,396	Quarterly prevalence ≥1 AP prescription	Q1 2008 Q4 2013	13% 8%	10% 6%	4% 3-4%
Kales et al. 2011	US	Community-dwelling	254,654 (3% female)	Quarterly prevalence ≥1 AP prescription	Q1 1999 Q1 2007	17.7% 12%	7.8% ~1%	10.7% ~11%
Gallini et al. 2014	France	Mixed but no data on AP use in NH	7,169	Monthly prevalence ≥1 AP dispensation	2003 2011	14.2% 10.2%	~11% ~5%	~3% ~5%

AD=Alzheimer's disease; AP=antipsychotic drug, AAP=atypical antipsychotic, CAP=conventional antipsychotic; Mixed=both community dwellers and individuals residing in institutional settings, NH=nursing home; Q=quarter, ~ =rough estimate of the prevalence

2.2.1 Persistence of antipsychotic use

Three studies have reported the persistence of antipsychotic use for community dwellers with dementia (Table 3). In a French study (Boucherie et al. 2017), 28% used antipsychotics for at least three months and were defined as long-term users. However, when hospital periods were included into the exposure time, the proportion of long-term antipsychotic users increased to 46%. When using data from the US Department of Veterans Affairs, Kim et al. (2015) similarly reported that 36% continued using the same antipsychotic drug for three months whereas 55% discontinued the use of these drugs. In contrast, a German study found a higher proportion of persistent use and reported that 76% of antipsychotic users living in the community continued drug use for at least six months and 55% for at least two years (Booker et al. 2016). In that study, the proportions of persistent users were higher for nursing home residents. In addition to possible differences in treatment practices between the three countries, differences in the results could be explained by varying methods used to define and measure persistent antipsychotic use. The German study was based on prescriptions from psychiatrists and defined discontinuation as at least 180 days without antipsychotic therapy (Booker et al. 2016). Whereas, the two other studies defined discontinuation more strictly as a gap longer than 7 days (Kim et al. 2015, Boucherie et al. 2017). Thus, the persistence of antipsychotic use might be overestimated in the German study and underestimated in the studies from US and France.

In addition to these three studies, five studies reported the persistence of antipsychotic use for persons with dementia living in mixed residential settings but did not report the results by residence (Table 3). The majority of study participants were most likely community dwellers but the proportion of nursing home residents was not reported in some of these studies (Guthrie et al. 2010, Mast et al. 2016). Three studies (Guthrie et al. 2010, Puyat et al. 2012, Mast et al. 2016) reported almost as high a proportion of persistent use as described in the German study (Booker et al. 2016). The proportions of antipsychotic users who continued antipsychotic use for over six months were 63% (Puyat et al. 2012) and 72% (Guthrie et al. 2010) in studies from Canada and the UK, respectively. Similarly, a more recent Canadian study (Mast et al. 2016) reported that 24% had discontinued use six months after initiation of antipsychotic use and 49% had stopped after two years. However, studies by Puyat et al. (2012) and Guthrie et al. (2010) did not consider discontinuation of use in their definitions for duration of antipsychotic use and included also prevalent users. On the other hand, Mast et al. (2016) included only new users but required them to have at least two dispensings of antipsychotics which by definition increases the number of persistent users.

The lowest proportions of persistent use was reported in studies with the most strict definitions and measures for duration and continuity of use (Kim et al. 2015, Nørgaard et al. 2016, Schmedt et al. 2016a, Boucherie et al. 2017). Two of these studies considered discontinuation as a gap longer than seven days (Kim et al. 2015, Boucherie et al. 2017). Nørgaard et al. (2016) used the assumption that one Defined Daily Dose (DDD) is equal to one day of treatment and defined duration as the sum of DDDs purchased during a year (Nørgaard et al. 2016). In contrast, Schmedt et al. (2016a) added 150% of the dispensed amount of DDDs to each antipsychotic prescription i.e. duration was calculated as *X DDDs + 1.5* X DDDs*. However, using the dose assumption of 1 DDD per day and even 0.4 DDD per day may have led to an underestimation of duration of use and persistent use as antipsychotics are often used with much lower doses in older persons (Rikala et al. 2013) and persons with AD (Taipale et al. 2014b). The two studies from Germany with different definitions, measures and data sources led to conflicting results. Schmedt et al. (2016a) reported that the median persistence among persons with dementia was 16 days and the median number of treatment episodes was 4. This differs from the results of Booker et al. (2016) who reported that 76% of users continued drug use for at least 6 months. These conflicting results illustrate that the methods used to define and measure persistent antipsychotic use can have a substantial impact on the reliability and comparability of the

results. In addition, Boucherie et al. (2017) demonstrated how different ways to handle hospital periods can affect the results. It is evident that more research is needed on the persistence of antipsychotic use among community dwellers with AD with specific focus on the methods used to define and measure continuous use.

Table 3. Persistence of antipsychotic use among persons with dementia living in the community or mixed residential settings

Reference, country	Years of data collection, setting	N	Age, sex	Definition and measures of antipsychotic use	Persistence of antipsychotic use
Boucherie et al. 2017 France	2009-2012, community dwellers	33,041 (2012)	43.1% aged ≥85 years, 72.7% female	Long-term use = over 3 months of successive use Discontinuation = time between dispensings over 35 days	Proportion of long-term users 27.6% excluding hospital periods 46.3% including hospital periods
Booker et al. 2016 Germany	2009-2015, Mixed, 52.1% NH but reports results by residence	12,979	≥60 years, mean age 82, 66.5% female	New users = First prescription from psychiatrist Discontinuation = at least 180 days without APs Drug supply calculated based on quantity and dosage information	Community dwellers used APs for ≥6 months 76.2% ≥2 years 55.0% NH residents used APs for ≥6 months 82.6% ≥2 years 63.9%
Kim et al. 2015 US	2005-2008, community dwellers	15,435	≥65 years, mean age 80.6, 2.3% female	New users identified with 1-year washout period Discontinuation = gap longer than 7 days	54.6% discontinued within 3 months, 36.0% continued using the same AP, 3.3% died while on index treatment, 6.2% changed to another psychotropic
Mast et al. 2016 Canada	2009-2013, Mixed	46,695	≥66 years, median age 84, 62% female	New users identified with 1-year washout period, at least 2 dispensings required Discontinuation = time between dispensings over 180 days	Cumulative % of those who had discontinued treatment after 6 months 24.4% after 1 year 35.1 % after 2 years 49.1%
Nørgaard et al. 2016 Denmark	2000-2012, Mixed, 49.4% NH in 2012	19,062 (2000) 34,553 (2012)	≥65 years, median 82.2-83.3 65-68% female	Duration of use = 1 DDD refers to 1 day of treatment Long-term use = over 12 weeks	Proportion of long-term users 18.1% in 2000 27.3% in 2012
Schmedt et al. 2016a Germany	2005-2011, Mixed, 7.6-15.3% NH	298,847 with and without dementia	≥65 years, mean age 78, 67.7% female	New users identified with 1-year washout period Duration of use = X DDDs + 1.5* X DDDs	Users with dementia showed a higher median number of treatment episodes (4 vs. 2) and a lower median persistence of use (16 vs. 20 days)
Puyat et al. 2012 Canada	2005 Mixed, 23.3% LTC	33,633	≥65 years, 60.3% female	Filled ≥1 prescriptions for APs in 2005 Duration = accumulated number of days' supply	Used APs for >6 months 62.6%
Guthrie et al. 2010 UK	2006-2007, Mixed	10,058	≥65 years, 70.3% female	Duration = interval between first and last recorded prescriptions for the drug currently being prescribed Prolonged = prescribed for >16 or 24 weeks before the most recent prescription	Current and same AP for >4 months 79.4% for >6 months 72.0% Median duration 293 days

AP=antipsychotic drug; LTC=long-term care residents, Mixed=both community dwellers and individuals residing in institutional settings, NH=nursing home; DDD=Defined Daily Dose

2.3 SERIOUS ADVERSE EVENTS ASSOCIATED WITH ANTIPSYCHOTIC USE

Several studies have investigated the association between antipsychotic use and serious adverse events such as cerebrovascular events, myocardial infarction, venous thromboembolism, pneumonia, hip fracture and death (Sacchetti et al. 2010, Mittal et al. 2011, Barbui et al. 2014, Nosè et al. 2015, Yu et al. 2016, Lee et al. 2017). Due to the low number of studies focusing on individuals diagnosed with AD or any type of dementia, this present literature review regarding the risk of serious adverse events associated with antipsychotic use included also studies conducted among older people in general. The literature review was restricted to studies published since the year 2000 as the launch of risperidone, olanzapine and quetiapine after the mid-1990s resulted in a major change away from the conventional antipsychotics towards the atypical antipsychotics.

2.3.1 Risk of hip fracture associated with antipsychotic use

Antipsychotic use is a known risk factor for falling (Woolcott et al. 2009). Thus, antipsychotic use could also increase the risk of falling related injuries, including the risk of hip fracture. Studies related to the association between antipsychotic drug use and risk of hip fracture are summarized in Tables 4 and 5. All studies comparing antipsychotic users with nonusers found an association between antipsychotic use and increased risk of hip fracture. The risk of hip fracture was similar among users of atypical and conventional antipsychotic drugs when users were compared with nonusers (Liperoti et al. 2007, Bakken et al. 2016). According to studies comparing users of conventional and atypical antipsychotics directly, the risk of hip fracture is similar (Rigler et al. 2013) or perhaps slightly higher (Huybrechts et al. 2011a, Huybrechts et al. 2012a) among conventional antipsychotic users than among atypical antipsychotic users. Three studies reported the risk of hip fracture separately for the most frequently used antipsychotic drugs (Liperoti et al. 2007, Jalbert et al. 2010, Leach et al. 2015) and two new-user cohort studies conducted direct drug-drug comparisons (Rigler et al. 2013, Huybrechts et al. 2012a). Rigler et al. (2013) found no differences in the hip fracture risk between individual antipsychotic drugs when risperidone (n=2,231), olanzapine (n=620) and quetiapine (n=165) users were compared with haloperidol users (n=454). However, the number of users of individual antipsychotics was small, limiting the power to detect differences. According to Huybrechts et al. (2012a), the risk of hip fracture was similar among olanzapine (n=25,068), aripiprazole (n=1,989) and ziprasidone (n=1,158) users compared with risperidone users (n=30,945). However, they concluded that quetiapine users (n=17,336) possibly displayed a slightly higher risk of hip fracture compared with risperidone users (high-dimensional propensity score adjusted HR 1.17; 95% CI 0.96-1.43).

Two studies analyzed the dose-response relationship for risk of hip fracture (Huybrechts et al. 2012a, Rigler et al. 2013). Rigler et al. (2013) found that every 100 mg dose increase in chlorpromazine equivalents tripled the risk of hip fracture (HR 2.96; 95% CI 1.33-6.57). A dose increase of 100 mg in chlorpromazine equivalents corresponds to 2 mg of risperidone, 2 mg of haloperidol, 5 mg of olanzapine or 75 mg of quetiapine. Huybrechts et al. (2012a) reported that use of antipsychotics with doses >50 mg chlorpromazine equivalents was associated with a higher risk of hip fracture compared with a dose of ≤50 mg (high-dimensional propensity score adjusted HR 1.28; 95% CI 1.10-1.49). The results were similar when dose-analyses were restricted to atypical antipsychotic users.

Three studies analyzed the risk of hip fracture according to the duration of antipsychotic use, with varying results (Tables 4 and 5). The case-control study by Jalbert et al. (2010) did not find any increased risk with less than six months of antipsychotic use among nursing home residents with dementia. However, the use of antipsychotics for 6-12 months or >12 months was associated with a higher risk of hip fracture compared with nonusers. On the contrary, in the self-controlled case-series analysis of Pratt et al. (2011), the risk of hip fracture

was highest during the first week after initiation of atypical antipsychotic use and although it attenuated, it remained significant with >3 months of continuous use. Similarly, the risk of hip fracture was increased after one week of initiation of conventional antipsychotic use and remained significantly higher with >3 months of continuous use. In a cohort study of primary care patients diagnosed with dementia and their matched controls, antipsychotic use was associated with an increased risk of hip fracture when used for less than one month but decreased the risk of hip fracture when used for more than ten months (Bohlken et al. 2015). These conflicting results might be explained by potential biases in study designs. In addition, the case-control study by Jalbert et al. (2010) included a small number of short-term users and therefore chance, selection and limited power could explain why they did not detect any risk during short-term use. Both Jalbert et al. (2010) and Bohlken et al. (2015) included prevalent users causing under-detection of hip fractures occurring soon after the initiation of antipsychotic use. Bohlken et al. (2015) did not clearly describe the definition of exposure to antipsychotics in the methods section of their article. Although the three-year follow-up for hip fractures started from the index date, it seemed that the exposure to antipsychotics was based on prescriptions prior to the index date and the number of prescriptions corresponded to months of use. This may have caused exposure misclassification as the use of antipsychotics might have changed (discontinued/ initiated/ continued) during the three-year follow-up. In addition, survival bias could explain the decreased risk of hip fracture among those with more than ten prescriptions. Defining duration of prior drug use at the start of follow-up leads to bias, as these prevalent users are survivors and do not include users whose duration of use is comparable but discontinued use because of adverse events before the study follow-up (Ray 2003). Thus, these results should be interpreted with caution.

In summary, the methods and methodological quality of the studies have varied substantially. Five studies applied a washout period for previous antipsychotic use and included only new users of antipsychotics (Table 4). The length of the washout period was 2 months (Rigler et al. 2013), 6 months (Huybrechts et al. 2011a, Huybrechts et al. 2012a, Fraser et al. 2015) or 12 months (Pratt et al. 2011). In addition, Bakken et al. (2016) conducted a sensitivity analysis for recently started antipsychotic use including the first 14 days of antipsychotic use after a 360-day washout period. Other studies may be skewed by prevalent user bias (Ray 2003, Schneeweiss 2010). If many prevalent users are included, the result may be an underestimate of the risk because adverse events occurring soon after treatment initiation will not be quantified. Two studies (Kolanowski et al. 2006, Bohlken et al. 2015) had poor methodological quality due to susceptibility to both prevalent user bias and exposure misclassification. In both of these studies, the measurement of exposure to antipsychotics was not clearly described in relation to the follow-up for hip fracture. It seemed that in the report of Kolanowski et al. (2006), the exposure group was classified based on antipsychotic prescriptions at any time during the three-year follow-up and the odds ratio for hip fracture was calculated based on hip fractures occurring at any time during the follow-up. Thus, in addition to possible misclassification of exposure time, it was unclear whether the outcome could have occurred before the exposure. Kolanowski et al. (2006) also had a small number of antipsychotic users (n=259), limiting the power of the study to detect risk of hip fracture among users of different antipsychotic groups.

All studies included some amount of exposure misclassification as prescribed or purchased antipsychotics are not necessarily always actually taken by the patient. Bakken et al. (2016) used a time-varying exposure to antipsychotics and exposure periods were calculated with the assumption of dose of 0.5 DDD per day. This strict fixed assumption of dose may have caused misclassification of exposure time as antipsychotics are used with varying doses and frequently at doses lower than 0.5 DDD per day among older persons (Rikala et al. 2013) and persons with AD (Taipale et al. 2014b). This has probably lead to misclassification of exposed time as nonexposed time. In addition, Bakken et al. (2016) did not censor the follow-up if persons were admitted to nursing homes or hospitals although they did not have data on drugs used in these institutional settings. Due to these

misclassifications of antipsychotic exposure time as nonexposed time, the risk estimates reported by Bakken et al. (2016) should be considered as conservative.

The association between antipsychotic use and hip fracture could be confounded by indication. BPSD such as agitation could increase the risk of falling and subsequent fractures. In addition, cognitive and physical functioning could affect both risk of hip fracture and prescribing of antipsychotics. If these factors are not controlled, the result may be an overestimation of the association between antipsychotic use and hip fracture. The possibility of confounding by indication might be larger in studies that included both persons with and without dementia, as dementia is a risk factor for hip fracture (Baker et al. 2011, Tolppanen et al. 2016b) and antipsychotics are more frequently used among persons with dementia than those without it (Laitinen et al. 2011, Taipale et al. 2014a). Three studies focused on persons diagnosed with dementia (Kolanowski et al. 2006, Jalbert et al. 2010, Dennis et al. 2017). Four studies did not report the prevalence of dementia in the study population (Wang et al. 2001, Pratt. et al. 2011, Leach et al. 2015, Bakken et al. 2016) and in the rest of the studies, the dementia prevalence varied from 43% (Liperoti et al. 2007) to 75% (Huybrechts et al. 2012a). However, Fraser et al. (2015) and Rigler et al. (2013) matched antipsychotic users and nonusers with propensity scores which resulted in well-balanced groups with equal prevalence e.g. of dementia. Rigler et al. (2013) and Huybrechts et al. (2012a) had data on functional, cognitive and behavioral performance which are often lacking from register-based studies. The results of comparative safety of atypical and conventional antipsychotics as well as individual antipsychotics were similar in stratified analyses with respect to the presence of dementia, behavioral disturbances or delirium (Huybrechts et al. 2012a).

Two studies used a within-person study design to control unmeasured confounding due to patient-specific factors such as cognitive and physical impairment, disease severity and lifestyle factors that remain constant over the study period (Pratt et al. 2011, Leach et al. 2015). However, these designs cannot remove confounding by factors that vary over short periods of time including changes in BPSD. Pratt et al. (2011) found that the risk of hip fracture was highest in the week preceding conventional antipsychotic initiation (IRR 10.99; 95% CI 7.94-15.21) but not prior to atypical antipsychotic initiation (IRR 2.83; 95% CI 2.09-3.85) which most likely reflects selective prescribing following a hip fracture. Case-only designs are most suitable for studying acute risks of accurately recorded transient exposures (Maclure et al. 2012). The case-crossover design used by Leach et al. (2015) includes only intermittent users and is not suitable for estimating the hip fracture risk associated with long-term antipsychotic use. If long-term use is frequent, applying this design can also cause selection bias as only those that need to change their medication are included (de Groot et al. 2016). On the other hand, the self-controlled case-series design assumes that the outcome event does not affect the probability of exposure nor the length of the observation period (Farrington et al. 2011, Maclure et al. 2012). Pratt et al. (2011) used a pre-initiation period to account for the former but could not evaluate whether the occurrence of hip fracture affected the observation period.

Five studies were restricted to residents of nursing homes (Liperoti et al. 2007, Jalbert et al. 2010, Huybrechts et al. 2011a, Huybrechts et al. 2012a, Rigler et al. 2013), one to community dwellers (Kolanowski et al. 2006) and others included both community dwellers and individuals residing in institutional settings. However, in all of these studies with mixed residential settings, the majority of study populations consisted of community dwellers.

In conclusion, antipsychotic use has been associated with an increased risk of hip fracture among older persons with and without dementia living in various settings. However, none of the studies focused on community-dwelling persons with AD. More information is needed on hip fracture risk in relation to the duration of antipsychotic use as the results of previous studies were conflicting and only one study reported the risk in long-term use (>365 days of use) (Jalbert et al. 2010). Furthermore, only one study (Huybrechts et al. 2012a) had adequate number of users to compare the risk of hip fracture between individual antipsychotic drugs. Thus, more research is needed on the comparative safety of individual antipsychotics.

Table 4. Summary of studies with new-user design focused on association of antipsychotic use with hip fracture among older people

Reference, country	Study design	Years of data collection, follow-up	Study population				Hazard ratio (HR) or other risk measures (95% CIs)
			N	Age, sex	Residential setting	Dementia	
Fraser et al. 2015 Canada	Exposure-matched new-user cohort	2003-2011, 90 days ITT	97,777 AAP users 97,777 nonusers	≥65 years, mean 81, 65% female	Mixed, LTC 23.9% in both groups	53.9% in both groups	AAP vs. nonuse OR 1.67 (1.53-1.81)
Rigler et al. 2013 US	Exposure-matched new-user cohort	1999, 1-293 days, mean 93 days	4,131 AP users 4,131 nonusers	≥65 years, 72% female	NH	61% in both groups	Any AP vs. nonuse HR 1.76 (1.08-2.87) AAP vs. CAP HR 0.79 (0.39-1.63)
Huybrechts et al. 2012a US	New-user cohort	2001-2005, max 180 days	83,959	≥65 years, mean 83, 75% female	NH	75.0% AAP 70.3% CAP	CAPs vs. AAPs HR 1.29 (0.95-1.76)
Huybrechts et al. 2011a Canada	New-user cohort	1996-2006, max 180 days	1,942 AAP users 1,902 CAP users	≥65 years, mean 84, 57% female	NH	56.2% AAP 49.8% CAP	CAPs vs. AAPs As treated IRR 1.49 (0.93-2.41) ITT IRR 1.12 (0.77-1.62)
Pratt et al. 2011 Australia	Self-controlled case-series with new-users	2005-2008, max 4 years	8,234 cases	≥65 years, median 86, not reported	not reported	not reported	CAP vs. nonuse[a] 1 week IRR 1.04 (0.40-2.70) 2-8 weeks IRR 2.23 (1.65-3.02) 9-12 weeks IRR 1.79 (1.12-2.84) >12 weeks IRR 2.19 (1.62-2.95) AAP vs. nonuse[a] 1 week IRR 2.17 (1.54-3.06) 2-8 weeks IRR 1.27 (1.04-1.55) 9-12 weeks IRR 1.23 (0.92-1.63) >12 weeks IRR 1.43 (1.23-1.66)
Bakken et al. 2016 Norway	Nationwide cohort, time-varying exposure	2004-2010, max 6 years	906,422	≥60 years, mean 73, 56% female	Mixed, although no data on AP use during hospital or NH stay	Not reported	Any AP vs. nonuse SIR 2.1 (1.9-2.2) CAPs vs. nonuse SIR 2.0 (1.8-2.2) AAPs vs. nonuse SIR 2.2 (1.9-2.4) Recently started AP use SIR 1.8 (1.3-2.4)

AP=antipsychotic drug, AAP=atypical antipsychotic, CAP=conventional antipsychotic; LTC=long-term care residents, Mixed=both community dwellers and individuals residing in institutional settings, NH=nursing home; IRR=incidence rate ratio, ITT=intention-to-treat, OR=odds ratio, SIR=standardized incidence ratio

[a] 'Nonuse' included un-exposed person-time over 20 weeks prior to the initiation of AP use and possible remaining person-time after discontinuation of AP use.

Table 5. Summary of other studies focused on association of antipsychotic use with hip fracture among older people

Reference, country	Study design	Years of data collection, follow-up	Study population				Hazard ratio (HR) or other risk measures (95% CIs)
			N	Age, sex	Residential setting	Dementia	
Leach et al. 2015 Australia	Case-crossover	2008-2012, 45-day case and control windows[a]	8,828 cases	≥65 years, median 88, 63% female	Mixed, LTC 36%	Not reported	Any AP vs. nonuse OR 1.47 (1.21-1.80)
Jalbert et al. 2010 US	Nested case-control	2001-2002	764 cases 3,582 controls	≥65 years, mean 83, 74% female	NH	All had diagnosis of dementia	Current AP vs. nonuse OR 1.26 (1.05-1.52) Past AP vs. nonuse OR 0.98 (0.68-1.42) Duration of AP use vs. nonuse <90 days Not applicable 91-180 days OR 0.95 (0.49-1.85) 181-365 days OR 1.44 (1.07-1.93) >365 days OR 1.32 (1.11-1.67)
Liperoti et al. 2007 US	Case-control	1998-1999	1,787 cases 5,606 controls	≥65 years, mean 83, 76% female	NH	49.7% cases 43.3% controls	AAPs vs. nonuse OR 1.37 (1.11-1.69) CAPs vs. nonuse OR 1.35 (1.06-1.71)
Wang et al. 2001 US	Case-control	1993-1995	1,222 cases 4,888 controls	≥65 years, mean 82, 84% female	Mixed NH 20-32%	Not reported	Any AP vs. nonuse OR 1.61 (1.29-2.01)
Dennis et al. 2017 UK	Cohort	2003-2011, max 2 years	9,674	≥65 years, mean 82, 67% female	Mixed	All had diagnosis of dementia	Any AP vs. nonuse PERR 1.62 (1.59-1.65)
Bohlken et al. 2015 Germany	Cohort	2010-2015, max 3 years	53,156 dementia patients 53,156 matched controls	65-90 years, mean 81, 61% female	Mixed, NH 18.2% of dementia patients, NH 3.2% of controls	Primary care patients newly diagnosed with dementia 2010-2013	Duration of AP use vs. nonuse 1 month HR 1.20 (1.01-1.41) 2 months HR 1.17 (0.94-1.47) 3-5 months HR 1.19 (0.99-1.42) 6-10 months HR 0.97 (0.78-1.20) >10 months HR 0.75 (0.62-0.91)
Kolanowski et al. 2006 US	Cohort	1998-2001, max 3 years	959	≥45 years, mean 75, 58% female	Community-dwelling	All had diagnosis of dementia	AAP vs. nonuse OR 1.47 (0.82-2.65) CAP vs. nonuse OR 2.33 (1.08-5.03) Both AAP and CAP OR 2.64 (1.04-6.72)

AP=antipsychotic drug, AAP=atypical antipsychotic, CAP=conventional antipsychotic; Mixed=both community dwellers and individuals residing in institutional settings, NH=nursing home; IRR=incidence rate ratio, OR=odds ratio, PERR=prior event rate ratio

[a] Primary case window 1-45 days preceding the hip fracture and a primary control window 91-135 days before the hip fracture.

2.3.2 Risk of mortality associated with antipsychotic use

The first warnings of an increased risk of mortality among atypical antipsychotic users with dementia were issued in 2005 (FDA 2005). The warning was based on data from 17 placebo-controlled trials including a total of 5,106 patients with dementia related behavioral disorders. The mortality risk was 1.6 to 1.7 times higher among patients treated with atypical antipsychotics compared with placebo-treated patients. The specific causes of death were cardiovascular events such as heart failure and sudden cardiac death, and infections mainly pneumonia. In 2008, the warnings were expanded to cover conventional antipsychotics (FDA 2008, EMA 2008) as evidence from observational studies indicated that the risk of mortality was likely to be similar or higher among conventional antipsychotic users compared with atypical antipsychotic users (Gill et al. 2007, Schneeweiss et al. 2007). This literature review regarding the association between antipsychotic use and risk of mortality included studies conducted with new-user design which did not require survival after initiation of antipsychotic use. These criteria were applied to ensure that the results were not biased by selection of survivors that were able to tolerate the antipsychotic drug (Ray 2003, Suissa 2007, Schneeweiss 2010). Studies that fulfilled these inclusion criteria are summarized in Tables 6 and 7.

Since these warnings were issued, several studies have assessed the difference in mortality risk between conventional and atypical antipsychotic drugs (Table 6). All studies except Kales et al. (2007) found a higher risk of mortality associated with conventional antipsychotics. Two studies were restricted to patients diagnosed with dementia (Gill et al. 2007, Kales et al. 2007). In the rest of the studies, the prevalence of dementia varied from 9% to 71% among users of conventional antipsychotics and from 12% to 76% among users of atypical antipsychotics. Three of these studies conducted stratified analyses according to dementia status and consistently found a higher risk of mortality among users of conventional antipsychotics compared with atypical antipsychotic users irrespective of dementia status (Wang et al. 2005, Schneeweiss et al. 2007, Huybrechts et al. 2011a). Similar results have been reported in studies either restricted to residents of nursing homes (Huybrechts et al. 2011a, Huybrechts et al. 2011b, Aparasu et al. 2012) or to community dwellers (Sikirica et al. 2014, Jackson et al. 2015). In addition, two studies conducted stratified analyses by nursing home residence and consistently found higher risk of mortality associated with conventional antipsychotics (Wang et al. 2005, Schneeweiss et al. 2007).

Kales et al. (2007) reported that antipsychotic users had a higher risk of mortality than users of other psychotropic drugs (antidepressants, anticonvulsants, anxiolytics/hypnotics) but in contrast to other studies (Table 6), they found no difference in mortality risk between users of atypical and conventional antipsychotics. This contrasting finding might be explained by differences in study designs and populations. Kales et al. (2007) had the lowest number of conventional antipsychotic users (n=353), the population was predominantly male, and they followed new users for 12 months after initiation of use without censoring at discontinuation (intention-to-treat approach). In most of the other studies, the follow-up lasted for 180 days (Table 6). Four studies reported the difference in mortality risk between conventional and atypical antipsychotics by duration of use (Wang et al. 2005, Gill et al. 2007, Schneeweiss et al. 2007, Aparasu et al. 2012). In these studies, conventional antipsychotics were associated with the highest increase in mortality during the first 40 days of use (Wang et al. 2005, Schneeweiss et al. 2007, Aparasu et al. 2012) but the risk difference persisted up to 180 days of use (Wang et al. 2005, Gill et al. 2007, Schneeweiss et al. 2007, Aparasu et al. 2012). However, Kales et al. (2007) reported that they found no evidence for increasing or decreasing risks or differential risks across drug groups over time.

Several studies have indicated that instead of group differences, the risk of mortality might be different between individual antipsychotic drugs (Table 7). In drug-drug comparisons, haloperidol has been associated with higher mortality compared with risperidone (Schneeweiss et al. 2007, Huybrechts et al. 2012b, Kales et al. 2012, Vasilyeva et al. 2013,

Gerhard et al. 2014, Sahlberg et al. 2015, Schmedt et al. 2016b) and olanzapine (Hollis et al. 2007a, Hollis et al. 2007b). In contrast, quetiapine has been associated with lower mortality as compared with risperidone (Huybrechts et al. 2012b, Kales et al. 2012, Gerhard et al. 2014, Sahlberg et al. 2015, Schmedt et al. 2016b). The results with regard to olanzapine are conflicting. Four studies did not find any difference in the mortality risk between olanzapine and risperidone (Schneeweiss et al. 2007, Huybrechts et al. 2012b, Kales et al. 2012, Sahlberg et al. 2015). However, three studies (Hollis et al. 2007a, Hollis et al. 2007b, Schmedt et al. 2016b) found a lower risk for olanzapine as did Gerhard et al. (2014) after adjusting for dose. There is less evidence of mortality risk differences between the other individual antipsychotic drugs. Chlorpromazine, levomepromazine, trifluoperazine, perazine, melperone, pimpamperone, ziprasidone, flupentixol, chlorprothixene, zuclopenthixol, loxapine, clozapine, tiapride, amisulpride, prothipendyl, and aripiprazole have been investigated in drug-drug comparisons, each in one or two studies (Table 7). Only one study reported the mortality risk associated with concomitant use of ≥2 antipsychotic drugs (Sahlberg et al. 2015). In that study, antipsychotic polypharmacy was associated with a higher risk of major adverse cardiovascular events and noncardiovascular mortality compared with risperidone monotherapy.

In the drug-drug comparison studies that were able to assess dose, risperidone, olanzapine and haloperidol, but not quetiapine, displayed a dose-response relationship (Rossom et al. 2010, Huybrechts et al. 2012b, Gerhard et al. 2014). Most of the drug-drug comparison studies focused on the first 180 days or less after antipsychotic initiation (Schneeweiss et al. 2007, Huybrechts et al. 2012b, Kales et al. 2012, Gerhard et al. 2014, Maust et al. 2015, Schmedt et al. 2016b). Differences in mortality risk between individual antipsychotic drugs were highest shortly after the initiation of use and declined thereafter (Kales et al. 2012, Huybrechts et al. 2012b, Gerhard et al. 2014, Sahlberg et al. 2015). In contrast, Rossom et al. (2010) reported that none of the antipsychotic drugs were associated with an elevated risk of mortality after the first 30 days compared with nonusers.

One study assessed the association between duration and dose of antipsychotic use and mortality separately in nursing home residents with severe mental illness, BPSD or delirium only (Simoni-Wastila et al. 2016). In all three groups, the risk of mortality was highest among residents using higher than recommended antipsychotic doses. Among residents with delirium or severe mental illness, the mortality risk was highest in the first 90 days of use and among residents with BPSD, the mortality risk remained similar for the entire 180 days of use. However, very few studies have examined and reported the risk of mortality for longer durations of antipsychotic use. In a placebo-controlled withdrawal trial investigating long-term care residents with AD, participants randomized to continue antipsychotic use for 12 months had an increased risk of mortality at 12 months compared with those who switched to placebo, and the difference seemed to be more pronounced after the first year of follow-up (Ballard et al. 2009). In one population-based cohort study, antipsychotic users with dementia had a doubled risk of mortality compared with users of other psychotropics and the risk remained constantly higher for over 6 years from the first dispensing of antipsychotic drug (Langballe et al. 2014).

Three of the investigations that conducted drug-drug comparisons were restricted to individuals diagnosed with dementia (Rossom et al. 2010, Kales et al. 2012, Maust et al. 2015). In the rest of the studies, prevalence of diagnosed dementia varied from 1% to 68% among users of individual antipsychotic drugs (Table 7). The lowest prevalence may reflect data coverage and under-recording of diagnoses rather than actual prevalence of dementia as the number of dementia drug users was higher than the number of persons with dementia diagnoses (Sahlberg et al. 2015). Three studies reported the results of drug-drug comparisons stratified by dementia status (Huybrechts et al. 2012b, Gerhard et al. 2014, Schmedt et al. 2016b). A higher mortality for haloperidol and a lower rate for quetiapine compared with risperidone were found in both users with and without dementia (Huybrechts et al. 2012b, Gerhard et al. 2014, Schmedt et al. 2016b). However, Schmedt et al. (2016b) analyzed the

mortality risk of 14 antipsychotic drugs compared with risperidone and some of the results were modified by dementia status. The lower risk for perazine, flupentixol, olanzapine, clozapine, tiapride, and prothipendyl observed in the main analyses tended towards a null effect in users with dementia. In addition, the mortality risk was higher for levomepromazine than for risperidone in users with dementia but no difference was found in users without dementia. For chlorprothixene, the risk of mortality was higher than for risperidone in users with dementia but lower in users without dementia. In addition, Sahlberg et al. (2015) claimed that they conducted stratified analyses according to dementia status. However, they had analyzed the effect of dementia in each drug-drug comparison (the reference group was always risperidone users without dementia) instead of analyzing drug-drug comparisons separately in those with dementia and those without dementia.

These findings have been criticized; it has been claimed that selective prescribing of conventional antipsychotics and haloperidol to patients who are frail and terminally ill has led to an overestimation of the association between conventional antipsychotics and mortality in observational studies (Luijendijk et al. 2016). Ten studies excluded persons with cancer (Schneeweiss et al. 2007, Setoguchi et al. 2008, Huybrechts et al. 2011a, Huybrechts et al. 2011b, Huybrechts et al. 2012b, Gerhard et al. 2014, Sikirica et al. 2014, Jackson et al. 2015, Schmedt et al. 2016b) or persons receiving palliative care (Gill et al. 2007, Schmedt et al. 2016b). In addition, in five studies, the outcome was restricted to non-cancer mortality with deaths due to cancer being excluded (Setoguchi et al. 2008, Huybrechts et al. 2011a, Huybrechts et al. 2012b, Vasilyeva et al. 2013, Gerhard et al. 2014). These exclusions were done to avoid confounding by selective prescribing of certain antipsychotics for cancer patients to treat nausea, agitation, confusion and pain. Fifteen studies adjusted for delirium to some extent (Wang et al. 2005, Gill et al. 2007, Kales et al. 2007, Schneeweiss et al. 2007, Setoguchi et al. 2008, Huybrechts et al. 2011a, Huybrechts et al. 2011b, Huybrechts et al. 2012b, Kales et al. 2012, Vasilyeva et al. 2013, Gerhard et al. 2014, Sikirica et al. 2014, Jackson et al. 2015, Maust et al. 2015, Sahlberg et al. 2015). However, the prevalence of delirium varied from 0.5% to 53.6%. In most of the studies, the prevalence was less than 10% and only three studies reported delirium prevalences over 40% (Huybrechts et al. 2011b, Kales et al. 2012, Maust et al. 2015). As delirium is poorly recognized and recorded in register-based data, residual confounding by delirium cannot be ruled out.

Data on the severity of dementia and BPSD was lacking in the majority of the studies. Only two studies had data on the severity of cognitive and functional impairment and BPSD (Huybrechts et al. 2011b, Huybrechts et al. 2012b). Schneeweiss et al. (2009) assessed the effect of unmeasured confounders including body mass index, smoking, and cognitive, functional and physical impairment on the mortality risk difference between conventional and atypical antipsychotics. They concluded that if these variables remain unadjusted, then the association between conventional antipsychotics and mortality would be underestimated rather than overestimated. In addition, examining the same study cohort as Huybrechts et al. (2012b), Park et al. (2015) reported that additional adjustment for mortality risk scores did not change the mortality risk estimates for conventional compared with atypical antipsychotics. However, a recent systematic review (Luijendijk et al. 2016) claimed that the mortality risk scores used in that study predicted short-term mortality poorly and thus, confounding by terminal illness may not have been fully removed. Overall, the systematic review by Luijendijk et al. (2016) concluded that terminal illness had not been adequately adjusted for in any of the previous observational studies i.e. confounding by terminall illness might entirely explain the higher risk of mortality associated with conventional antipsychotics. Similarly, a meta-analysis of randomized placebo-controlled trials did not indicate that conventional antipsychotics or specifically haloperidol would be associated with an increased risk of mortality (Hulshof et al. 2015).

Jackson et al. (2014a, 2014b, 2015) have assessed which adverse events could explain the observed mortality risk difference between conventional and atypical antipsychotics. Based on a meta-synthesis of observational studies, hip fracture, stroke, myocardial infarction, and

ventricular arrhythmias combined could explain 17-42% of the mortality difference assuming independent contributions (Jackson et al. 2014a). The same researchers conducted a retrospective cohort study based on Medicare claims data and reported that 15-45% of the difference could be mediated by stroke, ventricular arrhythmia, myocardial infarction and pneumonia (Jackson et al. 2015). Thus, a substantial part of the difference remained unexplained which might indicate residual confounding by indication or some role of unsuspected adverse events.

In conclusion, both the use of atypical and conventional antipsychotics has been associated with an increased risk of mortality among community dwellers and nursing home residents with and without dementia. Higher mortality risk for haloperidol and lower for quetiapine compared with risperidone have been observed in many studies. However, possible residual confounding by indication prevents concluding that some antipsychotic would be safer than others. Most of the previous studies have focused on the first 180 days after initiation of antipsychotic use. Thus, more research is needed on safety of antipsychotics in long-term use.

Table 6. Summary of new-user studies comparing mortality risk of conventional and atypical antipsychotics among older people

Reference, country	Years of data collection, follow-up	Study population				Hazard ratio (HR) or other risk measures (95% CIs)
		N	Age, sex	Residential setting	Dementia	
Jackson et al. 2015 US	1994-2005, 180 days ITT	17,137 AAP users 9,060 CAP users	≥65 years, mean 81.9-82.5, 79-81% female	CD	54.2% AAP 42.1% CAP	CAP vs. AAP RR 1.14 (1.06-1.22)
Sikirica et al. 2014 Italy	2009-2011, 180 days ITT	14,462 CAP users 9,219 AAP users	≥65 years, mean 78.9-82.1, 61-64% female	CD	11.5% AAP 11.0% CAP	CAPs vs. AAPs HR 1.47 (1.35-1.60)
Vasilyeva et al. 2013 Canada	2000-2007, max 1 year	7,779 AAP users 4,655 CAP users	≥65 years, mean 77.9-82.6, 57-63% female	Mixed, LTC 15-38%	AD 19.1% AAP, 4.9% CAP Dementia 32.5% AAP, 8.7% CAP	AAP vs. CAP HR 0.59 (0.47-0.74)
Aparasu et al. 2012 US	2001-2003, 180 days ITT	Matched 3,609 AAP users 3,609 CAP users	≥65 years, mean 83, 65% female	NH	26.8% AAP 25.6% CAP	CAP vs. AAP HR 1.41 (1.27-1.57)
Huybrechts et al. 2011a Canada	1996-2006, max 180 days	1,942 AAP users 1,902 CAP users	≥65 years, mean 83.0-84.0, 55-58% female	NH	56.2% AAP 49.8% CAP	CAP vs. AAP As treated IRR 1.52 (1.14-2.02) ITT IRR 1.32 (1.07-1.64)
Huybrechts et al. 2011b US	2001-2005 180 days ITT	74,760 AAP users 7,252 CAP users	≥65 years, mean 82.7-82.8 female 68-75%	NH	76.2% AAP 70.9% CAP	CAP vs. AAP RR 1.45 (1.37-1.52)
Setoguchi et al. 2008[a] Canada	1996-2004, 180 days ITT	24,359 AAP users 12,882 CAP users	≥65 years, mean 79.9-80.3, 60-65% female	Mixed, NH 27-31%	12.7% AAP 9.7% CAP	CAP vs. AAP Non-cancer mortality HR 1.27 (1.18-1.37)
Gill et al. 2007 Canada	1997-2003, max 180 days	Matched pairs CD 6,888 pairs LTC 7,235 pairs	≥66 years, mean 82-84, 60-67% female	CD and LTC cohorts	All had diagnosis of dementia	CD ≤30 days CAP vs. AAP HR 1.55 (1.19-2.02) LTC ≤30 days CAP vs. AAP HR 1.26 (1.04-1.53)
Schneeweiss et al. 2007[a] Canada	1996-2004, 180 days ITT	24,359 AAP users 12,882 CAP users	≥65 years, mean 79.9-80.3, 60-65% female	Mixed, NH 27-31%	12.7% AAP 9.7% CAP	CAP vs. AAP All cause mortality HR 1.32 (1.23-1.42)

AAP=atypical antipsychotic, CAP=conventional antipsychotic; CD=community-dwelling, LTC=long-term care residents, Mixed=both community dwellers and individuals residing in institutional settings, NH=nursing home; IRR=incidence rate ratio, ITT=intention-to-treat, RR=relative risk

[a] Same study cohort but different outcome definition

(Continued)

Table 6. (Continued)

Reference, country	Years of data collection, follow-up	Study population				Hazard ratio (HR) or other risk measures (95% CIs)
		N	Age, sex	Residential setting	Dementia	
Kales et al. 2007 US	2001-2005 1 year ITT	3,999 AAP users 353 CAP users 182 users of both	≥65 years, mean 79, 3% female	CD	All had diagnosis of dementia	Reference CAP AAP RR 0.93 (0.75-1.16) both RR 1.33 (0.94-1.86)
Wang et al. 2005 US	1994-2003, 180 days ITT	13,748 AAP users 9,142 CAP users	≥65 years, mean 83.2-83.5, 78-83% female	Mixed, NH 16-21%	52.5% AAP 40.8% CAP	CAPs vs. AAPs HR 1.37 (1.27-1.49)

AAP=atypical antipsychotic, CAP=conventional antipsychotic; CD=community-dwelling, Mixed=both community dwellers and individuals residing in institutional settings, NH=nursing home; ITT=intention-to-treat, RR=relative risk

Table 7. Summary of new-user studies comparing mortality risk of individual antipsychotic drugs among older people

Reference, country	Years of data collection, follow-up	Study population				Hazard ratio (HR) or other risk measures (95% CIs)
		N	Age, sex	Residential setting	Dementia	
Schmedt et al. 2016b Germany	2005-2011, 90 days ITT	137,713	≥65 years, mean 73-82, 49-74% female	Mixed, NH 5.4-27.5%	16.1-67.7%	Reference risperidone Melperone HR 1.13 (1.07-1.19) Pipamperone 1.06 (0.98-1.14) Haloperidol HR 1.45 (1.35-1.55) Quetiapine HR 0.74 (0.67-0.81) Prothipendyl HR 0.78 (0.67-0.92) Olanzapine HR 0.59 (0.47-0.75) Levomepromazine HR 1.34 (1.16-1.54) Tiapride HR 0.72 (0.57-0.91) Chlorprothixene HR 0.93 (0.73-1.20) Clozapine HR 0.65 (0.48-0.89) Perazine HR 0.51 (0.34-0.78) Flupentixol HR 0.26 (0.13-0.49) Amisulpride HR 0.89 (0.59-1.34) Zuclopenthixol HR 1.32 (1.02-1.71)
Sahlberg et al. 2015 Denmark	1997-2011, not reported	91,774	≥70 years, mean 79-84, 56-71% female	Mixed	1-19% diagnosis of dementia, 6-36% use of dementia medication	Reference risperidone <30 days of treatment Haloperidol IRR 4.17 (3.79-4.58) Levomepromazine IRR 11.06 (9.99-12.25) Olanzapine IRR 1.10 (0.96-1.25) Quetiapine IRR 0.76 (0.65-0.88) Flupentixol IRR 0.44 (0.35-0.55) Chlorprothixene IRR 0.83 (0.67-1.02) Ziprazidone IRR 1.10 (0.62-1.95) Multiple medications IRR 2.29 (2.04-2.57)
Maust et al. 2015 US	1998-2009, 180 days	45,393 users 45,393 matched nonusers	≥65 years, 2-3% female	Mixed, NH 4.8-7.1%	All had diagnosis of dementia	Reference nonuse Absolute risk difference %, NNH Risperidone 3.7 (2.2-5.3), 27 (19-46) Quetiapine 2.0 (0.7-3.3), 50 (30-150) Haloperidol 3.8 (1.0-6.6), 26 (15-99) Olanzapine 2.5 (0.3-4.7), 40 (21-312)

Mixed=both community dwellers and individuals residing in institutional setting, NH=nursing home; IRR=incidence rate ratio, ITT=intention-to-treat, NNH=number needed to harm

(Continued)

Table 7. (Continued)

Reference, country	Years of data collection, follow-up	Study population				Hazard ratio (HR) or other risk measures (95% CIs)
		N	Age, sex	Residential setting	Dementia	
Gerhard et al. 2014 US	2001-2005, max 180 days	136,393	≥65 years, mean 76-82 75-78% female	CD	25.7-35.6%	Reference risperidone Olanzapine HR 0.82 (0.74-0.90) Quetiapine HR 0.80 (0.72-0.89) Haloperidol HR 1.18 (1.06-1.33) Aripiprazole HR 0.62 (0.40-0.97)
Vasilyeva et al. 2013 Canada	2000-2007, max 1 year	11,076	≥65 years, mean 78-83, 57-63% female	Mixed, LTC 15.3-37.6%	AD 4.9-19.1% Dementia 8.7-32.5%	Reference haloperidol Risperidone HR 0.62 (0.45-0.87) Olanzapine HR 0.55 (0.36-0.84)
Huybrechts et al. 2012b US	2001-2005, max 180 days	75,445	≥65 years, mean 82-84, 72-76% female	NH	55.6-63.0%	Reference risperidone Olanzapine HR 1.01 (0.95-1.08) Quetiapine HR 0.83 (0.77-0.89) Haloperidol HR 1.81 (1.65-1.98) Aripiprazole HR 0.95 (0.78-1.15) Ziprasidone HR 0.90 (0.69-1.17)
Kales et al. 2012 US	1999-2008, max 180 days	33,604	≥65 years, 2-3% female	Mixed, NH 3.3-4.3%	All had diagnosis of dementia	Reference risperidone Quetiapine HR 0.74 (0.66-0.84) Olanzapine HR 1.07 (0.93-1.23) Haloperidol HR 1.56 (1.34-1.81)
Rossom et al. 2010 US	1998-2005, max 360 days	18,127 users, 72,508 matched nonusers	≥65 years, mean 77-78, 2-3% female	Mixed	All had diagnosis of dementia, 39-54% AD	Reference nonuse <30 days of treatment Risperidone HR 1.2 (1.0-1.4) Quetiapine HR 0.8 (0.6-1.1) Olanzapine HR 1.3 (1.0-1.7) Haloperidol HR 2.2 (1.7-2.9)
Hollis et al. 2007a Australia	2003-2004, max 2 years	16,634	≥65 years, mean 80-83, 33-59% female	Mixed, LTC 15-52%	4-30% AChEI users	Reference olanzapine Haloperidol RR 2.26 (2.08-2.47) Risperidone RR 1.23 (1.07-1.40) Chlorpromazine RR 1.39 (1.15-1.67) Trifluoperazine RR 0.55 (0.37-0.82)

AChEI=Acetylcholinesterase inhibitor, AD=Alzheimer's disease; CD=community-dwelling, Mixed=both community dwellers and individuals residing in institutional settings, NH=nursing home; RR=relative risk

(Continued)

Table 7. (Continued)

Reference, country	Years of data collection, follow-up	Study population				Hazard ratio (HR) or other risk measures (95% CIs)
		N	Age, sex	Residential setting	Dementia	
Hollis et al. 2007b Australia	2003-2004, max 2 years	6,602	≥65 years, mean 82-84, 42-61% female	LTC	14-31% AChEI users	Reference olanzapine Haloperidol RR 1.67 (1.50-1.84) Risperidone RR 1.19 (1.02 -1.38) Chlorpromazine RR 1.75 (1.31-2.34)
Schneeweiss et al. 2007 Canada	1996-2004, 180 days ITT	37,241	≥65 years, mean 80, 60-65% female	Mixed, NH 26.6-30.9%	9.7-12.7%	Reference risperidone Haloperidol HR 2.14 (1.86-2.45) Olanzapine HR 0.94 (0.80-1.09) Loxapine HR 1.29 (1.19-1.40)

AChEI=Acetylcholinesterase inhibitor; LTC=long-term care residents, Mixed=both community dwellers and individuals residing in institutional settings, NH=nursing home; ITT=intention-to-treat, RR=relative risk

2.3.3 Cardiovascular and other serious adverse events associated with antipsychotic use

Cardiovascular adverse events

According to a systematic review of nine observational studies, antipsychotic use has been associated with an increased risk of **myocardial infarction** (Yu et al. 2016). Based on the pooled results of three studies, the risk of myocardial infarction was highest in the first 30 days of use and attenuated thereafter (Yu et al. 2016). The methodological quality of some of the included studies was rated poor and there was significant heterogeneity across studies included in the meta-analysis. Only one study was conducted among older persons with dementia (Pariente et al. 2012), two others included patients aged >18 years with various diagnoses such as dementia, schizophrenia or mood disorders (Lin et al. 2014, Brauer et al. 2015). The pooled OR from these three studies was 1.82 (95% CI 1.16-2.84) for persons with dementia (Yu et al. 2016). Few studies have compared the risk of myocardial infarction between antipsychotic classes and individual antipsychotic drugs. Huybrechts et al. (2012a) did not find differences in the risk between quetiapine, olanzapine and risperidone among nursing home residents. However, they reported a tendency towards a higher risk associated with conventional in comparison with atypical antipsychotics (HR 1.23; 95% CI 0.81-1.86). On the contrary, Vasilyeva et al. (2013) found that atypical antipsychotics were associated with a higher risk of nonfatal myocardial infarction compared with conventional antipsychotics (HR 1.61; 95% CI 1.02-2.54).

In addition to myocardial infarction, studies indicate that antipsychotic use can increase the risk of **ventricular arrhythmias** and **sudden cardiac death** (Ray et al. 2009, Wu et al. 2015). Instead of a class effect, current evidence suggests that the risk varies between individual antipsychotic drugs and seems to be related to the potency of antipsychotics to block hERG potassium channels (Wu et al. 2015, Salvo et al. 2016). No studies have investigated these risks among antipsychotic users with dementia (Trifirò et al. 2014).

Antipsychotic use may be also associated with an increased risk of **venous thromboembolism** (OR 1.54; 95% CI 1.28-1.86) based on a meta-analysis of eleven observational studies (Barbui et al. 2014). However, the overall quality of evidence was rated as very low due to high heterogeneity between studies and concerns about comparability at baseline. An increased risk was found among both conventional and atypical antipsychotic users. The association between **pulmonary embolism** and antipsychotic use is unclear as the estimate pooled from three studies was highly heterogeneous and confidence interval included one with a huge range (OR 4.90; 95% CI 0.77-30.98). Three included studies focused on older persons; the pooled estimate from these studies did not reveal any increased risk of venous thromboembolism associated with antipsychotic use (OR 1.07; 95% CI 0.90-1.26). Two studies have investigated this association among persons with dementia (Schmedt and Garbe 2013, Dennis et al. 2017). In both of these studies, an increased risk of venous thromboembolism was associated with antipsychotic use. In the nested case-control study by Schmedt and Garbe (2013), the risk was found in current users, particularly among new users and among concurrent users of atypical and conventional antipsychotics.

Concerns about the elevated risk of **cerebrovascular adverse events** associated with antipsychotic use were first raised in 2002 (Health Canada 2002). Risperidone was found to be associated with cerebrovascular accidents such as stroke and transient ischemic attack in randomized controlled trials involving older persons with dementia. Two systematic reviews (Sacchetti et al. 2010, Mittal et al. 2011) including quantitative reviews, randomized controlled trials and observational studies, suggest that antipsychotics are associated with an increased risk of cerebrovascular adverse events. The higher risk has been found in older persons either with or without dementia. Conventional and atypical antipsychotics have been associated with a similar risk of cerebrovascular events but there was a lack of comparative studies analyzing the stroke risk of individual antipsychotic drugs. Similar to

other cardiovascular adverse events, the risk seemed to be highest at the beginning of treatment and to decline thereafter.

In conclusion, antipsychotic use has been associated with several serious cardiovascular adverse events such as myocardial infarction, ventricular arrhythmia and sudden cardiac arrest, venous thromboembolism, and cerebrovascular accidents, all of which could contribute to the increased mortality risk. A consensus guideline recommended that before prescribing antipsychotics for persons with dementia, it would be important to ascertain if there were any particular risk factors such as pre-existing cardiovascular diseases, history of cardiac arrhythmia and use of other medication that could prolong QT-interval; it was also recommended to conduct an ECG assessment before and during antipsychotic treatment (Zuidema et al. 2015).

Other serious adverse events

A systematic review and meta-analysis of observational studies suggested that antipsychotic use would be also associated with an increased risk of **pneumonia** (Nosè et al. 2015). According to a meta-analysis of six observational studies, the risk of pneumonia was increased for both conventional (OR 1.68; 95% CI 1.39-2.04) and atypical antipsychotics (OR 1.98; 95% CI 1.67-2.35) (Nosè et al. 2015). Most of the studies have focused on older persons but the increased risk of pneumonia was also found in young adults (Nosè et al. 2015). According to the review, no clear pattern in the risks in relation to duration of use was found although two studies reported that the risk was highest at the beginning of antipsychotic use. A more recent study found antipsychotics to be associated with increased risk of hospitalization or death due to pneumonia both in community-dwelling persons with AD (HR 2.01; 95% CI 1.90-2.13) and without AD (HR 3.43; 95% CI 2.99-3.93) (Tolppanen et al. 2016c). The risk was highest at the beginning of use and decreased but remained elevated with long-term use. The three most frequently used antipsychotic drugs had similar associations with pneumonia. However, quetiapine users showed some tendency towards a lower risk of pneumonia compared with risperidone users in subjects with AD. Haloperidol use was associated with a higher risk of pneumonia compared with risperidone use in both individuals with or without AD. There are only a few other studies that have compared the pneumonia risk between individual antipsychotic drugs and the results are conflicting (Huybrechts et al. 2012a, Mehta et al. 2015). Mehta et al. (2015) found risperidone and olanzapine to be associated with a higher risk of fatal or non-fatal pneumonia than quetiapine use among older persons. On the other hand, Huybrechts et al. (2012a) found no difference in hospitalization for pneumonia when olanzapine and quetiapine users were compared with risperidone users among nursing home residents.

Hwang et al. (2014) were the first to report an increased risk (RR 1.73; 95% CI 1.55-1.92) of **acute kidney injury** among new users of quetiapine, risperidone and olanzapine aged 65 years and older. In this large population-based cohort study using claims data from Ontario, Canada, use of antipsychotics was also associated with a higher 90-day risk of all-cause mortality and hospitalization for hypotension, acute urinary retention, pneumonia, myocardial infarction, and ventricular arrhythmia. Recently, a replication analysis conducted with US claims data found similar results (Ryan et al. 2017). However, the increased risks were not found in adapted analyses that used additional strategies to control for confounding. One study reported an increased risk of acute kidney injury among antipsychotic users with schizophrenia and bipolar disorder and found that the risk might differ between antipsychotic drugs (Jiang et al. 2017). Jiang et al. (2017) concluded that as the incidence of acute kidney injury is moderate, the risk should only be taken into account when treating older patients with other risk factors for acute kidney injury. Due to these conflicting results, it is clear that more research is needed to clarify the association between acute kidney injury and antipsychotic use.

2.3.4 Possible mechanisms contributing to serious adverse events

In addition to the blockade of dopamine receptors, antipsychotics antagonize serotonergic, histaminergic, muscarinic and α-adrenergic receptors (Miyamoto et al. 2012). Depending on the affinity of different antipsychotics for these receptors and their subtypes, antipsychotics can cause various degrees of adverse effects such as extrapyramidal symptoms, sedation, orthostatic hypotension, hyperprolactinemia, anticholinergic and metabolic effects (Leung et al. 2012, Miyamoto et al. 2012, Peuskens et al. 2014). It has been hypothesized that these adverse effects of antipsychotics could contribute to the increased risk of different serious adverse events in a multifactorial manner (Figure 2).

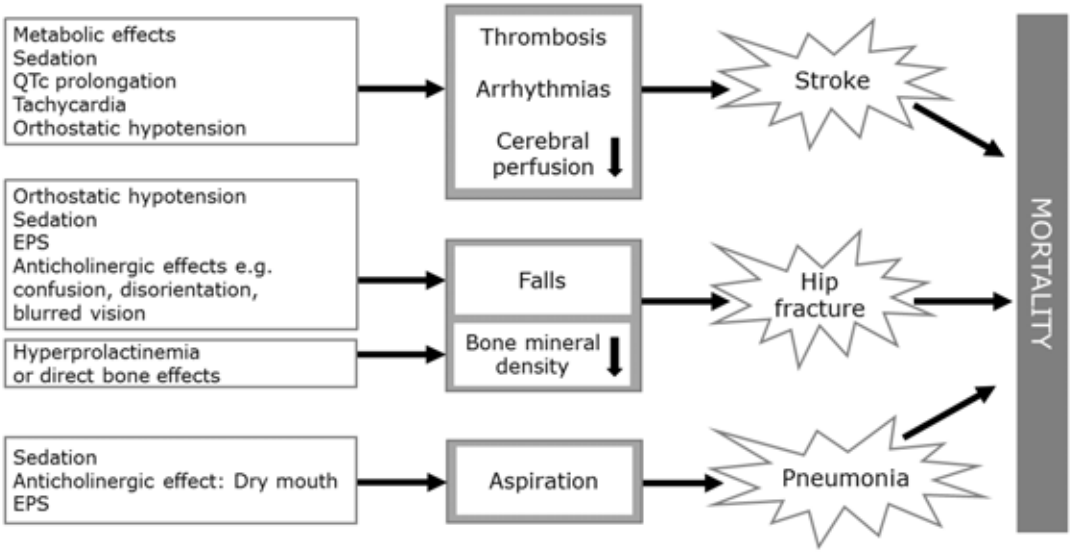

Figure 2. Some examples of possible mechanisms that could contribute to the increased risk of serious adverse events associated with antipsychotic use

Orthostatic hypotension is the most frequent vascular adverse effect of antipsychotics and it is more common among older persons (Leung et al. 2012). Orthostatic hypotension is often more problematic at the beginning of antipsychotic use and tolerance tends to occur within a few weeks. It seems plausible that antipsychotics cause orthostatic hypotension via blockade of peripheral α1-adrenoceptors. The risk of orthostatic hypotension has been found to positively correlate with the affinity for α1-adrenoceptors relative to dopamine D_2 receptors, for example quetiapine and risperidone have a moderate risk of orthostatic hypotension whereas haloperidol has a low risk. It has been suggested that orthostatic hypotension could contribute to the increased risk of ischemic stroke and transient ischemic attack by aggravating the deficit in cerebral perfusion in persons with pre-existing cerebrovascular insufficiency or atherosclerosis (Mittal et al. 2011). Other cardiovascular adverse effects of antipsychotics mediated via blockade of muscarinic and α-adrenergic receptors include tachycardia and lengthening of QTc interval which could lead to increased risk of ventricular arrhythmia and sudden cardiac death (Leung et al. 2012). Tachycardia induced by the antipsychotics has been postulated as another possible mechanism increasing the risk of stroke i.e. tachycardia might cause a decrease in cerebral perfusion or dislodge a thrombus if there is comorbid atrial fibrillation (Mittal et al. 2011). In addition, antipsychotics have been suggested to facilitate thrombus formation which could contribute to the increased risks of venous thromboembolism, stroke and myocardial infarction (Mittal et al. 2011, Barbui et al. 2014, Yu et al. 2016). Speculated mechanisms that could play a role in thrombosis

include immobilization caused by excessive sedation, metabolic effects, increased levels of antiphospholipid antibodies, enhanced platelet aggregation and hyperprolactinemia.

Although use of antipsychotics has been associated with metabolic effects including weight gain, lipid disturbances and hyperglycemia among persons with schizophrenia or bipolar disorder, it is unclear whether older persons with dementia experience these kinds of metabolic disturbances (Trifirò et al. 2014). Metabolic effects could contribute to the increased risk of cardiovascular events. However, these factors cannot explain the acute increase in the risks since the highest risks of stroke, myocardial infarction and venous thromboembolism have been observed at the beginning of antipsychotic use (Sacchetti et al. 2010, Mittal et al. 2011, Schmedt and Garbe 2013, Yu et al. 2016). Sedation mediated via H_1 receptor blockade could lead to development of venous stasis and/or dehydration and hemoconcentration (Herrmann and Lanctôt 2005).

Antipsychotics can cause disinhibition of prolactin secretion by blocking dopamine D_2 receptors on the membrane of the anterior pituitary lactotroph cells (Peuskens et al. 2014). Antipsychotics differ in their tendencies to elevate prolactin levels. With respect to the atypical antipsychotics, amisulpride, risperidone and paliperidone cause the highest rates of hyperprolactinemia whereas quetiapine and aripiprazole have the lowest potential to elevate prolactin levels. It has been speculated that as hyperprolactinemia has been associated with endothelial dysfunction, decreased insulin sensitivity and increased platelet aggregation, it could accelerate atherosclerosis (Herrmann and Lanctôt 2005). However, again this mechanism is unlikely to explain the highest increases in the risks of stroke, myocardial infarction and venous thromboembolism observed in short-term use (Sacchetti et al. 2010, Mittal et al. 2011, Schmedt and Garbe 2013, Yu et al. 2016).

D_2 receptor blockade in the nigrostriatal pathway can lead to extrapyramidal symptoms (EPS) such as parkinsonism, dystonia, akathisia, and tardive dyskinesia (Weiden 2007, Miyamoto et al. 2012). In general, atypical antipsychotics are thought to be safer than conventional antipsychotics in this respect. Different explanations for the lower risk of EPS associated with atypical antipsychotics have been proposed including a lower affinity for and a more rapid dissociation from D_2 receptors, high affinity for 5-HT_{2A} receptors increasing dopaminergic transmission in the nigrostriatal pathway, regionally selective binding to cortico-limbic rather than nigrostriatal D_2 receptors, partial agonism of D_2, and antagonism of M_1 receptors. As atypical antipsychotics differ in their receptor profiles, their propensity to cause EPS also varies. Risperidone is associated with the highest risk of EPS and the risk increases with increasing dose whereas clozapine and quetiapine are associated with low risk of EPS (Weiden 2007). In a population-based cohort study including older persons with dementia, the risk of parkinsonism was found to be similar among high-dose atypical antipsychotic users, mainly risperidone users, and among high-potency typical antipsychotic users (Rochon et al. 2005). In the same study cohort, atypical and conventional antipsychotics were associated with a similar risk of tardive dyskinesia and EPS other than parkinsonism (Lee et al. 2005).

EPS along with orthostatic hypotension and sedation have been suggested to contribute to the increased risks of falls and subsequent fractures (Hugenholtz et al. 2005, Pouwels et al. 2009). EPS impair postural stability (Ikay et al. 2016), orthostatic hypotension leads to dizziness (Shaw and Claydon 2014), and sedation impairs physical functioning (Bourin and Briley 2004), all of which are factors that may predispose to falls. In addition, anticholinergic effects of antipsychotics such as confusion, disorientation, and blurred vision may further contribute to the increased risk of falling (Nishtala et al. 2016). It has also been hypothesized that with long-term use, antipsychotic induced hyperprolactinemia could lead to reduced bone mineral density resulting in an increased risk of hip fracture should the individual fall (Hugenholtz et al. 2005, Pouwels et al. 2009). On the other hand, it has been speculated that antipsychotics may also directly affect bone homeostasis; for example, risperidone might affect osteoblast proliferation and differentiation via blockade of 5-HT_{2B} and α_1-adrenoceptors (Bakken et al. 2016).

Similarly to other serious adverse events, the hypothesized mechanisms leading to pneumonia are multifactorial. It has been suggested that antipsychotic induced excessive sedation, extrapyramidal symptoms and dryness of mouth could lead to dysphagia and thereby contribute to the increased risk of aspiration pneumonia (Trifirò et al. 2009, Nosè et al. 2015). In addition, it has been speculated that antipsychotics could have direct or indirect effects on the immune system (Nosè et al. 2015).

An insufficiently evaluated explanation for the increased risk of serious adverse events with antipsychotic use involves a role for drug-drug interactions (Liperoti et al. 2017). Dementia and age-related physiological changes in conjunction with multiple comorbidities and polypharmacy can make older antipsychotic users with dementia particularly susceptible to suffer drug-drug interactions (Trifirò and Spina 2011). A recent study by Liperoti et al. (2017) found that nearly half of older antipsychotic users with cognitive impairment residing in nursing homes were prescribed at least one potentially interacting drug. Antipsychotic users that were exposed to potentially interacting drugs had a higher risk of death compared to those unexposed to such interactions.

3 Aims of the Study

The overall objective of this study was to investigate antipsychotic use and the risk of serious adverse events among community-dwelling Finns with AD.

The specific aims were:

1. to describe the incidence of antipsychotic use in relation to the diagnosis of AD (Study I);

2. to determine the duration of antipsychotic use and factors associated with long-term use among community dwellers with AD (Study II);

3. to investigate whether antipsychotic use would be associated with an increased risk of hip fracture and non-cancer mortality (Studies III and IV). A further aim was to compare the risks:

    - according to duration of antipsychotic use,
    - between the most frequently used antipsychotic drugs,
    - between antipsychotic monotherapy and polypharmacy.

4 Materials and Methods

4.1 STUDY COHORTS AND DATA SOURCES

This thesis is based on data from two nationwide register-based MEDALZ (Medication use and Alzheimer's disease) cohorts (Table 8). The MEDALZ-2005 cohort included all community-dwelling persons diagnosed with AD residing in Finland on 31 December 2005 (N=28,093) and one age-, sex- and region of residence-matched control without AD (Tolppanen et al. 2013). A larger MEDALZ cohort without constraints on survival was extracted to enable more detailed analyses on the associations between drug use and adverse outcomes. This larger cohort included all Finns who received a clinically verified diagnosis of AD between 2005 and 2011 and were community-dwelling at the time of diagnosis (N=70,718) (Tolppanen et al. 2016a). The number of individuals included in the MEDALZ-2005 and MEDALZ cohorts according to the year of AD diagnosis are described in Figure 3.

Table 8. Description of the MEDALZ study cohorts

	MEDALZ-2005 (Studies I and II)	**MEDALZ (Studies III and IV)**
Inclusion criteria	Entitlement for reimbursed antidementia drugs, community-dwelling and alive on December 31, 2005	Received entitlement for reimbursed antidementia drugs between 2005 and 2011 and were community-dwelling at the time of AD diagnosis
N of persons with AD	28,093	70,718
Age at baseline, years		
Mean (SD), range	79.7 (6.8), 42-101	79.6 (7.1), 34-104
Sex distribution, % (n)		
Female	67.8% (19,043)	65.2% (46,116)
Male	32.2% (9,050)	34.8% (24,602)
Data from the Social Insurance Institution of Finland (SII)		
Special reimbursements	1972-2009	1972-2012
Prescription drug purchases	1995-2009	1995-2012
Decisions for long-term institutional care	1995-2009	1995-2012
Data from the National Institute of Health and Welfare (NIHW)		
Hospital discharges	1972-2009	1972-2012
Data from the Statistics Finland		
Causes of death	2006-2009	2005-2012

MEDALZ=Medication use and Alzheimer's disease, AD=Alzheimer's disease, SD=Standard deviation

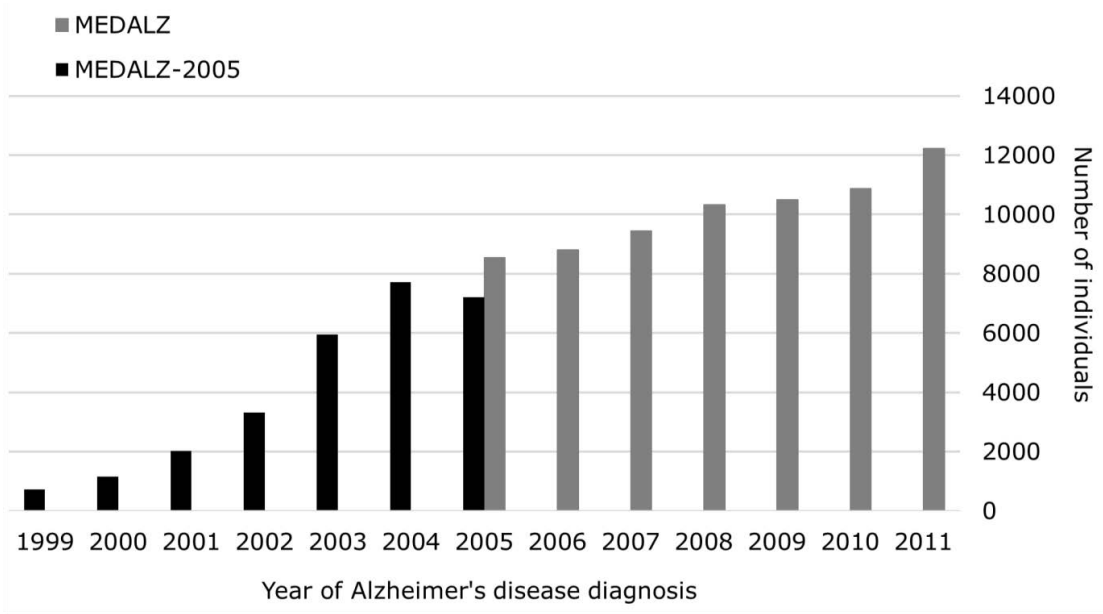

Figure 3. Number of individuals included in the MEDALZ-2005 and MEDALZ study cohorts by the year of AD diagnosis

Both MEDALZ cohorts contain data from several nationwide registers including the Finnish Prescription Register, the Special Reimbursement Register, the Hospital Discharge Register and data from the Statistics Finland for each individual (Table 8). Data obtained from each register are summarized in Table 9.

4.1.1 Diagnostic criteria of Alzheimer's disease

Individuals with AD were identified from the Special Reimbursement Register (Table 9). The Social Insurance Institution (SII) provides reimbursement for antidementia drugs if predefined diagnostic criteria, based on the NINCDS-ADRDA (McKhann et al. 1984) and DSM-IV criteria (American Psychiatric Association 1994), for AD were met. The NINCDS-ADRDA criteria for the clinical diagnosis of probable AD include deficits in at least two areas of cognition; progressive worsening of memory and other cognitive functions; no other diseases that could account for these progressive deficits; and onset between ages 40 and 90. According to the DSM-IV criteria, AD is defined as the development of memory impairment and at least one other cognitive deficit, such as aphasia, apraxia, agnosia or disturbance in executive functioning. A decline in cognitive function should represent a significant change from the previous level and cause significant impairment in social or occupational functioning. The onset of symptoms is gradual and decline is progressive and cannot be accounted for by other diseases. In addition to the evaluation of cognition also an assessment of daily and social activities, functioning, nutrition is included into the diagnostic process. Laboratory tests are used for differential diagnostics and magnetic resonance imaging or computed tomography of the brain is applied to identify the characteristic changes caused by AD (Memory disorders: Current Care Guidelines 2017).

The SII required that the medical statement must verify that the patient has: (a) symptoms consistent with AD; (b) experienced a decrease in social capacity over a period of at least 3 months; (c) received a computed tomography/magnetic resonance imaging scan; (d) had possible alternative diagnoses excluded; and (e) received confirmation of the diagnosis by a registered geriatrician or neurologist. Since 2007, persons with dementia related to Parkinson disease have been entitled to receive special reimbursement for rivastigmine but these persons were excluded from the MEDALZ cohort.

Table 9. Description of data obtained from different nationwide registers

	Finnish Prescription Register	**Special Reimbursement Register**	**Hospital Discharge Register**	**Statistics Finland**
Data content	All reimbursed purchases of prescription drugs	Entitlements to special reimbursement due to chronic diseases such as AD, diabetes, epilepsy, asthma	All inpatient days in primary and specialized hospitals	Causes of death
Essential variables	Purchase dates, name, strength and dosage form of the drug, ATC code, Nordic Article number of the package, package size, number of packages, purchased amount in DDDs, and costs	Special reimbursement code of the disease, diagnosis (ICD-code), first date of entitlement, last date of entitlement or permanent entitlement	Hospital admission/ visit dates, reason for hospital stay (ICD-codes), specialty of the caring unit, and where the patient was discharged to. Date of procedure and up to five operational codes (NOMESCO classification)	Date of death, and direct, underlying, intervening and up to four contributing causes of death (ICD-codes)
Limitations/ Strengths	Does not cover nonreimbursed drugs, OTC drugs or drugs used in hospitals or public nursing homes Drugs may be dispensed for a maximum of three months treatment per purchase No information on prescribed dose	The diagnosis must be based on explicit predefined criteria, written documentary evidence including results of diagnostic tests must be provided to the SII	Outpatient data missing Main diagnosis for >99% of admissions Auxiliary diagnoses lacking Validity of coding varies	Collected from death certificates and based on clinical examination or forensic/medical autopsy

ATC=Anatomical Therapeutic Chemical, DDD=Defined Daily Dose, OTC=over-the-counter, AD=Alzheimer's disease, ICD=International Classification of Diseases, NOMESCO=Nordic Medico-Statistical Committee, SII=Social Insurance Institution

4.2 ANTIPSYCHOTIC DRUG EXPOSURE

In this study, antipsychotics were defined as class N05A according to the Anatomical Therapeutic Chemical (ATC) Classification system maintained by the World Health Organization (WHO 2016). However, prochlorperazine (N05AB04), which is commonly used in the treatment of nausea and dizziness, and lithium (N05AN01) were excluded from the definition.

4.2.1 Modeling of drug use

To study duration of antipsychotic use and associations with serious adverse events, antipsychotic drug purchases extracted from the Prescription Register needed to be converted into drug use periods. A drug use period refers to the time period when continuous drug use started and ended. Previously it has been shown that dosage assumptions of one tablet per day or one DDD per day are not valid for measuring the duration of antipsychotic use among older people and use of these dosage assumptions may lead to severe exposure misclassification (Rikala et al. 2013).

Thus, a new approach to modeling drug exposure from drug purchases was used. The PRE2DUP (Prescriptions to drug use periods) method was developed by Tanskanen A and it is based on mathematical modeling of personal purchasing behavior (Tanskanen et al. 2015). The method uses individual purchase histories to calculate temporal sliding averages of daily dose (in DDDs). It decides whether the purchased amount is sufficient to last to the next purchase by calculating the expected refill time according to the personal temporal daily dose. In these decisions, the method takes into account stockpiling of drugs, personal purchase regularity and possible periods of hospital and nursing home care when drugs are provided by these institutions and are not recorded in the Prescription Register. The method constructs drug use periods for each person and for each ATC code. The overall operation of the PRE2DUP method is described in Figure 4.

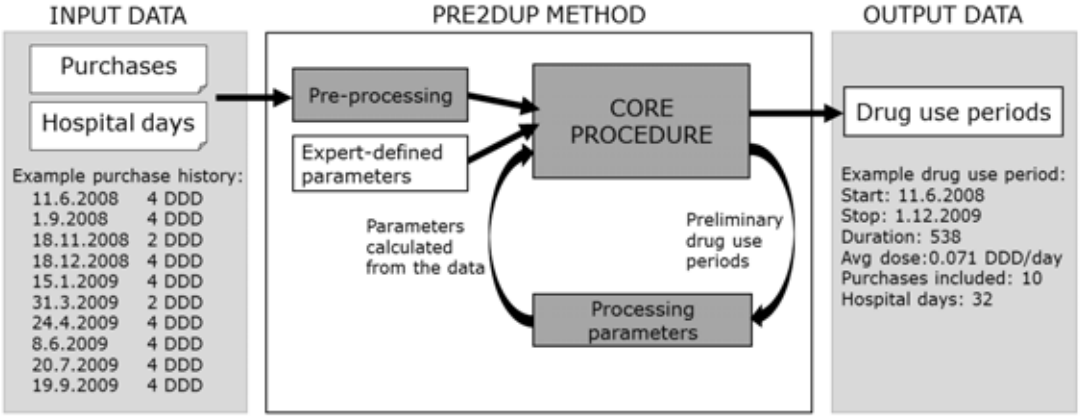

Figure 4. Overall operation of the PRE2DUP method with an example purchase history of risperidone. Avg=Average, DDD=Defined Daily Dose

Before applying the PRE2DUP modeling method, missing and changed ATC code and DDD values in the Prescription Register data were corrected. After these corrections, purchases for each person and each ATC code were arranged in chronological order. In the pre-processing phase (Figure 4), the PRE2DUP calculated temporal averages and statistics describing the regularity of each person's purchase history for each ATC code. This included calculation of refill times between purchases of each ATC code, the number of hospital days between purchases, temporal sliding averages of daily doses, and variation of the daily dose. These variables were used by the core process where the decision is made about which consecutive purchases belong to the same drug use period. To control the joining of purchases in the core process, expert-defined parameters were formulated. These parameters restrict the joining of purchases over unrealistically long time periods and ensure the clinical and pharmaceutical correctness of the method. The finest level of expert-defined parameters are package level parameters. For example for each antipsychotic drug package (417 packages identified by Nordic Article number) maximum, typical and minimum refill lengths and corresponding DDD per day values were defined. These package level parameters are based on the pharmaceutical properties of the drug in terms of dosage form, the assumed pattern of use, longevity after opening, and the number of dividable units. After the preprocessing phase and formulation of expert-defined parameters, the core process calculated the drug use periods for the first time. Based on this first run, the method calculated refill length distribution for each drug package (identified by Nordic Article number). The most common refill length in the study population for each drug package was extracted from these distributions and was used as a new parameter in the next run of the core process. The first drug use periods and the most common refill lengths were reviewed and changes were made to expert-defined parameters if necessary. The core process and

calculation of paramaters from the data were iterated until the results were stable. If a person had only one purchase of a certain ATC code, the method used the most common refill length for the purchased package in the study population. If the most common refill length was not available, due to rarity of purchases of the package, the expert-defined typical DDD per day value for that package was used to calculate the length for that single purchase. The logic and operation of the PRE2DUP method has been described in more detail by Tanskanen et al. 2015.

Use of antipsychotics was first modeled separately for each individual antipsychotic drug (each ATC code). Drug use periods of individual antipsychotic drugs were combined to retrieve use of "any antipsychotics". During the periods of "any antipsychotic" use, subjects were allowed to switch between different antipsychotic drugs and use more than one antipsychotic concomitantly. In the monotherapy and polypharmacy comparisons, overlapping drug use periods of individual antipsychotic drugs was identified as concomitant use of two or more antipsychotics (polypharmacy).

4.3 OUTCOME MEASURES

4.3.1 Incidence of antipsychotic use (I)

The rate of new antipsychotic users per 100 person-years was calculated for every 6 months up to 8 years before and 4 years after the AD diagnosis. A new user was defined as a person who had no antipsychotic purchases during the washout period but had at least one antipsychotic purchase during the 12-year follow-up.

4.3.2 Long-term antipsychotic use (II)

Long-term use was defined as continuous use of any antipsychotic for at least 365 days from the first initiation of use regardless of switches between individual antipsychotic drugs.

4.3.3 Hip fracture (III)

Hip fractures were identified from the Hospital Discharge Register based on ICD-10 codes: S72.0 (fracture of neck of femur), S72.1 (pertrochanteric fracture) and S72.2 (subtrochanteric fracture). Persons who had experienced a hip fracture before the beginning of the follow-up were excluded. Thus, the main outcome was first incident hip fracture.

4.3.4 Mortality (IV)

The date and cause of death for each person was received from Statistics Finland. The main outcome was non-cancer mortality. Cancer deaths (direct cause ICD-10 codes C00-C97) were not considered as they are unlikely to be caused by antipsychotic use and their inclusion could overestimate the mortality related to antipsychotic use if antipsychotics were used for cancer-related nausea treatment. Persons were censored for cancer death.

4.4 STUDY DESIGNS

The first substudy included those persons diagnosed with AD in 2005 (n=7,217) and their matched controls without AD (n=7,217) from the MEDALZ-2005 study cohort. Study designs of substudies I and II are summarized in Figure 5. Study II was similarly restricted to persons diagnosed with AD in 2005 but matched controls were excluded as the aim was to describe duration of antipsychotic use in the treatment of BPSD. Based on the results of Study I, the follow-up for antipsychotic use was started three years before AD diagnosis in Study II. In both substudies I and II the follow-up was censored at the time of long-term hospitalization/institutionalization, death or at the end of study period (December 31, 2009).

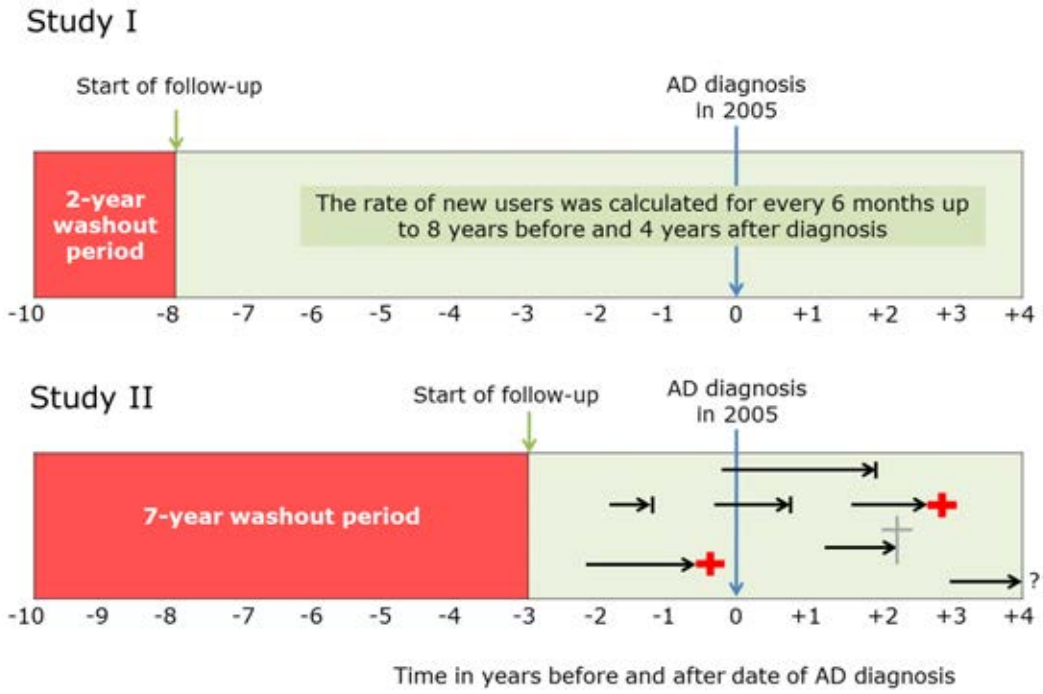

Figure 5. Study designs in substudies I and II. Black arrows represent use of antipsychotics. Follow-up was censored at the time of long-term hospitalization/institutionalization (red cross), death (grey cross) or at the end of study period (question mark, December 31, 2009).

Both substudies III and IV included all 70,718 persons diagnosed with AD between 2005 and 2011 from the MEDALZ cohort and had similar study designs which are summarized in Figure 6. The follow-up started at the date of AD diagnosis in the main analysis comparing antipsychotic use with nonuse. From the start of follow-up, the antipsychotic use status was treated as a time-dependent variable. The follow-up was censored at the date of death, start of long-term institutionalization/ hospitalization (≥90 days), discontinuation of antipsychotic use or at the end of the study period (December 31, 2012) whichever occurred first. In addition, in Study III the follow-up was censored at the date of first hip fracture and in Study IV at the date of cancer diagnosis or start of antineoplastic drug use.

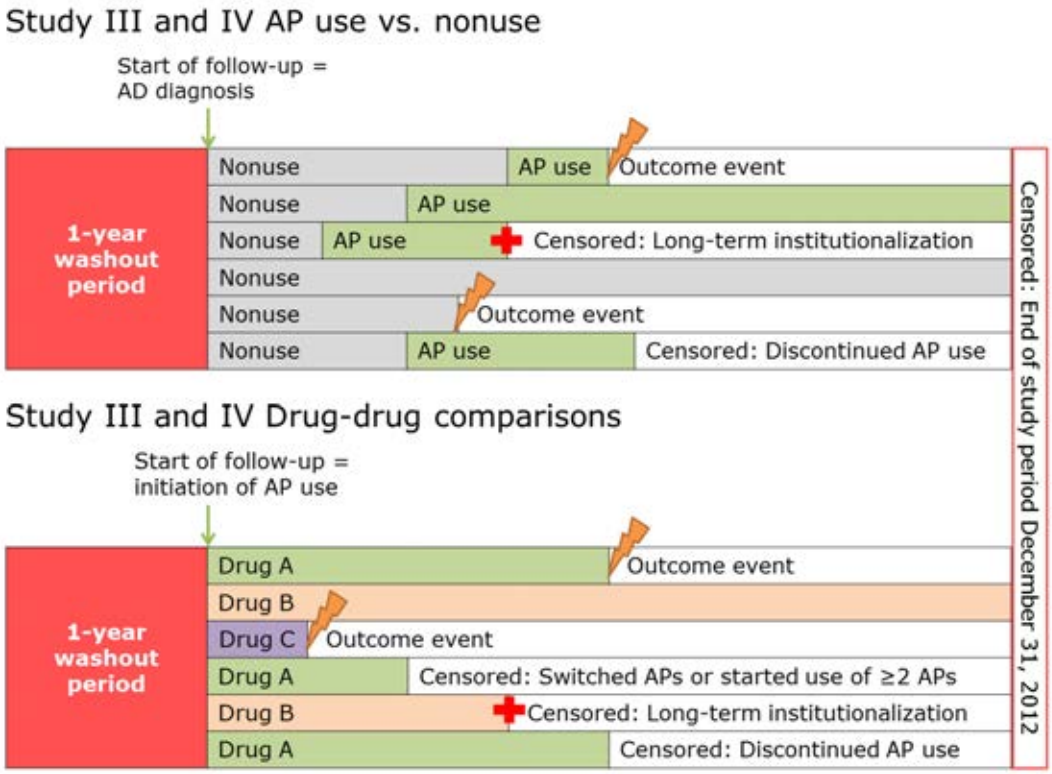

Figure 6. Study designs in substudies III and IV

In drug-drug comparisons of Studies III and IV, all new antipsychotic users were identified after the date of AD diagnosis and follow-up started at the date of initiation of first antipsychotic use (Figure 6). The follow-up was censored for the same reasons as in the main analyses. Additionally in drug-drug comparisons, the follow-up was censored if the user switched to a different antipsychotic drug or started using two or more antipsychotics concomitantly.

The exclusion criteria and the final study samples of each of the four substudies (I-IV) are summarized in Table 10. All persons using antipsychotics during the study specific washout period were excluded. In addition, as the Prescription Register does not cover drugs used in public nursing homes and hospitals, persons who were in long-term institutional/ hospital care (≥90 days) at the start of follow-up (substudies I and II) or during the washout period (substudies III and IV) were excluded. In more detail, in substudies III and IV, those individuals who were hospitalized or institutionalized for ≥6 months during the 1-year washout period or had an ongoing hospital stay of ≥3 months at the end of washout period, or were hospitalized the entire follow-up were excluded. In all substudies, persons with a history of schizophrenia, schizotypal or delusional disorders, or bipolar disorder were excluded as the aim was to study antipsychotic use and risks associated with use in the treatment of BPSD.

Table 10. Summary of the formation of final study sample in each substudy (I-IV)

	Study I	**Study II**	**Studies III and IV** **AP use vs. nonuse**	**Studies III and IV** **drug-drug comparisons**
Data	MEDALZ-2005	MEDALZ-2005	MEDALZ	MEDALZ
Initial study sample	n=7,217 persons diagnosed with AD in 2005 and n=7,217 matched controls without AD	n=7,217 persons diagnosed with AD in 2005	n=70,718 persons with AD	n=20,305 persons initiated AP use after AD diagnosis
Reasons for exclusion				
AP use during washout period	n=280	n=347	n=7,632	n=479
Long-term hospitalization/ institutionalization	n=8, at the start of follow-up	n=7, at the start of follow-up	n=2,224 (III) n=2,220 (IV) during washout period	n=1,384 during washout period
History of schizophrenia, schizotypal or delusional disorders of bipolar disorder	n=298, diagnosed before AD diagnosis	n=123, diagnosed at least 3 years before AD diagnosis	n=477, diagnosed at least 5 years before AD diagnosis	n=214, diagnosed at least 5 years before AD diagnosis
Study specific exclusion criteria	n=33 matched control had temporary reimbursement for AD before 2005 n=511 matched control received new AD diagnosis during 2006-2009	-	n=2,797 had hip fracture before AD diagnosis (III) n=2,643 had cancer at the time of AD diagnosis (IV)	n=1,166 hip fracture before initiation of AP use (III) n=407 had cancer at the time of initiation of AP use (IV) n=90 (III)/ n=91 (IV) initiated use with ≥2 APs
Final study sample	n=6,087 persons with and without AD	n=6,740 persons with AD of which n=2,287 AP users	n=57,588 persons with AD (III) n=57,755 persons with AD (IV)	n=16,972 new AP users (III) n=17,731 new AP users (IV)

MEDALZ=Medication use and Alzheimer's disease, AD=Alzheimer's disease, AP=Antipsychotic drug

4.5 COVARIATES

Data on comorbidities were extracted from the Special Reimbursement and Hospital Discharge registers and information on use of other drugs was extracted from the drug use periods modeled with the PRE2DUP method from the Prescription Register data. The definition and measurement points for each covariate are described in Table 11. Measurement point may vary in specific substudies.

Table 11. Definitions of covariates used in substudies I-IV

Covariates	Measurement point	Definition
Covariates extracted from the Special Reimbursement Register		
Cardiovascular diseases (II, III), Asthma/COPD (II), Diabetes (II, III), Epilepsy (III), Glaucoma (III), Rheumatoid arthritis (II, III)	Since 1972 until - the initiation of AP use (II) - the start of follow-up (III)	Cardiovascular diseases included entitlement to special reimbursement for chronic heart failure, chronic arterial hypertension, coronary artery disease or chronic arrhythmias. Other covariates were based on entitlement to special reimbursement for chronic asthma/COPD, diabetes, epilepsy, glaucoma, or rheumatoid arthritis and disseminated connective tissue diseases
Cancer	Since 1972 until the initiation of AP use (II)	Cancer included entitlement to special reimbursement for leukemia and other malignant diseases of blood and bone marrow as well as malignant diseases of the lymphatic system, breast cancer, prostate cancer, cancers of the female genital tract, and malignant neoplasms not mentioned above
Modified Charlson Comorbidity Index score (Charlson et al. 1987)	Since 1972 until the start of follow-up (IV)	Score was computed on the basis of comorbidities extracted from the Special Reimbursement Register Score of 1: asthma or COPD, coronary artery disease, heart failure, diabetes, rheumatoid arthritis and disseminated connective tissue disease Score of 2: uremia requiring dialysis, severe anemia in connection with chronic renal failure, leukemia, other malignant diseases of blood and bone marrow, malignant neoplasms, gynecological, breast and prostate cancers
Covariates extracted from the Hospital Discharge Register		
History of bipolar disorder or mania History of schizophrenia, schizotypal or delusional disorders	Since 1972 - until the diagnosis of AD (I) - diagnosed at least 3 years before AD diagnosis (II) - diagnosed at least 5 years before AD diagnosis (III, IV)	Bipolar disorder or mania included diagnoses extracted using ICD-10 codes F30-F31, ICD-9 codes 2962, 2963, 2964, 2967, and ICD-8 codes 29610,29620, 29630, 29688, 29699 Schizophrenia, schizotypal or delusional disorders included diagnoses extracted using ICD-10 codes F20-F29, ICD-9 codes 295*, 297*, 298*, 3010, 3012, and ICD-8 codes 295*, 297*, 298*, 29999, 30100, 30120
History of ischemic cardiac events	Diagnoses since 1972 and revascularization procedures since 1996 until the start of follow-up (IV)	Diagnoses extracted using ICD-10 codes I20-I25, ICD-9 codes 410-414, and ICD-8 codes 410-414 Or record of revascularization procedures by bypass (NOMESCO Classification of Surgical Procedures codes FNA*, FNC*, FNE*) or angioplasty (NOMESCO codes FNG00, FNG10, FN1AT, FN1BT, FN1YT)
History of hip fracture	Since 1972 until the start of follow-up (III, IV)	Hip fracture included diagnoses extracted using ICD-10 codes S72.0-S72.2, ICD-9 codes 820, and ICD-8 codes 82000, 82010, 82090, 82001, 82011, 82091

ICD=International Classification of Diseases; NOMESCO=Nordic Medico-Statistical Committee

(Continued)

Table 11. (Continued)

Covariates	Measurement point	Definition
Covariates extracted from the Hospital Discharge Register		
History of stroke	Since 1972 until the start of follow-up (III, IV)	Stroke included diagnoses extracted using ICD-10 codes I60-I64 , ICD-9 codes 430, 431, 432, 4339A, 4340A, 4341A, 4349A, 4360, and ICD-8 codes 430, 431, 432, 433, 434
Covariates extracted from the Prescription Register		
Osteoporosis	Since 1995 until the start of follow-up (III)	A history of use of drugs affecting bone structure and mineralization (M05B) was used as a proxy for osteoporosis
Number of drugs	At the time of AP initiation (II)	Number of ongoing drug use periods of other drugs (all ATC codes excluding antipsychotics)
Use of antidementia drugs	At the time of AP initiation (II)	Ongoing drug use periods of N06DA (acetylcholinesterase inhibitors) or N06DX01 (memantine)
Use of antidepressants	Time-dependent use during follow-up (IV) At the time of AP initiation (drug-drug comparisons in Study IV)	Ongoing drug use periods of N06A (antidepressants) or N06CA (antidepressants in combination with psycholeptics)
Use of benzodiazepines and related drugs	Time-dependent use during follow-up (IV) At the time of AP initiation (drug-drug comparisons in Study IV)	Ongoing drug use periods of N05BA, N05CF (benzodiazepines) or N05CD (related drugs)
Use of other psychotropics	Time-dependent use during follow-up (III) At the time of AP initiation (Study II and drug-drug comparisons in Study III)	Ongoing drug use periods of N05BA, N05CF (benzodiazepines), N05CD (related drugs), N06A (antidepressants), or N06CA (antidepressants in combination with psycholeptics)
Use of opioids	Time-dependent use during follow-up (III, IV) At the time of AP initiation (drug-drug comparisons in Studies III and IV)	Ongoing drug use periods of N02A (opioids)
Covariates extracted based on data from all three above-mentioned registers		
Active cancer	Within 12 months before the start of follow-up (exclusion criteria in Study IV) During follow-up (censoring event in Study IV)	Any cancer as a main or an auxiliary diagnosis in the Hospital Discharge Register or anticancer drug purchases in the Prescription Register including L01 (antineoplastic agents), L02 (endocrine therapy), L03AA (colony stimulating factors), L03AB01 (interferon alpha natural), L03AB04 (interferon alpha-2a), L03AB05 (interferon alpha-2b), L03AC (interleukins), L03AX (other immunostimulants, excluding L03AX13, glatiramer acetate), L04AA10 (sirolimus), L04AA18 (everolimus), L04AA34 (alemtuzumab), L04AX02 (thalidomide) and L04AX03 or L01BA01 (methotrexate, excluding persons with entitlement to special reimbursement for rheumatoid arthritis).

ICD=International Classification of Diseases; NOMESCO=Nordic Medico-Statistical Committee

4.6 STATISTICAL ANALYSES

All analyses were performed using SAS software (with version 9.3; SAS Institute Inc., Cary, NC, USA).

In Study I, Poisson regression was used to compute incidence rate ratios (IRRs) and 95% confidence intervals (CIs) for every 6-month period to estimate if there were differences in the incidences of antipsychotic use between persons with and without AD.

In Study II, the duration of antipsychotic use was reported in days using medians and interquartile ranges (IQRs) and logistic regression was used to study factors associated with long-term use. Logistic regression analyses were restricted to antipsychotic users (n=1,563) with at least 365 days of follow-up time after the first initiation of antipsychotic use and thus, with a possibility to continue use of antipsychotics for at least one year. Factors included in the adjusted model were age at the time of initiation, sex, use of other psychotropic drugs, initiation of antipsychotic use before AD diagnosis and initial antipsychotic drug. A subanalysis was performed to study whether antidementia drug use differed between short- and long-term antipsychotic users who started antipsychotic use after the AD diagnosis. In addition, a second subanalysis was conducted to determine whether prescriber's specialty was associated with duration of antipsychotic use. Analysis was restricted to persons who initiated antipsychotic use between 2004 and 2009 as information on the prescriber's specialty was not available for the years 2002 and 2003.

In the primary analyses conducted in Studies III and IV, hazard ratios (HRs) with 95% CIs were calculated using Cox proportional hazards model with antipsychotic use as a time-dependent variable. Person-time was accounted for nonusers until or if the individual initiated antipsychotic use, after which, the person-time was accounted for antipsychotic use, until outcome event or censoring, whichever occurred first. In addition, in the analyses of antipsychotic monotherapy and polypharmacy compared with time without antipsychotics, person-time was classified time-dependently as antipsychotic monotherapy when only one antipsychotic drug was used and as polypharmacy during time periods when more than two antipsychotics were used concomitantly. In Study III, there was an insufficient power to compare antipsychotic polypharmacy and monotherapy, due to the low number of hip fractures (n=19) occurring during antipsychotic polypharmacy (615 person-years of use). Thus, these comparisons are not reported for the risk of hip fracture. To analyze whether the risk of hip fracture or mortality varied with the duration of exposure, the duration of antipsychotic use was classified time-dependently. All the primary analyses were adjusted for baseline and time-dependent covariates. In Study III, baseline covariates included age, sex, history of stroke, osteoporosis, rheumatoid arthritis, glaucoma, diabetes, cardiovascular disease and epilepsy and time-dependent covariates included use of other psychotropics and opioids during the follow-up. In Study IV, baseline covariates included age, sex, modified Charlson Comorbidity Index score, history of stroke, hip fracture and ischemic cardiac events and time-dependent covariates included use of other benzodiazepines and related drugs, antidepressants and opioids during the follow-up. To control better for the impact of AD severity and progression of the disease in Study IV, sensitivity analysis was conducted by matching two nonusers to each antipsychotic user for the date of initiation of antipsychotic use by incidence density sampling (exposure matched cohort). The matching criteria for nonuser-controls were time since AD diagnosis (±90 days), age (±2 years) and sex.

Drug-drug comparisons were restricted to the two (Study III) or three (Study IV) most frequently used antipsychotic drugs, due to the low number users of other antipsychotic drugs (Appendix I). Risperidone was used as the reference group in the Cox proportional hazards model because it was the most frequently used antipsychotic and it has been commonly used as a reference group in previous studies (Schneeweiss et al. 2007, Huybrechts et al. 2012a, Huybrechts et al. 2012b, Kales et al. 2012, Gerhard et al. 2014, Sahlberg et al. 2015, Schmedt et al. 2016b). In the drug-drug comparisons of Study III, the follow-up was restricted to the first 1,500 days of use and in Study IV to the first 1,000 days of use to account for data

sparsity. The sample log cumulative hazard functions were used to evaluate the proportional hazards assumption. According to these, the risk of hip fracture was equal among users of risperidone and quetiapine during the first 1,000 days, but thereafter, it remained higher for risperidone than for quetiapine. Thus, a cut-point of 1,000 days was applied along with the programming statement method. In Study III, drug-drug comparisons were adjusted for sex, age, history of stroke, osteoporosis, rheumatoid arthritis, glaucoma, diabetes, cardiovascular disease, epilepsy, use of other psychotropics and opioids at the time of initation of antipsychotic use. In study IV, drug-drug comparisons were adjusted for age, sex, time since AD diagnosis, Charlson Comorbidity Index score, history of stroke, hip fracture and ischemic cardiac event, and use of benzodiazepines, antidepressants and opioids at the time of antipsychotic initiation. In addition, the dose-dependent effects were analyzed in both Studies III and IV. The dose per day represented the average dose from the entire antipsychotic use period. Risperidone doses per day were categorized into ≤0.5 mg (0.1 DDD) (reference category) and >0.5 mg, quetiapine doses per day into ≤50 mg (0.125 DDD) and >50 mg and haloperidol doses per day into ≤1 mg (0.125 DDD) and >1 mg.

4.7 ETHICAL CONSIDERATIONS

According to the Finnish legislation, no ethics committee approval was required because only de-identified register-based data were used and the study participants were not contacted.

5 Results

5.1 INCIDENCE OF ANTIPSYCHOTIC USE (STUDY I)

During the 12-year follow-up, 32.8% (1,996/6,087) of community-dwelling persons with AD initiated antipsychotic use. The incidence of antipsychotic use was five times (IRR 5.17; 95% CI 4.64-5.77) the rate in the matched controls without AD, of which 6.3% (n=386) initiated antipsychotic use. The rate of new antipsychotic users among persons with AD significantly increased 2-3 years before AD diagnosis compared with the rate among the controls without AD (Figure 7). The incidence of antipsychotic use was highest during the first 6 months after the AD diagnosis (13.9 new users per 100 person-years) and remained at a high level thereafter (8.6-11.3 new users per 100 person-years). The incidence of antipsychotic use among the matched controls without AD remained stable during the 12-year follow-up ranging between 0.2 and 1.3 new users per 100 person-years.

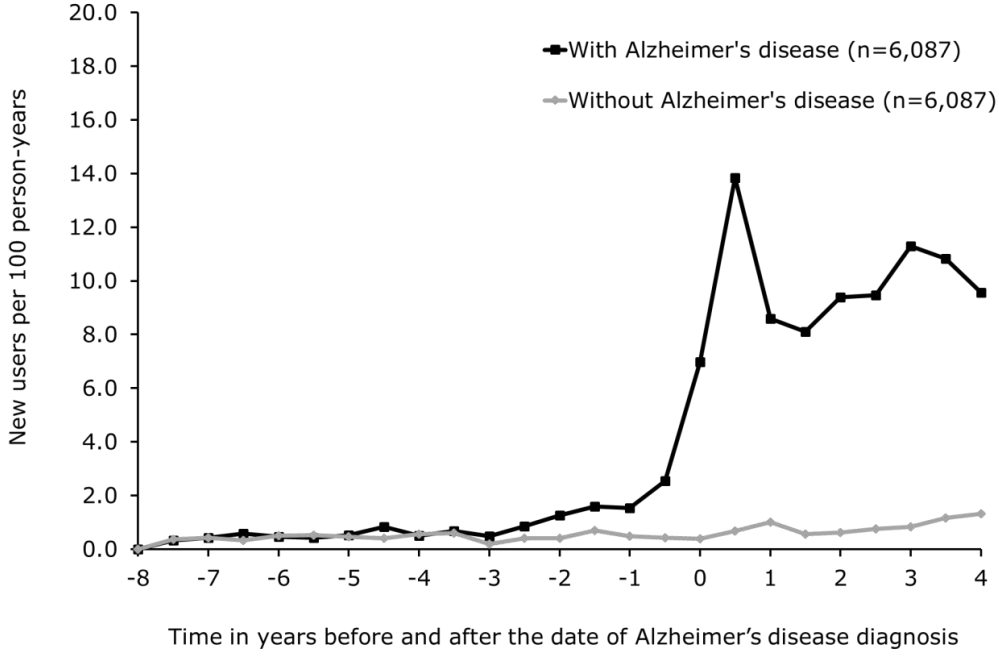

Figure 7. Incidence of antipsychotic use in relation to diagnosis of AD. The date of AD diagnosis of the person with AD was defined as the index date (point zero) for the matched control without AD. Reproduced with permission of The Royal College of Psychiatrists via PLSClear. The publication is available at RCPsych through http://dx.doi.org/10.1192/bjp.bp.114.162834.

5.2 DURATION OF ANTIPSYCHOTIC USE (STUDY II)

During the 7-year follow-up, 33.9% (2,287/6,740) of community dwellers with AD initiated antipsychotic use. The median duration of the first antipsychotic use period was 219 days (Table 12). The number of antipsychotic use periods per user varied from 1 to 11 and 25.2% (n=576) had more than one period of antipsychotic use. Of those who discontinued use (n=1,303), 44.2% restarted use later. The median duration of all periods counted together was 363 (IQR 126-747) days.

Table 12. Duration of first antipsychotic use period

	All antipsychotic users (n=2,287)	**Users with possibility to use antipsychotics over a year (n=1,563)[a]**
Median duration in days (IQR)	219 (85-583)	443 (126-763)
Antipsychotic lasted for, % (n)		
<3 months	25.7 (587)	16.0 (250)
3-6 months	19.2 (438)	15.7 (246)
6-12 months	16.1 (369)	11.1 (174)
12-24 months	20.8 (475)	30.4 (475)
≥24 months	18.3 (418)	26.7 (418)

[a]Including those persons with at least one year of follow-up time after initiating antipsychotic use

Of the first antipsychotic use periods, 39.0% lasted over a year (Table 12). However, during the first year after initiation, 20.7% of antipsychotic use periods ended due to hospitalization/institutionalization, death or the end of study period. Among users with at least one year of follow-up time after initiating antipsychotic use (n=1,563), the prevalence of long-term use was 57.1%. Long-term use was associated with the initiation of use after the AD diagnosis and choice of initial antipsychotic (Table 13). The duration of use was more likely to be shorter among haloperidol users and longer among quetiapine users than in risperidone users (Figure 8).

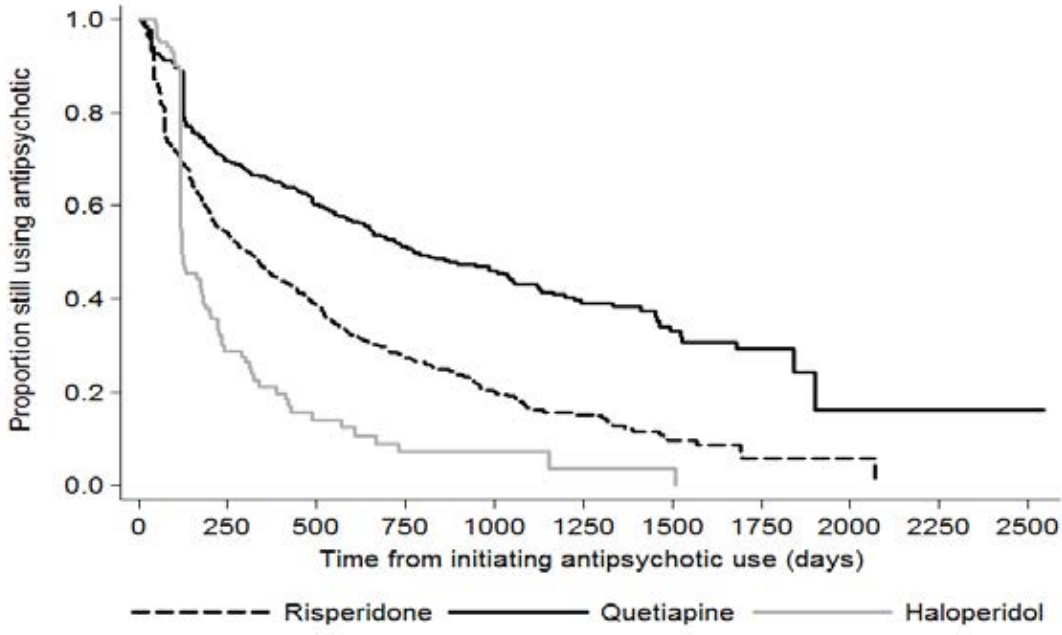

Figure 8. Time to discontinuation of antipsychotic use for three most frequently used antipsychotics. Users switching between antipsychotic drugs were excluded from this analysis.

Table 13. Factors associated with long-term antipsychotic use

	Duration of use <365 days n=670 N (%)	**Duration of use ≥365 days n=893 N (%)**	**Unadjusted OR (95% CI)**	**Adjusted OR (95% CI)**
Age at the time of initiation				
<75 years	110 (16.4)	172 (19.3)	1.00	1.00
75-84 years	367 (54.8)	496 (55.5)	0.86 (0.66-1.14)	0.84 (0.63-1.12)
≥85 years	193 (28.8)	225 (25.2)	0.75 (0.55-1.01)	0.69 (0.50-0.95)
Sex, female	463 (69.1)	613 (68.7)	0.98 (0.79-1.22)	1.05 (0.84-1.32)
Diabetes	82 (12.2)	97 (10.9)	0.87 (0.64-1.20)	
Cardiovascular disease	366 (54.6)	455 (51.0)	0.86 (0.71-1.06)	
Asthma/COPD	55 (8.2)	66 (7.4)	0.89 (0.62-1.30)	
Cancer	24 (3.6)	29 (3.3)	0.90 (0.52-1.57)	
Rheumatoid arthritis	21 (3.1)	45 (5.0)	1.64 (0.97-2.78)	
Number of drugs at the time of initiation				
≥10 drugs	73 (10.9)	92 (10.3)	0.94 (0.68-1.30)	
Other psychotropic drugs at the time of initiation				
No use	353 (52.7)	475 (53.2)	1.00	1.00
1 psychotropic drug	222 (33.1)	276 (30.9)	0.92 (0.74-1.16)	0.92 (0.73-1.16)
≥2 psychotropic drugs	95 (14.2)	142 (15.9)	1.11 (0.83-1.49)	1.14 (0.84-1.55)
Use was initiated				
Before AD diagnosis	228 (34.0)	228 (25.5)	1.00	1.00
After AD diagnosis	442 (66.0)	665 (74.5)	1.51 (1.21-1.87)	1.39 (1.10-1.75)
Initiating antipsychotic				
Risperidone	370 (55.2)	430 (48.2)	1.00	1.00
Quetiapine	142 (21.2)	336 (37.6)	2.04 (1.60-2.60)	2.06 (1.61-2.62)
Haloperidol	68 (10.1)	29 (3.2)	0.37 (0.23-0.58)	0.40 (0.25-0.63)
Melperone	34 (5.1)	47 (5.3)	1.19 (0.75-1.89)	1.31 (0.82-2.10)
Other	56 (8.4)	51 (5.7)	0.78 (0.52-1.17)	0.83 (0.54-1.26)

Factors included in the adjusted model were age, sex, use of other psychotropics, timing of initiation of antipsychotic use and initiating antipsychotic. COPD=chronic obstructive pulmonary disease

Persons aged 85 years or older were less likely to be long-term users compared with those aged less than 75 years (Table 13). According to the subanalyses (Study II), the use of antidementia drugs at the time of antipsychotic initiation was not associated with duration of antipsychotic use (Adjusted OR 1.02 95% CI 0.77-1.36). Half (52.8%) of the first antipsychotic prescriptions were written by specialists. No differences were found in the duration of antipsychotic use initiated by a physician without specialty compared with use initiated by specialists (OR 1.20 95% CI 0.97-1.49).

5.3 ANTIPSYCHOTIC USE AND RISK OF HIP FRACTURE AND MORTALITY (STUDIES III AND IV)

Antipsychotic use was associated with an increased risk of hip fracture (adjusted HR 1.54; 95% CI 1.39-1.70) and mortality (adjusted HR 1.61; 95% CI 1.53-1.70) among community dwellers with AD (Figure 9, Figure 10A). During antipsychotic use, the age-adjusted hip fracture rate was 2.70 (95% CI 2.46-2.95) per 100 person-years compared with 1.65 (95% CI 1.58-1.71) hip fractures occurring per 100 person-years of nonuse. The age-adjusted mortality rate was 9.34 (95% CI 8.91-9.77) per 100 person-years of antipsychotic use compared with 5.24 (95% CI 5.14-5.35) deaths per 100 person-years of nonuse. Both the risk of hip fracture and the risk of mortality were elevated from the first days of antipsychotic use and remained elevated with long-term use (Figure 9, Figure 10A).

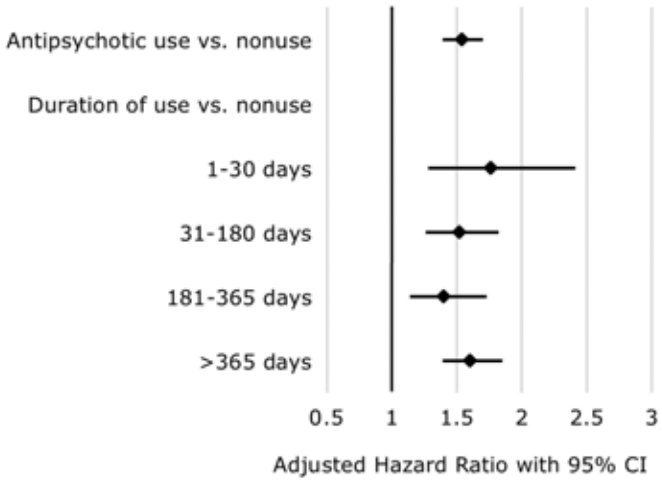

Figure 9. Adjusted hazard ratios for risk of hip fracture by antipsychotic use. Analyses were adjusted for sex, age, history of stroke, osteoporosis, rheumatoid arthritis, glaucoma, diabetes, cardiovascular disease and epilepsy. Use of other psychotropics and opioids treated as time-dependent covariates.

Compared with nonuse, antipsychotic polypharmacy (adjusted HR 2.88; 95% CI 2.38-3.49) was associated with higher mortality than monotherapy (adjusted HR 1.57; 95% CI 1.49-1.66) (Figure 10A). The age-adjusted mortality rates were 9.06 (95% CI 8.63-9.49) and 17.09 (95% CI 14.21-19.97) deaths per 100 person-years for monotherapy and antipsychotic polypharmacy, respectively. The most frequently used combination during antipsychotic polypharmacy was quetiapine and risperidone (54.4%) followed by haloperidol and risperidone (8.6%).

The results of sensitivity analyses comparing mortality risk of antipsychotic users with age-, sex- and time since AD diagnosis matched nonusers resulted in similar results as the main analyses although the HRs were somewhat attenuated (Figure 10B).

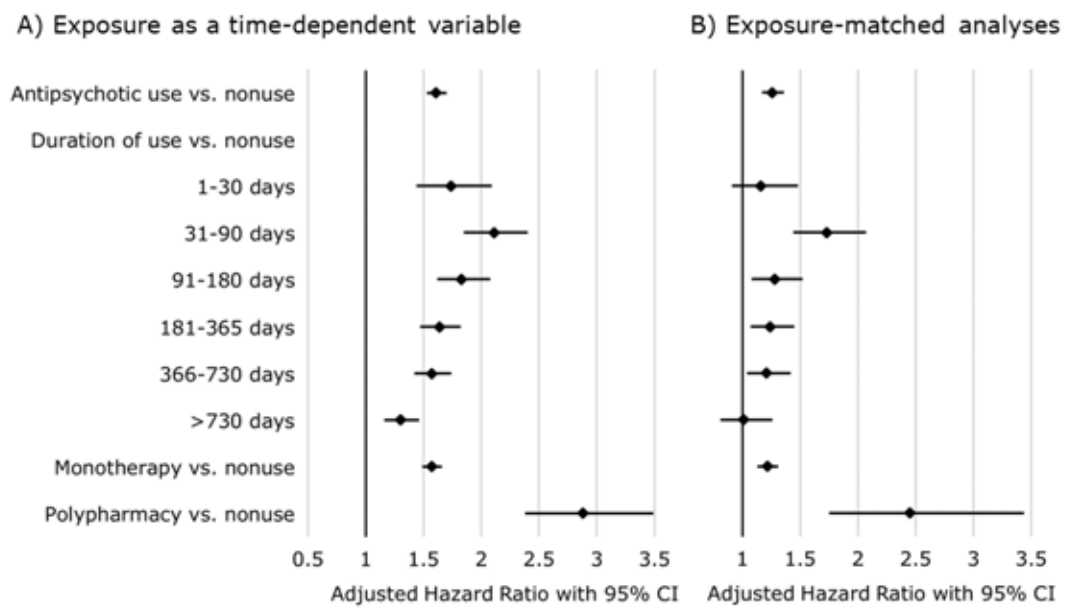

Figure 10. Adjusted hazard ratios for mortality by antipsychotic use (A) in main analyses with antipsychotic use as time-dependent variable and (B) in sensitivity analyses with exposure-matched cohort. Analyses were adjusted for sex, age, Charlson Comorbidity Index score, and for history of stroke, hip fracture and ischemic cardiac events. Use of benzodiazepines, antidepressants and opioids treated as time-dependent covariates.

5.3.1 Drug-drug comparisons between the most frequently used antipsychotics

Haloperidol use was associated with higher risk of mortality (adjusted HR 1.52; 95% CI 1.14-2.02) and quetiapine use with lower risk (adjusted HR 0.84; 95% CI 0.75-0.94) compared with risperidone use (Figure 11). There was no difference in the hip fracture risk between quetiapine and risperidone during the first 2.7 years of use (adjusted HR 0.98; 95% CI 0.79-1.21). However, from 2.7 to 4.1 years, the hip fracture risk was lower among quetiapine users compared with risperidone users (adjusted HR 0.24; 95% CI 0.10-0.59).

In comparison with low-dose (≤0.5 mg/day) risperidone use, higher risperidone doses per day were associated with a higher risk of hip fracture (adjusted HR 1.72; 95% CI 1.32-2.24) and mortality (adjusted HR 1.57; 95% CI 1.36-1.81) (Figure 11). Both low (≤50 mg) and higher doses (>50 mg) of quetiapine per day were associated with a similar risk of hip fracture as low-dose risperidone use. However, quetiapine dose ≤50 mg per day was associated with slightly higher mortality (adjusted HR 1.18; 95% CI 1.00-1.38) compared with low-dose risperidone use. Both haloperidol doses per day, ≤1 mg and >1 mg, (adjusted HR 1.66; 95% CI 1.10-2.50 and 2.55; 95% CI 1.70-3.85; respectively) were associated with an increased risk of mortality when compared with low-dose risperidone use.

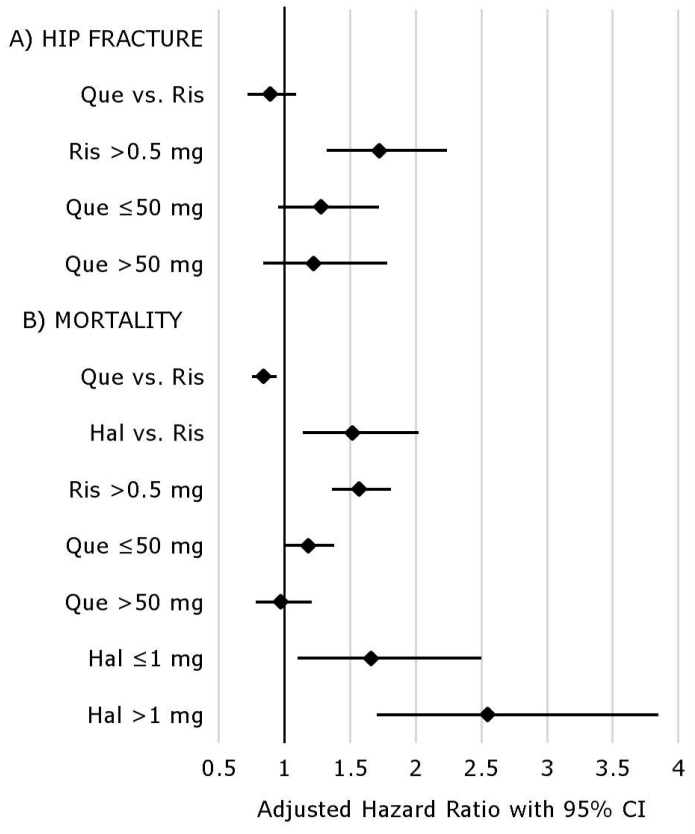

Figure 11. Adjusted hazard ratios for risk of hip fracture (A) and mortality (B) by most frequently used antipsychotic drugs and by dose of antipsychotic drugs. Quetiapine (Que) and haloperidol (Hal) use was compared with risperidone use (Ris). In dose analyses, risperidone use with dose ≤0.5 mg per day is the reference category. Hip fracture (A) analyses were adjusted for sex, age, history of stroke, osteoporosis, rheumatoid arthritis, glaucoma, diabetes, cardiovascular disease, epilepsy, use of other psychotropics and opioids at the time of initiation of antipsychotic use. Mortality (B) analyses were adjusted for sex, age, Charlson Comorbidity Index score, history of stroke, hip fracture and ischemic cardiac events, time since AD diagnosis, use of benzodiazepines, antidepressants and opioids at the time of initiation of antipsychotic use.

6 Discussion

6.1 INCIDENCE OF ANTIPSYCHOTIC USE IN RELATION TO DIAGNOSIS OF ALZHEIMER'S DISEASE (STUDY I)

The highest rate of new antipsychotic users was observed during the first six months after AD diagnosis and the incidence remained at a high level thereafter (Study I). A distinct increase in antipsychotic initiations occurred six months before and after the AD diagnosis. These findings are similar to the results of Martinez et al. (2013) who noted a sharp increase in the prevalence of antipsychotic use around the time of diagnosis among community-dwelling persons with dementia in the UK. However, antipsychotics are not the only psychotropic drugs that are initiated frequently around the time of AD diagnosis in Finland (Saarelainen et al. 2016, Puranen et al. 2017). The incidence of initiation of both antidepressants and benzodiazepines and related drug use was highest during the first six months after the AD diagnosis. The Finnish Current Care Guideline recommends that all individuals with AD should be treated with AChEIs and/or memantine unless there is a specific contraindication (Memory disorders: Current Care Guidelines 2017). Accordingly, the prevalence of antidementia drug use is high among community-dwelling persons with AD in Finland (Taipale et al. 2014c, Törmälehto et al. 2015). In addition to non-pharmacological treatment options, antidementia drugs are recommended as the first-line pharmacological treatment for BPSD in Finland (Memory disorders: Current Care Guidelines 2017). However, the high incidence of antipsychotic and other psychotropic use around the time of AD diagnosis indicates that the treatment of BPSD may not be following these guidelines. It seems that antipsychotics and other psychotropic drugs are frequently initiated soon after AD diagnosis which is also the time when AChEI therapy is initiated and the dose is optimized. It is recommended that both the tolerability and the optimal dose should be reviewed 2-3 months after initiation of AChEI use whereas the response should be assessed after 6 months of use (Memory disorders: Current Care Guidelines 2017). As antipsychotics and benzodiazepines and related drugs may further impair cognitive function (Barker et al. 2004, Vigen et al. 2011, Rosenberg et al. 2012, Defrancesco et al. 2015), the rationality of initiating these drugs when trying to obtain the best response to AChEI therapy is questionable.

The incidence of antipsychotic use was five-fold in community-dwelling Finns with AD compared with those without AD (Study I). The rate of antipsychotic initiations started to increase already 2 to 3 years before the diagnosis of AD. Similarly in the UK, Martinez et al. (2013) found an increasing prevalence of antipsychotic and antidepressant use in the years before the diagnosis of dementia. In addition, the use of anxiolytics and hypnotics started to increase in the single year before the dementia diagnosis. Accordingly, recent studies from the MEDALZ data have also shown that use of other psychotropics starts to increase before the diagnosis of AD. The incidence rate of antidepressant use was higher already nine years before AD diagnosis (Puranen et al. 2017) and the incidence of benzodiazepine and related drug use started to increase one year before the diagnosis (Saarelainen et al. 2016). Behavioral and psychological symptoms are frequent in individuals with MCI and have been associated with an increased risk of progressing to all cause or AD dementia (Monastero et al. 2009, Rosenberg et al. 2013, Forrester et al. 2016). Thus, the appearance of behavioral and psychological symptoms in the prodromal predementia phase of AD could explain the increased use of antipsychotics and other psychotropics before the diagnosis of AD dementia. On the other hand, the increased use of antipsychotics and benzodiazepines and related drugs before the diagnosis of AD could partly result from the treatment of delirium. Dementia is a major risk factor for delirium (Inouye et al. 2014) and delirium increases the

likelihood for being diagnosed with dementia in initially non-demented patients (Rockwood et al. 1999, Rahkonen et al. 2000). Thus, delirium might have prompted physicians to examine and recognize underlying cognitive impairment.

Of the individuals entitled to reimbursement for antidementia drugs, 21% have been shown to have dementia or AD related hospital visits before the AD diagnosis is recorded in the Special Reimbursement Register (Heiskanen et al. 2016). According to Heiskanen et al. (2016), hospital visits began to accumulate 2-3 years before the AD diagnosis with the vast majority, 90%, of the stays taking place within one year before AD diagnosis. Part of this delay is due to the diagnostic process that may take several months, even more than six months. Thus, the increasing incidence of antipsychotic use observed before the AD diagnosis is recorded may reflect the concurrent start of the diagnostic process.

Since behavioral and psychological disturbances may be among one of the earliest symptoms of AD, a better assessment of these signs might lead to earlier diagnosis (Lyketsos et al. 2011). Early diagnosis is important as it enables access to available antidementia drugs and non-pharmacological interventions (Prince et al. 2011). The aim of early treatment is to enhance cognition, maintain daily functioning, reduce BPSD, improve quality of life of persons with AD and their caregivers, and delay institutionalization. Some interventions might be more effective if therapy is initiated in the earliest phases of AD.

6.2 DURATION OF ANTIPSYCHOTIC USE AMONG COMMUNITY-DWELLING PERSONS WITH ALZHEIMER'S DISEASE (STUDY II)

Long-term use of antipsychotics was frequent among community-dwelling Finns with AD (Study II). More than half of new antipsychotic users who had at least one year of follow-up time continued to use these drugs for over a year. The observed duration of use is not in line with guidelines recommending time-limited use of antipsychotics (Azermai et al. 2012, Zuidema et al. 2015, APA 2016, Memory disorders: Current Care Guidelines 2017). Patients with AD can experience a wide variety of BPSD during the course of the disease but antipsychotics should be used only in the treatment of those symptoms for which there is a demonstrated efficacy (Kales et al. 2015). In short-term clinical trials, antipsychotics have been shown to have minor benefits on aggression and psychosis over 6-12 weeks (Lonergan et al. 2002, Ballard et al. 2006, Maher et al. 2011). However, there is less evidence for the efficacy of antipsychotics with longer treatment (Ballard and Corbett 2013, Declercq et al. 2013). Furthermore, the clinical implications of the small changes in overall behavioral rating scale scores are difficult to interpret (Sink et al. 2005, Ballard et al. 2006). It would be more useful to determine the impact of antipsychotics on specific clinically significant symptoms and outcomes such as nursing home placement, quality of life and caregiver burden.

The persistence of BPSD differs between individuals and individual symptoms (Eustace et al. 2002, Ryu et al. 2005). Delusions, aggression and agitation with any severity have been found to be moderately persistent among persons with AD with the time interval between evaluations varying from six months to one year (Eustace et al. 2002, Ryu et al. 2005). The persistence of clinically significant agitation/aggression was lower (38%) compared with symptoms with any severity (65%) at six months' evaluations (Ryu et al. 2005). Hallucinations were the least persistent symptoms (Eustace et al. 2002, Ryu et al. 2005). As symptoms may resolve by themselves, the need for antipsychotic use should be assessed regularly and withdrawal attempted after behavioral stability (Kales et al. 2015, Zuidema et al. 2015, Memory disorders: Current Care Guidelines 2017). The American Psychiatric Association recommends an attempt of withdrawal within 4 months after the initiation of antipsychotic use unless previous attempts have led to a recurrence of symptoms (APA 2016). Since the register-based data did not include information on the type and severity of BPSD, the necessity of long-term antipsychotic use could not be assessed. Furthermore, it is not known whether treatment with antipsychotics was effective or whether symptoms would

have remained stable, worsened or improved if antipsychotic drug use had been discontinued.

According to a Cochrane review, chronic antipsychotic use can be withdrawn successfully in many persons with AD without detrimental effects on their behavior (Declercq et al. 2013). However, some of the studies included in that review suggested that persons with more severe BPSD responding well to antipsychotics might benefit from continuation of antipsychotic use. Clinical trials have used varying approaches to withdraw antipsychotic use including abrupt discontinuation, short-term tapering and mixed tapering strategies based on the doses used (Tjia et al. 2015). Tjia et al. (2015) suggested that gradual tapering could lead to more successful discontinuation of use. A recent study indicated that if nursing home residents with dementia are subjected to an antipsychotic review, then this reduced antipsychotic use (Ballard et al. 2016). However, the antipsychotic review alone lead to worsening of overall BPSD although mortality was reduced. On the other hand, combining social interaction with an antipsychotic review reduced both antipsychotic use and mortality without leading to any deterioration of BPSD. These findings imply that combining non-pharmacological interventions with an antipsychotic review results in more successful discontinuation of antipsychotic use and improves outcomes. According to Ballard et al. (2016), the importance of evidence-based non-pharmacological interventions should be emphasized when updating treatment guidelines.

Other studies have reported varying results with regard to the persistence of antipsychotic use among persons with dementia living in the community (Kim et al. 2015, Booker et al. 2016, Boucherie et al. 2017) or mixed residential settings (Guthrie et al. 2010, Puyat et al. 2012, Mast et al. 2016, Nørgaard et al. 2016, Schmedt et al. 2016a). The comparability of the results is affected by the differences in methods used to define and measure duration and persistence of antipsychotic use. Four of these studies reported the persistence of use for over six months. The proportions of antipsychotic users continuing with the therapy have varied somewhat in the different studies i.e. 63% (Puyat et al. 2012), 72% (Guthrie et al. 2010) and 76% (Booker et al. 2016) and furthermore Mast et al. (2016) reported that 24% had discontinued use by six months after initiation. In Study II, 68% of incident users with AD continued antipsychotic use for six months or longer. Thus, in these four studies, the duration of use was similarly prolonged as in this Finnish cohort of community dwellers with AD. In a Cochrane review considering withdrawal of antipsychotic treatment in dementia, chronic use of antipsychotics was defined as duration of use lasting over three months (Declercq et al. 2013). In Study II, the actual proportion of those who discontinued use within less than three months was 16%. Three other studies have reported lower persistence of use for over three months (Kim et al. 2015, Nørgaard et al. 2016, Boucherie et al. 2017). Kim et al. (2015) reported that 55% discontinued within three months and 36% continued using the same antipsychotic drug. Both Boucherie et al. (2017) and Nørgaard et al. (2016) reported that approximately 27% of users continued antipsychotic drug use for over three months and were defined as long-term users. However, Boucherie et al. 2017 demonstrated that when hospital periods were included into the duration of use, the proportion of long-term users increased to 46%. Thus, the methods used to define continuous use can have a major impact on the results.

Long-term use was associated with the initiation of use after AD diagnosis (Study II). This might be due to differences in the severity or type of symptoms for which antipsychotics were used before and after AD diagnosis. As the disease progresses, the symptoms for which antipsychotics were prescribed after diagnosis could have been more severe. However, since the register-based data did not include information on either the type or the severity of symptoms or any knowledge of the severity stage of AD, these assumptions could not be tested. Part of the shorter antipsychotic use before AD diagnosis could be explained by use of antipsychotics to treat delirium, as delirium increases the likelihood of being diagnosed with dementia (Rockwood et al. 1999, Rahkonen et al. 2000). On the other hand, medication may have been reviewed at the time of AD diagnosis which may have prompted withdrawal of antipsychotic use in some persons that had been initiated before diagnosis.

Individuals with AD aged 85 years and over were less likely to be long-term users compared with those aged less than 75 years (Study II). This lower persistence of antipsychotic use may imply higher susceptibility to adverse effects leading to earlier discontinuation of use or to a more careful consideration of the risks and benefits of antipsychotic use among the oldest old. On the other hand, those aged less than 75 years might be less frail and they could be assessed as being more threatening to their caregiver, lowering the threshold for prolonged antipsychotic use to treat BPSD. Similarly, Boucherie et al. (2017) found that short-term users were more likely to be older than 85 years. On the contrary, Booker et al. (2016) found that higher age was associated with more persistent use. Unlike in Study II, in both of these studies, long-term users were more likely to be women. In addition, Boucherie et al. (2017) reported that long-term antipsychotic users were also more likely to be benzodiazepine users. Booker et al. (2016) found that living in nursing homes was associated with more persistent use whereas depression and Parkinson's disease decreased persistence. Mast et al. (2016) reported that antipsychotic users who initiated with a higher dose discontinued more frequently which may reflect a higher risk of adverse effects associated with higher doses. In summary, the actual reasons behind the frequent long-term use of antipsychotics observed in this and other studies were not revealed.

There is a lack of studies investigating barriers to discontinuation of antipsychotic use among community dwellers. Azermai et al. (2014) has studied nurses' and general practitioners' willingness to discontinue antipsychotic use in a nursing home setting. They found that nurses and general practitioners thought there were high barriers to discontinuation and would have been only willing to try discontinuation in a small proportion of residents, with a shared willingness in only 4% of the evaluated antipsychotic users. A higher willingness to attempt discontinuation existed for those antipsychotic users that were older, had high physical dependency, or were resident on a ward with controlled access. The main barriers were a belief that discontinuation would negatively affect the quality of life of the resident, BPSD would recur or there would be a risk of harm to the resident or others. General practitioners also felt that there were insufficient non-pharmacological alternatives. In a small qualitative study, psychiatrists treating older persons reported pressure to prescribe psychotropics for BPSD because of lack of viable alternatives, and lack of resources and time to implement non-pharmacological treatment approaches (Wood-Mitchell et al. 2008). They felt that guidelines are difficult to implement in clinical practice. These factors may explain why the duration of antipsychotic use is not in accordance with recommendations.

6.2.1 Differences in use patterns between the most common antipsychotics

Risperidone was the most frequently used antipsychotic drug among community-dwelling Finns with AD (Studies I-IV). Over half of the new antipsychotic users initiated use with risperidone. This is in line with the fact that risperidone is the only antipsychotic drug with an approved indication for the short-term treatment of severe aggression among persons with moderate to severe AD in Finland. The next most frequently used antipsychotic was quetiapine, almost 30% of antipsychotic users initiated use with that drug. Although risperidone, olanzapine and aripiprazole have been shown to have modest efficacy in the treatment of aggression and psychosis, there is a lack of evidence of benefits of quetiapine use in the treatment of BPSD (Ballard et al. 2006, Maher et al. 2011). Quetiapine is frequently used in the off-label treatment of insomnia (Carton et al. 2015) which could partly account for its high rate of use. The third most frequently used drug was haloperidol but it was used with a much lower rate as only about 6% initiated use with haloperidol in Study II and 3.5% in Studies III and IV. Haloperidol has efficacy in the treatment of aggression (Lonergan et al. 2002). In addition, haloperidol has been considered as a standard treatment option for delirium although atypical antipsychotics are thought to be as effective as haloperidol (Lonergan et al. 2007, Rea et al. 2007).

The duration of use differed between the three most frequently used antipsychotics (Study II); it was more likely to be longer for quetiapine users and shorter for haloperidol users when compared with risperidone users. These differences might be due to different indications for use e.g. more frequent use of quetiapine to treat insomnia and haloperidol to treat delirium might affect the use patterns in contrast to risperidone. However, as the Prescription Register does not contain data on indications for use, this assumption could not be confirmed. Another reason behind the observed differences could be related to different adverse effect profiles and their impact on time to discontinuation. Other studies have also found differences in use patterns between antipsychotic drugs among users with dementia (Kim et al. 2015, Booker et al. 2016). Booker et al. (2016) studied older Germans with dementia who received a first-time antipsychotic prescription from psychiatrist and found that atypical antipsychotic users were more likely to continue treatment than users of conventional antipsychotics. They suggested similarly that this difference in persistence may be explained by the properties of the drugs e.g. to the lower risk of developing serious adverse events with atypical than conventional antipsychotics. Kim et al. (2015) compared prescribing practice patterns in the 90 days after newly starting antipsychotic use among older persons with dementia using data from the US Department of Veterans Affairs. They found that continuing use over 90 days was more common with quetiapine (37.1%), followed by olanzapine (35.5%) and risperidone (34.7%). On the other hand, quetiapine was least frequently changed to another antipsychotic drug or psychotropic (5.7%), followed by risperidone (6.5%) and olanzapine (7.3%). However, they found no difference in treatment discontinuation between these three antipsychotics. Kim et al. (2015) discussed that if most common reasons for changing treatment are adverse events or lack of response, the results may suggest that quetiapine users may have experienced fewer adverse events or possibly responded better. However, similar to this register-based study (Study II), they did not have data on indications or the severity of symptoms and could not assess the response to antipsychotics. Thus, the findings of longer duration of quetiapine use should be interpreted with caution.

6.3 ANTIPSYCHOTIC USE ASSOCIATED WITH THE RISK OF HIP FRACTURE AND MORTALITY (STUDIES III AND IV)

Antipsychotics were associated with an increased risk of hip fracture and mortality among community-dwelling persons with AD (Studies III and IV). These results are in line with previous studies reporting increased risks of hip fracture and mortality among persons with and without dementia in various settings (Schneider et al. 2005, Rigler et al. 2013, Fraser et al. 2015, Maust et al. 2015, Simoni-Wastila et al. 2016).

Since the risks of both hip fracture and mortality were increased from the first days of use (Studies III and IV), the results of this thesis support the need to have a high threshold for prescribing antipsychotics to persons with AD. Although non-pharmacological options are recommended as the first-line treatment, antipsychotics may be needed to relieve the most severe symptoms including severe aggression and psychosis that cause unnecessary suffering or risk of harm to the patient or others (NICE 2006, Zuidema et al. 2015, APA 2016, Memory disorders: Current Care Guidelines 2017). If antipsychotic use is necessary, the response and emergence of adverse effects should be regularly and carefully monitored (Zuidema et al. 2015). A consensus guideline recommended monitoring of several medical risk factors including at least changes in cerebrovascular and cardiovascular status such as QT interval, cardiac arrhythmias and orthostatic hypotension, EPS, urine retention and sedation (Zuidema et al. 2015). Plans for monitoring the effects should be made already at initiating antipsychotics. According to Zuidema et al. (2015), a treatment plan should include a description of the target symptoms, treatment objectives, non-pharmacological interventions and how improvements and adverse effects will be monitored, time to evaluate

effects as well as routines for discontinuation. Detailed documentation of symptoms and medical risk factors is important as it aids in evaluating the effects of antipsychotics.

There is only a limited number of studies analyzing and reporting the risks associated with long-term antipsychotic use (Hugenholtz et al. 2005, Ballard et al. 2009, Pouwels et al. 2009, Jalbert et al. 2010, Langballe et al. 2014, Trifirò et al. 2014). The results of this thesis provide additional evidence that the risks of both hip fracture and mortality may remain elevated in long-term use (Studies III and IV). Thus, these results confirm the importance of limiting the duration of antipsychotic use to avoid excess risk of serious adverse events. In light of these findings, the frequent long-term antipsychotic use observed among community dwellers with AD is concerning (Study II). If antipsychotics are deemed necessary, the use should be reviewed and withdrawal should be attempted regularly according to recommendations of treatment guidelines (Azermai et al. 2012, Zuidema et al. 2015, APA 2016, Memory disorders: Current Care Guidelines 2017).

Differences in the severity of AD and severity of BPSD could explain at least part of the observed higher risk of hip fracture and mortality as antipsychotic use was compared with nonuse. Although the analyses were controlled for several covariates, the possibility of confounding by indication could not be excluded. Since worsened BPSD or delirium might be early manifestations of underlying illnesses, these underlying causes should be carefully assessed and treated to avoid unnecessary initiation of antipsychotic drugs.

6.3.1 Differences in the risks of hip fracture and mortality between the most common antipsychotics

According to the results of this thesis (Study III), there was no difference in the hip fracture risk between quetiapine and risperidone, at least for the first 2.7 years of use. From 2.7 to 4.1 years of use, the hip fracture risk seemed to be lower among quetiapine users compared with risperidone users. On the other hand, quetiapine was associated with a 16% decrease in mortality risk and haloperidol with a 52% increase compared with risperidone use (Study IV). These findings on mortality risk are consistent with studies reporting higher mortality for haloperidol and lower mortality for quetiapine compared with risperidone users with and without dementia living in community or nursing homes (Schneeweiss et al. 2007, Huybrechts et al. 2012b, Kales et al. 2012, Gerhard et al. 2014, Sahlberg et al. 2015, Schmedt et al. 2016b). However, the results regarding differences in risk of hip fracture have been conflicting. Rigler et al. (2013) found no difference in risk when risperidone, olanzapine and quetiapine users were compared with haloperidol among old nursing home residents during 1-293 (average 93) days of follow-up. Whereas Huybrechts et al. (2012a) concluded that quetiapine was possibly associated with a slightly higher risk of hip fracture compared with risperidone among old nursing home residents during 180 days of follow-up. Due to the low number of studies with conflicting results, none of the individual antipsychotic drugs can be considered to be safer than any of the others with respect to the risk of hip fracture and more research is needed.

According to previous studies, the differences in mortality between haloperidol, quetiapine and risperidone persisted after dose adjustment (Huybrechts et al. 2012b, Kales et al. 2012, Gerhard et al. 2014). In addition, a dose-response in mortality risk has been shown for risperidone and haloperidol (Rossom et al. 2010, Huybrechts et al. 2012b, Gerhard et al. 2014). Similarly, compared with low-dose risperidone use (≤0.5 mg per day) in Study IV, haloperidol use with dose ≤1 mg per day was associated with 1.7 times the risk of mortality whereas use with a dose >1.0 mg per day was associated with 2.6 times the risk. It should be noted that the overall higher risk of mortality associated with haloperidol may be partly explained by the fact that haloperidol was used with higher doses (median dose per day 1.0 mg; IQR 0.8-1.6) than risperidone (median dose per day 0.7 mg; IQR 0.5-1.0) in the MEDALZ cohort. In addition, the use of higher risperidone doses per day (>0.5 mg) were associated with 1.6 times the mortality risk (Study IV) and 1.7 times the hip fracture risk (Study III) compared with low-dose risperidone use. These findings of a dose-response in risks support

the recommendation to use the lowest among effective doses among persons with AD (Zuidema et al. 2015, APA 2016, Memory disorders: Current Care Guidelines 2017).

Although quetiapine was associated with a somewhat lower mortality compared with risperidone in Study IV, the dose analyses lead to conflicting results. Compared with low-dose risperidone use, the risk of mortality was slightly higher with quetiapine doses ≤50 mg per day but similar with quetiapine doses >50 mg per day. This might be due to a misclassification of dose categories. The doses used in the analyses represent the calculated average dose per day for the entire antipsychotic use period. The dose estimates are more reliable for those who survive longer as the average dose calculus is based on more than two purchases. Doses of single purchases were based on the most frequently used dose per day for the purchased package in the MEDALZ cohort and thus were more likely to be categorized in the low-dose category due to frequent use of low doses in the cohort. These limitations apply to the dose analyses in general and therefore, the results should be interpreted with caution. None of the previous studies have found a dose-response in mortality risk for quetiapine (Rossom et al. 2010, Huybrechts et al. 2012b, Gerhard et al. 2014). Gerhard et al. (2014) suggested that this lack of dose-response might be due to less variation in the clinical dosing of quetiapine. Similarly as in the previous studies (Huybrechts et al. 2012b, Gerhard et al. 2014), quetiapine was mainly administered in low doses in Studies III and IV. Approximately three out of every four users were estimated to consume quetiapine at doses ≤50 mg per day.

In addition to differences in dosing, confounding by indication may explain at least part of the observed differences in the mortality risk between the most frequently used antipsychotic drugs. Risperidone is the only antipsychotic drug with approved indication for the treatment of severe aggression in persons with moderate to severe AD. Haloperidol is used as a standard treatment of delirium and delirium itself is associated with an increased risk of mortality (Inouye et al. 2014). On the other hand, quetiapine is frequently used with low doses in the treatment of insomnia (Carton et al. 2015). Thus, it is possible that haloperidol and risperidone were more frequently used to treat delirium and more severe BPSD which could contribute to the observed higher mortality risks. The possibility of confounding by indication could not be excluded as the register-based data did not include indications for use or information on the severity of BPSD or AD. Nevertheless, due to the frequently reported higher mortality associated with haloperidol, a recent guideline recommended that haloperidol should be avoided as a first-line nonemergency antipsychotic in persons with dementia in the absence of delirium (APA 2016). Although the risk of mortality was somewhat lower among quetiapine than risperidone users, this does not mean that quetiapine use is safe and the current evidence does not support the use of quetiapine in the treatment of BPSD due to the lack of evidence of efficacy (Maher et al. 2011). On the other hand, there is evidence of modest efficacy of risperidone, olanzapine and aripiprazole in the treatment of aggression and psychosis (Ballard et al. 2006, Maher et al. 2011). Due to a low number of olanzapine (n=249/257) and aripiprazole (n=10/11) users, their hip fracture or mortality risk could not be evaluated (Appendix I). More research is need to compare a larger variety of individual antipsychotic drugs in representative new-user cohorts. Data on doses used and severity of dementia and BPSD would aid in correct interpretation of the findings. Accumulating evidence of comparative effectiveness and safety of different antipsychotic drugs is important for guiding the treatment practices and drug choices.

6.3.2 Antipsychotic polypharmacy and risk of mortality

Of antipsychotic users, 14% used two or more antipsychotics concomitantly. Antipsychotic polypharmacy was associated with an almost two times the risk of mortality than monotherapy among community dwellers with AD (Study IV). Another population-based cohort study found similarly that antipsychotic polypharmacy was associated with higher risk of major adverse cardiovascular events and noncardiovascular mortality compared with risperidone use among new antipsychotic users aged ≥70 years (Sahlberg et al. 2015). Overall,

there should be a high threshold for prescribing antipsychotics to treat BPSD and there is no evidence that antipsychotic polypharmacy would be more effective than monotherapy. The results of this thesis provide additional evidence that antipsychotic polypharmacy may not be safe among persons with AD. The Finnish Current Care Guideline states that preferably only one psychotropic drug should be used at a time to treat BPSD and concomitant use of drugs with similar effects should be avoided (Memory disorders: Current Care Guidelines 2017). Thus, there is no rationale to justify antipsychotic polypharmacy. As the Prescription Register data did not include indications for use, it is not known whether two or more antipsychotics were used concomitantly to treat the same or different symptoms. The antipsychotics that were most commonly used concomitantly were quetiapine and risperidone. If severe aggression, agitation or psychotic symptoms develop and a trial of risperidone is necessary, possible use of quetiapine for the treatment of insomnia should be reviewed and discontinued to avoid possible excess mortality risk. A recent study reported that drug-drug interactions may account for a part of the excess mortality associated with antipsychotic use (Liperoti et al. 2017). Liperoti et al. (2017) recommended that antipsychotics should be used with extreme caution among those persons using cardiovascular or other psychotropic drugs. More research is needed to increase knowledge on the risk of serious adverse events related to antipsychotic use and drug-drug interactions.

6.4 METHODOLOGICAL CONSIDERATIONS

A major strength of the conducted studies was the large nationwide MEDALZ data of community-dwelling Finns with clinically verified diagnoses of AD. Similar to other Nordic countries, the Finnish health care and prescription registers represent a comprehensive data source for pharmacoepidemiological research as all citizens are covered by the publicly funded health care services (Furu et al. 2010). The unique Finnish Special Reimbursement Register enabled the identification of all community dwellers entitled for reimbursed antidementia drugs and establishing the register-based MEDALZ cohort (Tolppanen et al. 2013, 2016a). Due to the explicit diagnostic criteria required by the SII, the positive predictive value of AD diagnoses is high (Solomon et al. 2014). The special reimbursement criteria for AD were introduced in 1999 and the sensitivity for AD has improved since the early years. Thus, the MEDALZ cohort was restricted to diagnoses from 2005 onwards (Tolppanen et al. 2016a) and in substudies I and II, only those diagnosed with AD in 2005 were included from the MEDALZ-2005 cohort.

Another strength was the long follow-up data of diagnoses from the Special Reimbursement and Hospital Discharge registers before and after AD diagnosis. This enabled substudy specific exclusions and adjustments for disease history to generate more reliable results. Individuals with a history of schizophrenia, schizotypal and delusional disorders or bipolar disorder were identified from Hospital Discharge Register data and excluded from all substudies to be sure that antipsychotic use was most likely to be related to treatment of BPSD. In Study III, persons with a history of previous hip fracture before the follow-up were excluded to ensure that the outcome was truly incident hip fracture. The Hospital Discharge Register has been shown to be a valid data source with good to very good accuracy for common diagnoses (Sund 2012). For example, it has been shown to capture nearly all hip fractures (98%) (Sund et al. 2007). In the Hospital Disharge Register, the most severe diseases that require hospital care are more accurately captured than conditions that are often treated in outpatient settings (Tolppanen et al. 2016a). However, many chronic diseases such as diabetes and asthma/COPD diagnosed in outpatient settings are captured by the Special Reimbursement Register and due to the explicit criteria required for reimbursement, the diagnoses are accurate. In addition to data on chronic diseases from Special Reimbursement Register, drug purchases recorded in the Prescription Register were used as proxies of diseases and symptoms.

Comprehensive register-based data with several years of follow-up made it possible to determine the incidence of antipsychotic use longitudinally over 12 years. In fact, Study I was the first to describe the incidence of antipsychotic use in relation to the diagnosis of AD. An additional strength of Study I was the ability to compare the incidence of antipsychotic use among persons with AD to the age-, sex-, and region of residence matched controls. This ensured that the changes in incidence among persons with AD are most likely to be related to the symptoms associated with AD as the incidence among the controls remained stable during a period of 12 years. One weakness of Study I is that the exact starting point of the diagnostic process is unknown. However, almost 80% of Finns receive entitlement for reimbursed antidementia drugs before they have any dementia or AD related hospital visits (Heiskanen et al. 2016).

The long follow-up also enabled studying the duration of antipsychotic use in a representative cohort of community dwellers with AD. Previous studies had mostly described the duration of antipsychotic use among patients with dementia in specific settings of care (Selbæk et al. 2008, Nobili et al. 2009, Wetzels et al. 2011, Barnes et al. 2012, Gustafsson et al. 2013, Rojas-Fernandez et al. 2014). In Study II, the analyses of long-term use were restricted to those persons with at least one year of follow-up time after initiating antipsychotic use. This was conducted to ascertain that short-term duration of antipsychotic use was due to discontinuation of use instead of lack of follow-up data or death. Analysis comparing the time to discontinuation for the three most frequently used antipsychotic drugs were restricted to persons using antipsychotic monotherapy. However, these restrictions may have introduced a minor selection and survival bias to the results.

Restricting the analyses to new antipsychotic users was also an important strength of the conducted studies. A new-user design was applied to avoid the prevalent user bias (Ray 2003, Schneeweiss 2010). It enabled capturing early adverse events occurring soon after treatment initiation and adjusting for covariates measured before the initiation of antipsychotic use. A large cohort with a long follow-up data enabled analyzing the risks according to the duration of use, comparisons between the most frequently initiated antipsychotic drugs and studying the risk of mortality associated with antipsychotic polypharmacy.

A general limitation of register-based data is that it is not known whether purchased drugs were actually taken. However, the Finnish Prescription Register has been shown to be a valid data source for measuring antipsychotic exposure among older persons (Rikala et al. 2010). The Finnish Prescription Register data lacks information on prescribed doses and previously it has been shown that dosage assumptions, such as one tablet or one DDD per day, are not valid for calculating the duration of antipsychotic use among older people (Rikala et al. 2013). Therefore, an important strength of the conducted studies was that instead of relying on fixed dosage assumptions which may lead to a severe exposure misclassification, the novel PRE2DUP modeling method was applied to calculate periods of antipsychotic use (Tanskanen et al. 2015). The validity of drug use periods calculated with PRE2DUP method has been demonstrated among older persons against self-reported drug use in an interview (Taipale et al. 2016). The agreement between PRE2DUP and interview was very good for antipsychotic drugs with a kappa value of 0.90 (95% CI 0.83-0.98).

By comparing the modeled drug use periods of each individual antipsychotic drug, it was possible to identify when drug use periods of two or more antipsychotics overlapped and this overlapping time period was defined as antipsychotic polypharmacy (Study IV). This definition has led to some misclassification of person-time between antipsychotic monotherapy and polypharmacy as some of the time classified as antipsychotic polypharmacy might actually consist of drug switches. However, this approach was chosen to avoid an immortal time bias (Suissa 2007). If polypharmacy would be defined as overlapping use of e.g. ≥60 days, to be classified as a concomitant user of two or more antipsychotics, the person must survive the first 60 days of concomitant use biasing the results.

In addition to modeling the start and end date of antipsychotic use, PRE2DUP method calculates the average dose per day during the entire antipsychotic use period (Tanskanen et al. 2015). This rough estimate of the dose per day was used to analyze dose-dependent effects (Studies III and IV). Due to possible temporal changes in dosage, it is important to note that the average dose per day does not necessarily reflect the dose at a certain time point such as dose at the time of death or when the hip fracture occurred. Furthermore, if a person had only one purchase of an antipsychotic drug, PRE2DUP adopted the most common refill length for the purchased package in the study population. Thus, the dose of a single purchase reflects the most typical dose for that particular drug package in the MEDALZ study population and may deviate from the personal dose actually used. These limitations may have caused some misclassification of the dose categories and therefore the results of dose-dependent analyses should be interpreted with caution.

These kinds of large population-based observational studies that represent the actual user population with multiple comorbidities and polypharmacy are needed to complement information on the risk of adverse events associated with antipsychotic use. However, there is a possibility of confounding by indication as the symptoms for which antipsychotics are initiated may be themselves associated with an increased risk of hip fracture and mortality. In Study IV, persons with active cancer at the start of follow-up were excluded and follow-up was censored at the date of cancer diagnosis or start of antineoplastic drug use. Cancer deaths were not considered as their inclusion could have overestimated the mortality related to antipsychotic use. However, the most important limitation of Studies III and IV is the lack of information on the severity of AD and BPSD. Drug-drug comparisons in Study IV were adjusted for time from AD diagnosis to initiation of antipsychotic use to better account for the possible differences in the severity of AD. In addition, adjusting for benzodiazepine and antidepressant use may have partly controlled for the BPSD and AD severity in both Studies III and IV. Further, additional analyses in Study IV were conducted by matching antipsychotic users to nonusers on the basis of age, sex and disease duration, indicated by time since AD diagnosis. In these matched analyses, the results were similar but the HRs attenuated which may indicate better control of disease severity. However, the severity of AD at the time of diagnosis as well as the rate of which the disease progresses can vary individually. Thus, residual confounding by indication cannot be ruled out. Although dose-response in risks may imply true drug effects, then again those persons who used higher antipsychotic doses or used two or more antipsychotics concomitantly could have more severe symptoms contributing to the higher mortality.

Since the Prescription Register does not cover any drugs used in public nursing homes or hospitals, the follow-up was censored at the beginning of long-term institutionalization and ≥90 days of hospitalization. Therefore, the results of the substudies reflect antipsychotic use among persons with AD in non-institutional settings. The results of Studies I and II are generalizable to community-dwelling Finns with AD. Incidence of antipsychotic use and prevalence of long-term use could be higher in institutional settings. The first two substudies were conducted with MEDALZ-2005 data and were restricted to those diagnosed with AD in 2005 and follow-up data until 2009. Since 2005, several studies have reported an increased risk of mortality associated with antipsychotic use among persons with dementia. Therefore, the increased awareness of the risks of antipsychotic use could have led to decreased prescribing of antipsychotics for persons with AD. Although it seems that antipsychotic use has remained frequent in Finland throughout the years (Taipale et al. 2014a, Tolppanen et al. 2017), especially the duration of antipsychotic use should be studied further with newer data to determine whether positive changes in prescribing practices have occurred since increasing awareness of the risks of antipsychotic use.

The results of Studies III and IV are generalizable to community dwellers with AD. Nursing home residents may be more susceptible to adverse events. However, similar results of the risk of hip fracture and mortality have been reported in both persons with and without dementia living in the community and nursing homes. On the other hand, censoring of

follow-up at the beginning of long-term institutionalization or hospitalization may have caused informative censoring (Schneeweiss 2010). This may have lead to an underestimation of the risks if discontinuation or long-term hospitalization was due to adverse effects of antipsychotics, which could contribute to hip fracture or mortality.

7 Conclusions

Based on the results of this thesis, the following conclusions can be drawn:

1. The highest increase in antipsychotic initiations occurred around the time of Alzheimer's disease diagnosis and the incidence remained at a high level thereafter.

2. Long-term use of antipsychotics was frequent among community-dwelling persons with Alzheimer's disease and it was associated with initiation of use after the diagnosis. Individuals with Alzheimer's disease aged 85 years and over were less likely to be long-term users compared with those aged less than 75 years.

3. Antipsychotic use was associated with increased risks of both hip fracture and mortality among community dwellers with Alzheimer's disease. The risk of these serious adverse events was increased from the first days of use and remained elevated with long-term use. Antipsychotic polypharmacy was associated with highest mortality.

8 Implications for the Future

8.1 CLINICAL IMPLICATIONS

Among persons with Alzheimer's disease:

1. The first-line treatment options for BPSD are non-pharmacological approaches and appropriate treatment of AD. The underlying causes of BPSD should be carefully assessed and treated to avoid unnecessary initiation of antipsychotic drugs.

2. If initiation of antipsychotic use is necessary, careful and regular monitoring is required to assess the response and possible emergence of adverse effects. Since symptoms may resolve by themselves, withdrawal of use should be attempted regularly according to recommendations of treatment guidelines.

3. Short-term antipsychotic use is emphasized as the results of this thesis provide further evidence that the risk of hip fracture and mortality remain elevated in long-term use. Already at initiating antipsychotics to persons with AD, plans should be made on how the effects of antipsychotic use will be monitored and at what point withdrawal of use will be attempted.

4. Antipsychotic polypharmacy should be avoided as it has been associated with higher risk of serious adverse events than monotherapy. If antipsychotic use is necessary, medication should be assessed to avoid unintentional antipsychotic polypharmacy. At the same time, the possibility of other drug interactions with antipsychotics that could increase the risk of serious adverse events should be considered.

8.2 SUGGESTIONS FOR FUTURE RESEARCH

1. More research is urgently needed to find effective and safe pharmacological treatment options for BPSD. Studies of the effectiveness and implementation of non-pharmacological approaches in representative cohorts are crucial to limit antipsychotic and psychotropic drug use only for the most severe symptoms.

2. Future studies should investigate concomitant use of psychotropic drugs and how these drugs accumulate in relation to the diagnosis of AD. Currently, it is not known how the use of psychotropics during the early phases of AD affects the course of disease.

3. More research is needed to gather knowledge on barriers to discontinuation of antipsychotic use especially in the community setting. This could facilitate planning and studying interventions to reduce long-term use of antipsychotics.

4. New studies should evaluate whether increasing awareness of the risks of antipsychotics has decreased long-term use.

5. Methodological development is needed to create valid methods to define and calculate persistent antipsychotic use.

6. Larger variety of individual antipsychotic drugs should be further compared in representative new-user cohorts preferably with data on doses used, duration of use and severity of dementia and BPSD. Evidence of comparative effectiveness and safety of individual antipsychotic drugs is important for guiding the treatment practices and drug choices.

7. The highest mortality risk associated with antipsychotic polypharmacy should be confirmed in future studies. Similarly, more research should be conducted on the risk of other serious adverse events associated with antipsychotic polypharmacy.

8. Future studies should focus more on investigating drug-drug and drug-disease interactions among antipsychotic users to identify those with the highest risk of developing serious adverse events.

9 References

Albert MS, DeKosky ST, Dickson D, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 7(3): 270-279, 2011.

Alzheimer's Association. 2016 Alzheimer's disease facts and figures. Alzheimers Dement 12(4):459-509, 2016.

Alzheimer's Association. Stages of Alzheimer's. Available at: http://www.alz.org/alzheimers_disease_stages_of_alzheimers.asp (Accessed 7 April 2017).

American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-IV. 4th edition. Washington, DC: American Psychiatric Association, 1994.

APA Work Group on Alzheimer's Disease and other Dementias, Rabins PV, Blacker D, et al. American Psychiatric Association practice guideline for the treatment of patients with Alzheimer's disease and other dementias. Second edition. Am J Psychiatry 164(12 Suppl): 5-56, 2007.

APA Practice Guideline Writing group, Reus VI, Fochtmann LJ, et al. The American Psychiatric Association practice guideline on the use of antipsychotics to treat agitation or psychosis in patients with dementia. American Psychiatric Association, http://dx.doi.org/10.1176/appi.books.9780890426807, 2016.

Aparasu RR, Chatterjee S, Mehta S, Chen H. Risk of death in dual-eligible nursing home residents using typical or atypical antipsychotic agents. Med Care 50(11): 961-969, 2012.

Azermai M, Petrovic M, Elseviers MM, Bourgeois J, Van Bortel LM, Vander Stichele RH. Systematic appraisal of dementia guidelines for the management of behavioural and psychological symptoms. Ageing Res Rev 11(1): 78-86, 2012.

Azermai M, Vander Stichele RR, Van Bortel LM, Elseviers MM. Barriers to antipsychotic discontinuation in nursing homes: an exploratory study. Aging Ment Health 18(3): 346-353, 2014.

Baker NL, Cook MN, Arrighi HM, Bullock R. Hip fracture risk and subsequent mortality among Alzheimer's disease patients in the United Kingdom, 1988-2007. Age Ageing 40(1): 49-54, 2011.

Bakken MS, Schjøtt J, Engeland A, Engesæter LB, Ruths S. Antipsychotic drugs and risk of hip fracture in people aged 60 and older in Norway. J Am Geriatr Soc 64(6): 1203-1209, 2016.

Ballard C, Waite J, Birks. The effectiveness of atypical antipsychotics for the treatment of aggression and psychosis in Alzheimer's disease. Cochrane Database Syst Rev (1): CD003476, 2006.

Ballard C, Hanney ML, Theodoulou M, et al. The dementia antipsychotic withdrawal trial (DART-AD): long-term follow-up of a randomised placebo-controlled trial. Lancet Neurol 8(2):151-157, 2009.

Ballard C, Corbett A. Agitation and aggression in people with Alzheimer's disease. Curr Opin Psychiatry 26(3): 252-259, 2013.

Ballard C, Orrell M, YongZhong S, et al. Impact of antipsychotic review and nonpharmacological intervention on antipsychotic use, neuropsychiatric symptoms, and mortality in people with dementia living in nursing homes: A factorial cluster-randomized controlled trial by the Well-Being and Health for People with Dementia (WHELD) program. Am J Psychiatry 173(3): 252-262, 2016.

Barbui C, Conti V, Cipriani A. Antipsychotic drug exposure and risk of venous thromboembolism: a systematic review and meta-analysis of observational studies. Drug Saf 37(2):79-90, 2014.

Barker MJ, Greenwood KM, Jackson M, Crowe SF. Cognitive effects of long-term benzodiazepine use: a meta-analysis. CNS Drugs 18(1): 37–48, 2004.

Barnes TR, Banerjee S, Collins N, Treloar A, McIntyre SM, Paton C. Antipsychotics in dementia: prevalence and quality of antipsychotic drug prescribing in UK mental health services. Br J Psychiatry 201(3): 221-226, 2012.

Beeri MS, Werner P, Davidson M, Noy S. The cost of behavioral and psychological symptoms of dementia (BPSD) in community dwelling Alzheimer's disease patients. Int J Geriatr Psychiatry 17(5): 403-408, 2002.

Bohlken J, Jacob L, Schaum P, Rapp MA, Kostev K. Hip fracture risk in patients with dementia in German primary care practices. Dementia (London), epub ahead of print, 2015.

Booker A, Jacob L, Bohlken J, Rapp MA, Kostev K. Persistence with antipsychotics in dementia patients in Germany. Int J Clin Pharmacol Ther 54(11): 835-840, 2016.

Boucherie Q, Gentile G, Chalançon C, et al. Long-term use of antipsychotics in community-dwelling dementia patients: prevalence and profile accounting for unobservable time bias because of hospitalization. Int Clin Psychopharmacol 32(1): 13-19, 2017.

Bourin M, Briley M. Sedation, an unpleasant, undesirable and potentially dangerous side-effect of many psychotropic drugs. Hum Psychopharmacol 19(2): 135-139, 2004.

Brauer R, Smeeth L, Anaya-Izquierdo K, et al. Antipsychotic drugs and risk of myocardial infarction: a self-controlled case series study. Eur Heart J 36(16):984-992, 2015.

Calvó-Perxas L, de Eugenio RM, Marquez-Daniel F, et al. Profile and variables related to antipsychotic consumption according to dementia subtypes. Int Psychogeriatr 24(6): 940-947, 2012.

Carton L, Cottencin O, Lapeyre-Mestre M, et al. Off-label prescribing of antipsychotics in adults, children and elderly individuals: a systematic review of recent prescription trends. Curr Pharm Des 21(23): 3280-3297, 2015.

Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 40(5): 373-383, 1987.

Cummings JL, Schneider L, Tariot PN, Kershaw PR, Yuan W. Reduction of behavioral disturbances and caregiver distress by galantamine in patients with Alzheimer's disease. Am J Psychiatry 161(3): 532-538, 2004.

Declercq T, Petrovic M, Azermai M, et al. Withdrawal versus continuation of chronic antipsychotic drugs for behavioural and psychological symptoms in older people with dementia. Cochrane Database Syst Rev (3):CD007726, 2013.

Defrancesco M, Marksteiner J, Fleischhacker WW, Blasko I. Use of benzodiazepines in Alzheimer's disease: A systematic review of literature. Int J Neuropsychopharmacol 18(10): pyv055, doi: 10.1093/ijnp/pyv055, 2015.

de Groot MC, Candore G, Uddin MJ, et al. Case-only designs for studying the association of antidepressants and hip or femur fracture. Pharmacoepidemiol Drug Saf 25(Suppl 1):103-113, 2016.

Dennis M, Shine L, John A, et al. Risk of adverse outcomes for older people with dementia prescribed antipsychotic medication: A population based e-cohort study. Neurol Ther 6(1): 57-77, 2017.

Donegan K, Fox N, Black N, Livingston G, Banerjee S, Burns A. Trends in diagnosis and treatment for people with dementia in the UK from 2005 to 2015: a longitudinal retrospective cohort study. Lancet Public Health 2:e149-156, 2017.

Dubois B, Feldman HH, Jacova C, et al. Revising the definition of Alzheimer's disease: a new lexicon. Lancet Neurol 9(11): 1118-1127, 2010.

European Medicines Agency (EMA). CHMP Assessment report on conventional antipsychotics. Procedure under Article 5(3) of Regulation (EC) No 726/2004. EMEA/CHMP/590557/2008. Last updated 20 November 2008. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2010/01/WC500054057.pdf (Accessed 7 April 2017).

European Medicines Agency (EMA). Pharmacovigilance Working Party (PhVWP) October 2011 plenary meeting. Monthly Report. Issue number 1110. EMA/CHMP/PhVWP/845939/2011. Last updated 27 October 2011. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Report/2011/10/WC500117061.pdf (Accessed 7 April 2017).

Eustace A, Coen R, Walsh C, et al. A longitudinal evaluation of behavioural and psychological symptoms of probable Alzheimer's disease. Int J Geriatr Psychiatry 17(10): 968-973, 2002.

Farré M, Haro JM, Kostov B, et al. Direct and indirect costs and resource use in dementia care: A cross-sectional study in patients living at home. Int J Nurs Stud 55: 39-49, 2016.

Farrington PC, Anaya-Izquierdo K, Whitaker HJ, Hocine MN, Douglas I, Smeeth L. Self-controlled case series analysis with event-dependent observation periods. J Am Stat Assoc 106: 417-426, 2011.

U.S. Food and Drug Administration (FDA). Public health advisory. Deaths with antipsychotics in elderly patients with behavioral disturbances. FDA ALERT [4/11/2005], Last updated 16 August 2013. Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm053171.htm (Accessed 7 April 2017).

U.S. Food and Drug Administration (FDA). Information for healthcare professionals. Conventional antipsychotics. FDA ALERT [6/16/2008]. Last updated 15 August 2013. Available at: http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124830.htm (Accessed 7 April 2017).

U.S. Food and Drug Administration (FDA). FDA Drug Safety Communication: Revised recommendations for Celexa (citalopram hydrobromide) related to a potential risk of abnormal heart rhythms with high doses. [3/28/2012]. Last updated 7 January 2016. Available at: https://www.fda.gov/Drugs/DrugSafety/ucm297391.htm (Accessed 7 April 2017).

Feast A, Moniz-Cook E, Stoner C, Charlesworth G, Orrell M. A systematic review of the relationship between behavioral and psychological symptoms (BPSD) and caregiver well-being. Int Psychogeriatr 28(11): 1761-1774, 2016.

Forrester SN, Gallo JJ, Smith GS, Leoutsakos JM. Patterns of neuropsychiatric symptoms in MCI and risk of dementia. Am J Geriatr Psychiatry 24(2): 117-125, 2016.

Fox C, Crugel M, Maidment I, et al. Efficacy of memantine for agitation in Alzheimer's dementia: a randomized double-blind placebo controlled trial. PloS One 7(5):e35185, doi: 10.1372/journal.pone.0035185, 2012.

Franchi C, Tettamanti M, Marengoni A, et al. Changes in trend of antipsychotics prescription in patients treated with cholinesterase inhibitors after warnings from Italian Medicines Agency. Results from the EPIFARM-Elderly project. Eur Neuropsychopharmacol 22(8):569-577, 2012.

Fraser LA, Liu K, Naylor KL, et al. Falls and fractures with atypical antipsychotic medication use: a population-based cohort study. JAMA Intern Med 175(3): 450-452, 2015.

Freund-Levi Y, Jedenius E, Tysen-Bäckström AC, et al. Galantamine versus risperidone treatment of neuropsychiatric symptoms in patients with probable dementia: an open randomized trial. Am J Geriatr Psychiatry 22(4): 341-348, 2014a.

Freund-Levi Y, Bloniecki V, Auestad B, et al. Galantamine versus risperidone for agitation in people with dementia: a randomized, twelve-week, single-center study. Dement Geriatr Cogn Disord 38(3-4): 234-244, 2014b.

Furu K, Wettermark B, Andersen M, Martikainen JE, Almarsdottir AB, Sørensen HT. The Nordic countries as a cohort for pharmacoepidemiological research. Basic Clin Pharmacol Toxicol 106(2): 86-94, 2010.

Gallini A, Andrieu S, Donohue JM, Oumouhou N, Lapeyre-Mestre M, Gardette V. Trends in use of antipsychotics in elderly patients with dementia: Impact of national safety warnings. Eur Neuropsychopharmacol 24(1): 95-104, 2014.

Gauthier S, Loft H, Cummings J. Improvement in behavioural symptoms in patients with moderate to severe Alzheimer's disease by memantine: a pooled data analysis. Int J Geriatr Psychiatry 23(5): 537-545, 2008.

Gerhard T, Huybrechts K, Olfson M, et al. Comparative mortality risks of antipsychotic medications in community-dwelling older adults. Br J Psychiatry 205(1): 44-51, 2014.

Gerho (Kuopio Research Centre of Geriatric Care). Research. MEDALZ study. Available at: http://www.uef.fi/en/web/gerho/tutkimus

Gill SS, Bronskill SE, Normand SL, et al. Antipsychotic drug use and mortality in older adults with dementia. Ann Intern Med 146(11): 775-786, 2007.

Gustafsson M, Karlsson S, Lövheim H. Inappropriate long-term use of antipsychotic drugs is common among people with dementia living in specialized care units. BMC Pharmacol Toxicol 14:10 doi: 10.1186/2050-6511-14-10, 2013.

Guthrie B, Clark SA, McCowan C. The burden of psychotropic drug prescribing in people with dementia: a population database study. Age Ageing 39(5): 637-642, 2010.

Guthrie B, Clark SA, Reynish EL, McCowan C, Morales DR. Differential impact of two risk communications on antipsychotic prescribing to people with dementia in Scotland: segmented regression time series analysis 2001-2011. PloS One 8(7):e68976 doi: 10.1371/journal.pone.0068976, 2013.

Health Canada. Important drug safety information: Risperdal (Risperidone) and cerebrovascular adverse events in placebo-controlled dementia trials – Janssen-Ortho Inc. Dear Healthcare Professional Letter. October 11, 2002. Available at: http://www.healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2002/14720a-eng.php Accessed March 15, 2017.

Heiskanen J, Hartikainen S, Taipale H, Tolppanen AM. Periods of hospital treatment and hospital visits before entitlement to special reimbursement for antidementia medication. In Finnish with English summary. Suomen Lääkärilehti 71(22): 1607-1611, 2016.

Herrmann N, Lanctôt KL. Do atypical antipsychotics cause stroke? CNS Drugs 19(2):91-103, 2005.

Herrmann N, Lanctôt KL, Sambrook R, et al. The contribution of neuropsychiatric symptoms to the cost of dementia care. Int J Geriatr Psychiatry 21(10): 972-976, 2006.

Herrmann N, Lanctôt KL, Hogan DB. Pharmacological recommendations for the symptomatic treatment of dementia: the Canadian Consensus Conference on the Diagnosis and Treatment of Dementia 2012. Alzheimers Res Ther 5(Suppl 1):S5 doi: 10.1186/alzrt201., 2013a.

Herrmann N, Gauthier S, Boneva N, Lemming OM; 10158 Investigators. A randomized, double-blind, placebo-controlled trial of memantine in behaviorally enriched sample of patients with moderate-to-severe Alzheimer's disease. Int Psychogeriatr 25(6): 919-927, 2013b.

Hilmer SN, Gnjidic D, Abernethy DR. Pharmacoepidemiology in the postmarketing assessment of the safety and efficacy of drugs in older adults. J Gerontol A Biol Sci Med Sci 67(2): 181-188, 2012.

Hollis J, Grayson D, Forrester L, Brodaty H, Touyz S, Cumming R. Antipsychotic medication dispensing and risk of death in veterans and war widows 65 years and older. Am J Geriatr Psychiatry 15(11): 932-941, 2007a.

Hollis J, Forrester L, Brodaty H, Touyz S, Cumming R, Grayson D. Risk of death associated with antipsychotic drug dispensing in residential aged care facilities. Aust N Z J Psychiatry. 41(9): 751-758, 2007b.

Howard RJ, Juszczak E, Ballard CG, et al. Donepezil in the treatment of agitation in Alzheimer's disease. N Engl J Med 357(14):1382-1392, 2007.

Hugenholtz GW, Heerdink ER, van Staa TP, Nolen WA, Egberts AC. Risk of hip/femur fractures in patients using antipsychotics. Bone 37(6): 864-870, 2005.

Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL. A new clinical scale for the staging of dementia. Br J Psych 140: 566-572, 1982.

Hulshof TA, Zuidema SU, Ostelo RW, Luijendijk HJ. The mortality risk of conventional antipsychotics in elderly patients: a systematic review and meta-analysis of randomized placebo-controlled trials. J Am Med Dir Assoc 16(10): 817-824, 2015.

Huybrechts KF, Rothman KJ, Silliman RA, Brookhart MA, Schneeweiss S. Risk of death and hospital admission for major medical events after initiation of psychotropic medications in older adults admitted to nursing homes. CMAJ 183(7): e411-419, 2011a.

Huybrechts KF, Brookhart MA, Rothman KJ, et al. Comparison of different approaches to confounding adjustment in a study on the association of antipsychotic medication with mortality in older nursing home patients. Am J Epidemiol 174(9): 1089-1099, 2011b.

Huybrechts KF, Schneeweiss S, Gerhard T, et al. Comparative safety of antipsychotic medications in nursing home residents. J Am Geriatr Soc 60(3): 420-429, 2012a.

Huybrechts KF, Gerhard T, Crystal S, et al. Differential risk of death in older residents in nursing homes prescribed specific antipsychotic drugs: population based cohort study. BMJ 344:e977, doi: 10.1136/bmj.e977, 2012b.

Hwang YJ, Dixon SN, Reiss JP, et al. Atypical antipsychotic drugs and the risk for acute kidney injury and other adverse outcomes in older adults: a population-based cohort study. Ann Intern Med 161(4): 242-248, 2014.

Ikay S, Uchida H, Suzuki T, Tsunoda K, Fujii Y, Mimura M. Postural sway and flexibility in patients with schizophrenia-spectrum disorders: a cross-sectional study. Asian J Psychiatr 19: 14-18, 2016.

Inouye SK, Westendorp RGJ, Saczynski JS. Delirium in elderly people. Lancet 383(9920): 911-922, 2014.

Jack CR Jr, Knopman DS, Jagust WJ, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet Neurol 9(1): 119-128, 2010.

Jack CR Jr, Albert MS, Knopman DS, et al. Introduction to the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 7(3): 257-262, 2011.

Jackson JW, Schneeweiss S, VanderWeele TJ, Blacker D. Quantifying the role of adverse events in the mortality difference between first and second-generation antipsychotics in older adults: systematic review and meta-synthesis. Plos One 9(8):e105376. doi: 10.1371/journal.pone.0105376, 2014a.

Jackson JW, VanderWeele TJ, Viswanathan A, Blacker D, Schneeweiss S. The explanatory role of stroke as a mediator of the mortality risk difference between older adults who initiate first- versus second-generation antipsychotic drugs. Am J Epidemiol 180(8): 847-852, 2014b.

Jackson JW, VanderWeele TJ, Blacker D, Schneeweiss S. Mediators of first- versus second-generation antipsychotic-related mortality in older adults. Epidemiology 26(5): 700-709, 2015.

Jalbert JJ, Eaton CB, Miller SC, Lapane KL. Antipsychotic use and the risk of hip fracture among older adults afflicted with dementia. J Am Med Dir Assoc 11 (2): 120-127, 2010.

Jiang Y, McCombs JS, Park SH. A retrospective cohort study of acute kidney injury risk associated with antipsychotics. CNS Drugs 31(4):319-326, 2017.

Johnell K, Religa D, Eriksdotter M. Differences in drug therapy between dementia disorders in the Swedish Dementia Registry: A nationwide study of over 7,000 patients. Dement Geriatr Cogn Disord 35(5-6): 239-248, 2013.

Kales HC, Valenstein M, Kim HM, et al. Mortality risk in patients with dementia treated with antipsychotics versus other psychiatric medications. Am J Psychiatry 164(10):1568-1576, 2007.

Kales HC, Zivin K, Kim HM, et al. Trends in antipsychotic use in dementia 1999-2007. Arch Gen Psychiatry 68(2):190-197, 2011.

Kales HC, Kim HM, Zivin K, et al. Risk of mortality among individual antipsychotics in patients with dementia. Am J Psychiatry 169(1): 71-79, 2012.

Kales HC, Gitlin LN, Lyketsos CG. Assessment and management of behavioral and psychological symptoms of dementia. BMJ 350:h369, doi:10.1136/bmj.h369, 2015.

Kim HM, Chiang C, Weintraub D, Schneider LS, Kales H. Treatment changes among older patients with dementia treated with antipsychotics. Int J Geriatr Psychiatry 30(12):1238-1249, 2015.

Kolanowski A, Fick D, Waller JL, Ahern F. Outcomes of antipsychotic drug use in community-dwelling elders with dementia. Arch Psychiatr Nurs 20(5): 217-225, 2006.

Laitinen ML, Bell JS, Lavikainen P, Lönnroos E, Sulkava R, Hartikainen S. Nationwide study of antipsychotic use among community-dwelling persons with Alzheimer's disease in Finland. Int Psychogeriatr 23(10): 1623-1631, 2011.

Langa KM, Larson EB, Crimmins EM, et al. A comparison of the prevalence of dementia in the United States in 2000 and 2012. JAMA Intern Med 177(1):51-58, 2017.

Langballe EM, Engdahl B, Nordeng H, Ballard C, Aarsland D, Selbæk G. Short- and long-term mortality risk associated with the use of antipsychotics among 26,940 dementia outpatients: a population-based study. Am J Geriatr Psychiatry 22(4):321-331, 2014.

Leach MJ, Pratt NL, Roughead EE. Psychoactive medicine use and the risk of hip fracture in older people: a case-crossover study. Pharmacoepidemiol Drug Saf 24(6): 576-582, 2015.

Lee PE, Sykora K, Gill SS, et al. Antipsychotic medications and drug-induced movement disorders other than parkinsonism: a population-based cohort study in older adults. J Am Geriatr Soc 53:1374-1379, 2005.

Lee SH, Hsu WT, Lai CC, et al. Use of antipsychotics increases the risk of fracture: a systematic review and meta-analysis. Osteoporosis Int. 28(4): 1167-1178, 2017.

Leinonen A, Koponen M, Hartikainen S. Systematic review: Representativeness of participants in RCTs of acetylcholinesterase inhibitors. Plos One 10(5):e0124500 doi: 10.1371/journal.pone.0124500, 2015.

Leung JY, Barr AM, Procyshyn RM, Honer WG, Pang CC. Cardiovascular side-effects of antipsychotic drugs: The role of the autonomic nervous system. Pharmacol Ther 135(2): 113-122, 2012.

Lin ST, Chen CC, Tsang HY, et al. Association between antipsychotic use and risk of acute myocardial infarction. A nationwide case-crossover study. Circulation 130(3): 235-243, 2014.

Liperoti R, Onder G, Lapane KL, et al. Conventional or atypical antipsychotics and the risk of femur fracture among elderly patients: results of a case-control study. J Clin Psychiatry 68(6): 929-934, 2007.

Liperoti R, Sganga F, Landi F, et al. Antipsychotic drug interactions and mortality among nursing home residents with cognitive impairment. J Clin Psychiatry 78(1):e76-e82, 2017.

Lonergan E, Luxenberg J, Colford J. Haloperidol for agitation in dementia. Cochrane Database Syst Rev (2): CD002852, 2002.

Lonergan E, Britton AM, Luxenberg J, Wyller T. Antipsychotics for delirium. Cochrane Database Syst. Rev. (2): CD005594, 2007.

Luijendijk HJ, de Bruin NC, Hulshof TA, Koolman X. Terminal illness and the increased mortality risk of conventional antipsychotics in observational studies: a systematic review. Pharmacoepidemiol Drug Saf 25(2): 113-122, 2016.

Lyketsos CG, Carrillo MC, Ryan JM, et al. Neuropsychiatric symptoms in Alzheimer's disease. Alzheimers Dement 7(5): 532-539, 2011.

Maclure M, Fireman B, Nelson JC, et al. When should case-only designs be used for safety monitoring of medical products? Pharmacoepidemiol Drug Saf 21(Suppl 1):50-61, 2012.

Maher AR, Maglione M, Bagley S, et al. Efficacy and comparative effectiveness of atypical antipsychotic medications for off-label uses in adults: a systematic review and meta-analysis. JAMA 306(12): 1359-1369, 2011.

Martinez C, Jones RW, Rietbrock S. Trends in the prevalence of antipsychotic drug use among patients with Alzheimer's disease and other dementias including those treated with antidementia drugs in the community in the UK: a cohort study. BMJ Open 3(1):e002080. doi: 10.1136/bmjopen-2012-002080, 2013.

Mast G, Fernandes K, Tadrous M, Martins D, Herrmann N, Gomes T. Persistence of antipsychotic treatment in elderly dementia patients: a retrospective, population-based cohort study. Drugs Real World Outcomes 3(2): 175-182, 2016.

Matsunaga S, Kishi T, Iwata N. Memantine monotherapy for Alzheimer's disease: A systematic review and meta-analysis. PloS One 10(4):e0123289. doi: 10.1371/journal.pone.0123289, 2015.

Maust DT, Kim HM, Seyfried LS, et al. Antipsychotics, other psychotropics and the risk of death in patients with dementia. Number needed to harm. JAMA Psychiatry 72(5): 438-445, 2015.

McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's disease. Neurology 34 (7): 939-944, 1984.

McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 7(3): 263-269, 2011.

Mehta S, Pulungan Z, Jones BT, Teigland C. Comparative safety of atypical antipsychotics and the risk of pneumonia in the elderly. Pharmacoepidemiol Drug Saf 24 (12):1271-1280, 2015.

Memory disorders (online). Current Care Guidelines. Working group set up by the Finnish Medical Society Duodecim, Societas Gerontologica Fennica, Finnish Geriatricians, the Finnish Neurological Society, Finnish Psychogeriatric Association and the Finnish Association for General Practice. Helsinki: The Finnish Medical Society Duodecim, 2017. Available at [in Finnish]: http://www.kaypahoito.fi (Accessed 17 Feb 2017)

Mittal V, Kurup L, Williamson D, Muralee S, Tampi RR. Risk of cerebrovascular adverse events and death in elderly patients with dementia when treated with antipsychotic medications: A literature review of evidence. Am J Alzheimers Dis Other Demen 26(1):10-28, 2011.

Miyamoto S, Miyake N, Jarskog LF, Fleischhacker WW, Lieberman JA. Pharmacological treatment of schizophrenia: a critical review of the pharmacology and clinical effects of current and future therapeutic agents. Mol Psychiatry 17(12): 1206-1227, 2012.

Monastero R, Mangialasche F, Camarda C, Ercolani S, Camarda R. A systematic review of neuropsychiatric symptoms in mild cognitive impairment. J Alzheimers Dis 18(1): 11-30, 2009.

National Institute for Health and Care Excellence (NICE). Dementia: supporting people with dementia and their carers in health and social care. Clinical guideline [CG42]. November 2006. Last updated September 2016. Available at: https://www.nice.org.uk/guidance/cg42 (Accessed 13 April 2014).

National Institute for Health and Care Excellence (NICE). Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease. Technology appraisal guidance [TA217]. 23 March 2011. Last updated 11 May 2016. Available at: https://www.nice.org.uk/guidance/ta217 (Accessed 13 April 2017).

Nishtala PS, Salahudeen MS, Hilmer SN. Anticholinergics: theoretical and clinical overview. Expert Opin Drug Saf 15(6): 753-768, 2016.

Nobili A, Pasina L, Trevisan S, et al. Use and misuse of antipsychotic drugs in patients with dementia in Alzheimer special care units. Int Clin Psychopharmacol 24(2): 97-104, 2009.

Nørgaard A, Jensen-Dahm C, Gasse C, Hansen HV, Waldemar G. Time trends in antipsychotic drug use in patients with dementia: a nationwide study. J Alzheimers Dis 49(1):211-220, 2016.

Nosè M, Recla E, Trifirò G, Barbui C. Antipsychotic drug exposure and risk of pneumonia: review and meta-analysis of observational studies. Pharmacoepidemiol Drug Saf 24(8):812-820, 2015.

Pariente A, Fourrier-Réglat A, Ducruet T, et al. Antipsychotic use and myocardial infarction in older patients with dementia. Arch Intern Med 172(8):648-653, 2012.

Park Y, Franklin JM, Schneeweiss S, et al. Antipsychotics and mortality: adjusting for mortality risk scores to address confounding by terminal illness. J Am Geriatr Soc 63(3): 516-523, 2015.

Peters ME, Schwartz S, Han D, et al. Neuropsychiatric symptoms as predictors of progression to severe Alzheimer's dementia and death: The Cache County Dementia Progression Study. Am J Psychiatry 172(5): 460-465, 2015.

Peuskens J, Pani L, Detraux J, De Hert M. The effects of novel and newly approved antipsychotics on serum prolactin levels: a comprehensive review. CNS Drugs 28(5): 421-453, 2014.

Porsteinsson AP, Drye LT, Pollock BG, et al. Effect of citalopram on agitation in Alzheimer's disease: the CitAD randomized clinical trial. JAMA 311(7):682-691, 2014.

Pouwels S, van Staa TP, Egberts AC, Leufkens HG, Cooper C, de Vries F. Antipsychotic use and the risk of hip/femur fracture: a population-based case-control study. Osteoporos Int 20(9): 1499-1506, 2009.

Pratt N, Roughead EE, Ramsay E, Salter A, Ryan P. Risk of hospitalization for hip fracture and pneumonia associated with antipsychotic prescribing in the elderly: a self-controlled case-series analysis in an Australian health care claims database. Drug Saf 34(7): 567-575, 2011.

Prince M, Bryce R, Ferri C. Alzheimer's Disease International. World Alzheimer Report 2011. The benefits of early diagnosis and intervention. Alzheimer's Disease International, 2011. Available at: https://www.alz.co.uk/research/WorldAlzheimerReport2011.pdf (Accessed 21 April 2017).

Prince M, Wimo A, Guerchet M, Ali GC, Wu YT, Prina M. World Alzheimer Report 2015. The global impact of dementia. An analysis of prevalence, incidence, cost and trends. Alzheimer's Disease International, London, 2015. Available at: https://www.alz.co.uk/research/WorldAlzheimerReport2015.pdf (Accessed 17 Feb 2017).

Prince M, Ali GC, Guerchet M, Prina AM, Albanese E, Wu YT. Recent global trends in the prevalence and incidence of dementia, and survival with dementia. Alzheimers Res Ther 8(1):23, doi: 10.1186/s13195-016-0188-8, 2016.

Puranen A, Taipale H, Koponen M, et al. Incidence of antidepressant use in community-dwelling persons with and without Alzheimer's disease: 13-year follow-up. Int J Geriatr Psychiatry 32(1):94-101, 2017.

Puyat JH, Law MR, Wong ST, Sutherland JM, Morgan SG. The essential and potentially inappropriate use of antipsychotics across income groups: an analysis of linked administrative data. Can J Psychiatry 57(8): 488-495, 2012.

Rabins PV, Rovner BW, Rummans T, Schneider LS, Tariot PN. Guideline watch (October 2014): Practice guideline for the treatment of patients with Alzheimer's disease and other dementias. American Psychiatric Association, 2014. Available at: http://psychiatryonline.org/pb/assets/raw/sitewide/practice_guidelines/guidelines/alzheimerwatch.pdf (Accessed 14 March 2017).

Rahkonen T, Luukkainen-Markkula R, Paanila S, Sivenius J, Sulkava R. Delirium episode as a sign of undetected dementia among community dwelling elderly subjects: a 2 year follow up study. J Neurol Neurosurg Psychiatry 69(4): 519-521, 2000.

Rattinger GB, Burcu M, Dutcher SK, et al. Pharmacotherapeutic management of dementia across settings of care. J Am Geriatr Soc 61(5): 723-733, 2013.

Ray WA. Evaluating medication effects outside of clinical trials: new-user designs. Am J Epidemiol 158(9): 915-920, 2003.

Ray WA, Chung CP, Murray KT, Hall K, Stein CM. Atypical antipsychotic drugs and the risk of sudden cardiac death. N Engl J Med 360(3): 225-235, 2009.

Rea RS, Battistone S, Fong JJ, Devlin JW. Atypical antipsychotics versus haloperidol for treatment of delirium in acutely ill patients. Pharmacotherapy 27(4): 588-594, 2007.

Rigler SK, Shireman TI, Cook-Wiens GJ, et al. Fracture risk in nursing home residents initiating antipsychotic medications. J Am Geriatr Soc 61(5): 715-722, 2013.

Rikala M, Hartikainen S, Sulkava R, Korhonen MJ. Validity of the Finnish Prescription Register for measuring psychotropic drug exposures among elderly Finns: a population-based intervention study. Drugs Aging 27(4): 337-349, 2010.

Rikala M, Hartikainen S, Saastamoinen LK, Korhonen MJ. Measuring psychotropic drug exposures in register-based studies – validity of a dosage assumption of one unit per day in older Finns. Int J Methods Psychiatr Res, 22(2): 155-165, 2013.

Rochon PA, Stukel TA, Sykora K, et al. Atypical antipsychotics and parkinsonism. Arch Intern Med 165(16):1882-1888, 2005.

Rockwood K, Cosway S, Carver D, Jarrett P, Stadnyk K, Fisk J. The risk of dementia and death after delirium. Age Ageing 28(6): 551-556, 1999.

Rojas-Fernandez C, Mikhail M, Brown SG. Psychotropic and cognitive-enhancing medication use and its documentation in contemporary long-term care practice. Ann Pharmacother 48(4): 438-446, 2014.

Rosenberg PB, Mielke MM, Han D, et al. The association of psychotropic medication use with the cognitive, functional, and neuropsychiatric trajectory of Alzheimer's disease. Int J Geriatr Psychiatry 27(12): 1248-1257, 2012.

Rosenberg PB, Mielke MM, Appleby BS, Oh ES, Geda YE, Lyketsos CG. The association of neuropsychiatric symptoms in MCI with incident dementia and Alzheimer disease. Am J Geriatr Psychiatry 21(7): 685-695, 2013.

Rossom RC, Rector TS, Lederle FA, Dysken MW. Are all commonly prescribed antipsychotics associated with greater mortality in elderly male veterans with dementia? J Am Geriatr Soc 58(6): 1027-1034, 2010.

Ryan PB, Schuemie MJ, Ramcharran D, Stang PE. Atypical antipsychotics and the risks of acute kidney injury and related outcomes among older adults: A replication analysis and an evaluation of adapted confounding control strategies. Drugs Aging 34(3):211-219, 2017.

Ryu SH, Katona C, Rive B, Livingston G. Persistence of and changes in neuropsychiatric symptoms in Alzheimer disease over 6 months: the LASER-AD study. Am J Geriatr Psychiatry 13(11): 976-983, 2005.

Saarelainen L, Taipale H, Koponen M, et al. The incidence of benzodiazepine and related drug use in persons with and without Alzheimer's disease. J Alzheimer Dis 49(3):809-818, 2016.

Sacchetti E, Turrina C, Valsecchi P. Cerebrovascular accidents in elderly people treated with antipsychotic drugs. A systematic review. Drug Saf 33(4): 273-288, 2010.

Sahlberg M, Holm E, Gislason GH, Køber L, Torp-Pedersen C, Andersson C. Association of selected antipsychotic agents with major adverse cardiovascular events and noncardiovascular mortality in elderly persons. J Am Heart Assoc 4(9); e001666 doi: 10.1161/JAHA.114.001666, 2015.

Salvo F, Pariente A, Shakir S, et al. Sudden cardiac and sudden unexpected death related to antipsychotics: a meta-analysis of observational studies. Clin Pharmacol Ther 99(3):306-314, 2016.

Schmedt N, Garbe E. Antipsychotic drug use and the risk of venous thromboembolism in elderly patients with dementia. J Clin Psychopharmacol 33(6):753-758, 2013.

Schmedt N, Jobski K, Kollhorst B, et al. Treatment patterns and characteristics of older antipsychotic users in Germany. Int Clin Psychopharmacol 31(3):159-169, 2016a.

Schmedt N, Kollhorst B, Enders D, et al. Comparative risk of death in older adults treated with antipsychotics: A population-based cohort study. Eur Neuropsychopharmacol 26(9): 1390-1400, 2016b.

Schneeweiss S, Setoguchi S, Brookhart A, Dormuth C, Wang PS. Risk of death associated with the use of conventional versus atypical antipsychotic drugs among elderly patients. CMAJ 176(5): 627-632, 2007.

Schneeweiss S, Setoguchi S, Brookhart MA, Kaci L, Wang PS. Assessing residual confounding of the association between antipsychotic medications and risk of death using survey data. CNS Drugs 23(2): 171-180, 2009.

Schneeweiss S. A basic study desing for expedited safety signal evaluation based on electronic healthcare data. Pharmacoepidemiol Drug Saf 19(8): 858-868, 2010.

Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia. Meta-analysis of randomized placebo-controlled trials. JAMA 294(15): 1934-1943, 2005.

Schulze J, Glaeske G, van den Bussche H, et al. Prescribing of antipsychotic drugs in patients with dementia: a comparison with age-matched and sex-matched non-demented controls. Pharmacoepidemiol Drug Saf 22(12):1308-1316, 2013a.

Schulze J, van den Bussche H, Glaeske G, Kaduszkiewicz H, Wiese B, Hoffmann F. Impact of safety warnings on antipsychotic prescriptions in dementia: nothing has changed but the years and the substances. Eur Neuropsychopharmacol 23(9): 1034-1042, 2013b.

Seitz DP, Adunuri N, Gill SS, Gruneir A, Herrmann N, Rochon P. Antidepressants for agitation and psychosis in dementia. Cochrane Database Syst Rev (2): CD008191, 2011.

Selbæk G, Kirkevold Ø, Engedal K. The course of psychiatric and behavioral symptoms and the use of psychotropic medication in patients with dementia in Norwegian nursing homes--a 12-month follow-up study. Am J Geriatr Psychiatry 16(7): 528-536, 2008.

Setoguchi S, Wang PS, Brookhart MA, Canning CF, Kaci L, Schneeweiss S. Potential causes of higher mortality in elderly users of conventional and atypical antipsychotic medications. J Am Geriatr Soc 56(9): 1644-1650, 2008.

Shaw BH, Claydon VE. The relationship between orthostatic hypotension and falling in older adults. Clin Auton Res 24(1): 3-13, 2014.

Sikirica S, Marino M, Gagne JJ, De Palma R, Maio V. Risk of death associated with the use of conventional vs. atypical antipsychotic medications: evaluating the use of the Emilia-Romagna Region database for pharmacoepidemiological studies. J Clin Pharm Ther 39(1): 38-44, 2014.

Simoni-Wastila L, Wei YJ, Lucas JA, et al. Mortality risk of antipsychotic dose and duration in nursing home residents with chronic or acute indications. J Am Geriatr Soc 64(5): 973-980, 2016.

Sink KM, Holden KF, Yaffe K. Pharmacological treatment of neuropsychiatric symptoms of dementia. A review of the evidence. JAMA 293(5): 596-608, 2005.

Solomon A, Ngandu T, Soininen H, Hallikainen MM, Kivipelto M, Laatikainen T. Validity of dementia and Alzheimer's disease diagnoses in Finnish national registers. Alzheimers Dement 10(3): 303-309, 2014.

Sperling RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 7(3): 280-292, 2011.

Suissa S. Immortal time bias in observational studies of drug effects. Pharmacoepidemiol Drug Saf 16(3): 241-249, 2007.

Sultana J, Fontana A, Giorgianni F, et al. The effect of safety warnings on antipsychotic drug prescribing in elderly persons with dementia in the United Kingdom and Italy: a population-based study. CNS Drugs 30(11):1097-1109, 2016a.

Sultana J, Leal I, de Ridder M, Sturkenboom M, Trifirò G. Antipsychotic use in dementia patients in a general practice setting: a Dutch population-based study. Epidemiol Psychiatr Sci 25(4): 403-406, 2016b.

Sund R, Nurmi-Lüthje I, Lüthje P, Tanninen S, Narinen A, Keskimäki I. Comparing properties of audit data and routinely collected register data in case of performance assessment of hip fracture treatment in Finland. Methods Inf Med 46(5): 558-566, 2007.

Sund R. Quality of the Finnish Hospital Discharge Register: A systematic review. Scand J Public Health 40(6): 505-515, 2012.

Taipale H, Koponen M, Tanskanen A, Tolppanen AM, Tiihonen J, Hartikainen S. High prevalence of psychotropic drug use among persons with and without Alzheimer's disease in Finnish nationwide cohort. Eur Neuropsychopharmacol 24(11): 1729-1737, 2014a.

Taipale H, Koponen M, Tanskanen A, Tolppanen AM, Tiihonen J, Hartikainen S. Antipsychotic doses among community-dwelling persons with Alzheimer's disease in Finland. J Clin Psychopharmacol 34(4): 435-440, 2014b.

Taipale H, Tanskanen A, Koponen M, Tolppanen AM, Tiihonen J, Hartikainen S. Antidementia drug use among community-dwelling individuals with Alzheimer's disease in Finland: a nationwide register-based study. Int Clin Psychopharmacol 29(4): 216-223, 2014c.

Taipale H, Tanskanen A, Koponen M, Tolppanen AM, Tiihonen J, Hartikainen S. Agreement between PRE2DUP register data modeling method and comprehensive drug use interview among older persons. Clin Epidemiol 8: 363-371, 2016.

Tanskanen A, Taipale H, Koponen M, et al. From prescription drug purchases to drug use periods – a second generation method (PRE2DUP). BMC Med Inform Decis Mak, 15:21, 2015, doi: 10.1186/s12911-015-0140-z.

Tjia J, Reidenberg MM, Hunnicutt JN, et al. Approaches to gradual dose reduction of chronic off-label antipsychotics used for behavioral and psychological symptoms of dementia. Consult Pharm 30(10): 599-611, 2015.

Tolppanen AM, Taipale H, Koponen M, et al. Use of existing data sources in clinical epidemiology: Finnish health care registers in Alzheimer's disease research - the Medication use among persons with Alzheimer's disease (MEDALZ-2005) study. Clin Epidemiol 5: 277-285, 2013.

Tolppanen AM, Taipale H, Koponen M, et al. Cohort profile: the Finnish Medication and Alzheimer's disease (MEDALZ) study. BMJ Open, 6(7): e012100, doi: 10.1136/bmjopen-2016-012100, 2016a.

Tolppanen AM, Taipale H, Tanskanen A, Tiihonen J, Hartikainen S. Comparison of predictors of hip fracture and mortality after hip fracture in community-dwellers with and without Alzheimer's disease – exposure-matched cohort study. BMC Geriatrics 16(1):204, doi: 10.1186/s12877-016-0383-2, 2016b.

Tolppanen AM, Koponen M, Tanskanen A, et al. Antipsychotic use and risk of hospitalization or death due to pneumonia in persons with and those without Alzheimer disease. Chest 150(6): 1233-1241, 2016c.

Tolppanen AM, Voutilainen A, Taipale H, et al. Regional changes in psychotropic use among Finnish persons with newly diagnosed Alzheimer's disease in 2005-2011. PloS One 12(3): e0173450, doi:10.1371/journal.pone.0173450, 2017.

Toot S, Swinson T, Devine M, Challis D, Orrell M. Causes of nursing home placement for older people with dementia: a systematic review and meta-analysis. Int Psychogeriatr 29(2): 195-208, 2017.

Trifirò G, Spina E, Gambassi G. Use of antipsychotics in elderly patients with dementia: Do atypical and conventional agents have a similar safety profile? Pharmacol Res 59(1): 1-12, 2009.

Trifirò G, Spina E. Age-related changes in pharmacodynamics: Focus on drugs acting on central nervous and cardiovascular systems. Curr Drug Metab 12(7):611-620, 2011.

Trifirò G, Sultana J, Spina E. Are the safety profiles of antipsychotic drugs used in dementia the same? An updated review of observational studies. Drug Saf 37(7): 501-520, 2014.

Törmälehto SM, Martikainen JA, Väätäinen ST, et al. Use of anti-dementia drugs in relation to change in cognition, behavior, and functioning in Alzheimer's disease over a three-year period: Kuopio ALSOVA Study. J Alzheimers Dis 48(4): 1033-1041, 2015.

Vasilyeva I, Biscontri RG, Enns MW, Metge CJ, Alessi-Severini S. Adverse events in elderly users of antipsychotic pharmacotherapy in the province of Manitoba: a retrospective cohort study. J Clin Psychopharmacol 33(1): 24-30, 2013.

Vigen CL, Mack WJ, Keefe RS, et al. Cognitive effects of atypical antipsychotic medications in patients with Alzheimer's disease: outcomes from CATIE-AD. Am J Psychiatry 168(8): 831-839, 2011.

Wang PS, Bohn RL, Glynn RJ, Mogun H, Avorn J. Zolpidem use and hip fractures in older people. J Am Geriatr Soc 49(12): 1685-1690, 2001.

Wang PS, Schneeweiss S, Avorn J, et al. Risk of death in elderly users of conventional vs. atypical antipsychotic medications. N Engl J Med 353(22): 2335-2341, 2005.

Wastesson JW, Ringbäck Weitoft G, Johnell K. Educational disparities in antipsychotic drug use among older people with and without dementia in Sweden. Acta Psychiatr Scand 132(1): 20-28, 2015.

Weiden PJ. EPS Profiles: The atypical antipsychotics are not all the same. J Psychiatr Pract 13(1): 13-24, 2007.

Wettermark B, Zoëga H, Furu K, et al. The Nordic prescription databases as a resource for pharmacoepidemiological research – a literature review. Pharmacoepidemiol Drug Saf 22(7): 691-699, 2013.

Wetzels RB, Zuidema SU, de Jonghe JF, Verhey FR, Koopmans RT. Prescribing pattern of psychotropic drugs in nursing home residents with dementia. Int Psychogeriatr 23(8): 1249-1259, 2011.

WHO Collaborating Centre for Drug Statistics Methodology. The Anatomical Therapeutic Chemical Classification System. Last updated 16 Dec 2015. Available at: http://www.whocc.no/atc_ddd_index/ (Accessed 11 Oct 2016).

Wood-Mitchell A, James IA, Waterworth A, Swann A, Ballard C. Factors influencing the prescribing of medications by old age psychiatrists for behavioural and psychological symptoms of dementia: a qualitative study. Age Ageing 37(5): 547-552, 2008.

Woolcott JC, Richardson KJ, Wiens MO, et al. Meta-analysis of the impact of 9 medication classes on falls in elderly persons. Arch Intern Med 169(21): 1952-1960, 2009.

Wu CS, Tsai YT, Tsai HJ. Antipsychotic drugs and the risk of ventricular arrhythmia and/or sudden cardiac death: A nationwide case-crossover study. J Am Heart Assoc 4(2): e001568, doi: 10.1161/JAHA.114.001568, 2015.

Yu ZH, Jiang HY, Shao L, Zhou YY, Shi HY, Ruan B. Use of antipsychotics and risk of myocardial infarction: a systematic review and meta-analysis. Br J Clin Pharmacol 82(3): 624-632, 2016.

Zuidema SU, Johansson A, Selbæk G, et al. A consensus guideline for antipsychotic drug use for dementia in care homes. Bridging the gap between scientific evidence and clinical practice. Int Psychogeriatr 27(11): 1849-1859, 2015.

Appendix 1. Number of hip fractures and deaths among users of individual antipsychotic drugs in Studies III and IV

	Study III			Study IV		
Antipsychotic drug	**Number of users**	**Person years of use**	**Hip fractures**	**Number of users**	**Person years of use**	**Deaths**
Risperidone	10,630	8933.4	272	11,144	8745.9	901
Quetiapine	4,990	5343.9	143	5,186	5043.0	446
Haloperidol	597	305.3	8	612	299.2	50
Olanzapine	249	232.2	9	257	230.3	20
Melperone	198	155.0	3	212	160.3	14
Perphenazine	127	107.9	4	131	105.9	9
Levomepromazine	57	43.4	0	56	39.0	8
Periciazine	39	29.2	1	40	27.9	1
Flupentixol	28	24.3	3	29	26.0	2
Sulpiride	23	15.5	0	27	20.3	2
Aripiprazole	10	6.9	0	11	7.0	1
Zuclopenthixol	7	2.4	1	7	2.9	0
Chlorprotixene	6	6.7	0	6	6.2	0
Chlorpromazine	5	1.7	0	6	1.8	1
Clozapine	3	2.0	0	3	2.0	0
Dixyrazine	2	0.3	0	2	0.3	0
Ziprasidone	1	0.5	0	1	0.5	0
Pimozide	0	0	0	1	0.1	0

MARJAANA KOPONEN

Antipsychotics are recommended only for short-term treatment of the most severe behavioral and psychological symptoms of dementia. This nationwide register-based study determined the incidence and duration of antipsychotic use in community-dwelling Finns with Alzheimer's disease. Furthermore, the associations between antipsychotic use and risk of hip fracture and mortality were investigated.

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