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LAURA SAARELAINEN

BENZODIAZEPINE AND RELATED DRUG USE AND ASSOCIATED ADVERSE OUTCOMES

The Medication Use and Alzheimer's Disease Study

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ABSTRACT

Alzheimer's disease (AD) is the most common neurodegenerative disorder. Behavioral and psychological symptoms of dementia (BPSD) are frequent in all stages of the disease. The treatment of these symptoms is complex and psychotropic drugs, including benzodiazepines and related drugs (BZDR), may be prescribed.

The aims of this thesis were to investigate (I) the incidence of BZDR use among persons with and without AD, (II) the risk of hip fracture associated with incident BZDR use among persons with and without AD, and (III) the risk of death associated with incident BZDR use among persons with AD.

This thesis was based on the register-based Medication use and Alzheimer's disease (MEDALZ) cohort, which consisted of all community-dwelling persons who had been diagnosed with AD in Finland from 2005 to 2011 (n=70,718) and age- and gender-matched comparison persons without AD. Data were obtained from several sources; the Special Reimbursement Register, the Prescription Register, the Hospital Discharge Register, and Statistics Finland. Drug use periods were modelled from the purchase-based data with the PRE2DUP modeling method. Prevalent BZDR users were excluded by applying a one-year washout period. The incidence of BZDR use was investigated from two years before until three years after the AD diagnosis. A cohort design was applied to investigate the risk of hip fracture associated with BZDR use with a five-year follow-up and the risk of death with a six-month follow-up. In these analyses, BZDR use was compared with non-use.

Persons with AD were more likely to initiate BZDR use (26%) than persons without AD (17%). Among persons with AD, the incidence peaked during the six months following the diagnosis. BZDR use was associated with a 40–60% increased risk of hip fracture in individuals with and without AD, and the risk was at its highest during the first 30 days of use. Furthermore, BZDR use was associated with a 40% increased risk of death among persons with AD. The associated risk of death was elevated from the initiation of BZDR use.

In conclusion, BZDR use was initiated more frequently among persons with AD, and BZDR use was associated with an increased risk of adverse outcomes among persons with and without AD. These and other known risks should be thoroughly weighed against the benefits before any BZDR use is initiated, as even short-term use of these drugs seems to increase the risk of severe adverse outcomes.

National Library of Medicine Classification: QV 56, QV 77.2, QV 77.9, WE 855, WT 155
Medical Subject Headings: Alzheimer Disease; Benzodiazepines; Psychotropic Drugs; Incidence; Prevalence; Drug-Related Side Effects and Adverse Reactions; Risk; Hip Fractures; Mortality; Cohort Studies; Longitudinal Studies; Follow-Up Studies; Pharmacoepidemiology; Drug Utilization; Registries; Finland

Saarelainen, Laura
Bentsodiatsepiinien ja niiden kaltaisten lääkkeiden käyttö sekä käyttöön liittyvät haittatapahtumat, Medication Use and Alzheimer's Disease -tutkimus
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TIIVISTELMÄ

Alzheimerin tauti (AT) on yleisin etenevä muistisairaus. Taudin kaikkiin vaiheisiin kuuluu käytösoireita, joiden hoito on haasteellista. Hoidossa saatetaan käyttää keskushermostoon vaikuttavia lääkeaineita, kuten bentsodiatsepiineja ja niiden kaltaisia lääkkeitä.

Tämän väitöskirjan tavoitteena oli tutkia (I) bentsodiatsepiinien ja niiden kaltaisten lääkkeiden käytön ilmaantuvuutta AT:a sairastavilla henkilöillä ja heidän vertailuhenkilöillään, (II) käytön yhteyttä lonkkamurtuman riskiin AT:a sairastavilla ja vertailuhenkilöillä sekä (III) käytön yhteyttä kuoleman riskiin AT:a sairastavilla henkilöillä.

Tässä väitöskirjassa käytettiin rekistereistä poimittua Medication Use and Alzheimer's Disease (MEDALZ) -aineistoa, jossa olivat mukana kaikki kotona asuvat suomalaiset, jotka saivat AT:n lääkkeiden rajoitetun peruskorvausoikeuden vuosina 2005–2011 (70 718 henkilöä) sekä iän ja sukupuolen suhteen kaltaistetut vertailuhenkilöt, joilla ei tätä tautia ollut. Tietoja poimittiin lääkkeiden erityiskorvausoikeus-, resepti- ja hoitoilmoitusrekisteristä sekä Tilastokeskukselta. PRE2DUP-mallinnusmenetelmää käytettiin lääkkeiden ostotietojen muuttamiseen laskennallisiksi käyttöajoiksi. Kaikista tutkimuksista suljettiin pois henkilöt, jotka olivat käyttäneet bentsodiatsepiineja ja niiden kaltaisia lääkkeitä edellisen vuoden aikana. Lääkkeiden käytön ilmaantuvuutta tutkittiin ajanjaksolla, joka alkoi kaksi vuotta ennen ja päättyi kolme vuotta AT:n diagnoosin jälkeen. Yhteyttä haittatapahtumiin tutkittiin kohorttiasetelmalla. Lonkkamurtumariskiä tutkittiin viiden vuoden ja kuoleman riskiä kuuden kuukauden ajalta. Haittatapahtumien riskiä tutkittiin vertaamalla bentsodiatsepiinien ja niiden kaltaisten lääkkeiden käyttöaikaa aikaan, jolloin näitä lääkkeitä ei käytetty.

AT:a sairastavilla henkilöillä bentsodiatsepiinien ja niiden kaltaisten lääkkeiden käytön ilmaantuvuus oli suurempi (26 %) kuin vertailuhenkilöillä (17 %). Ilmaantuvuus oli korkeimmillaan AT:n diagnoosia seuraavan puolen vuoden aikana. Bentsodiatsepiinien ja niiden kaltaisten lääkkeiden käyttö oli yhteydessä 40–60 % korkeampaan lonkkamurtumariskiin sekä AT:a sairastavilla että vertailuhenkilöillä. Lonkkamurtumariski oli korkeimmillaan 30 ensimmäisen päivän ajan. Bentsodiatsepiinien ja niiden kaltaisten lääkkeiden käyttö oli yhteydessä myös 40 % korkeampaan kuoleman riskiin AT:a sairastavilla henkilöillä, ja tämä riski oli koholla heti käytön alusta alkaen.

Bentsodiatsepiinien ja niiden kaltaisten lääkkeiden käytön ilmaantuvuus näyttää olevan korkeampi AT:a sairastavilla henkilöillä kuin vertailuhenkilöillä. Näiden lääkkeiden käyttö oli yhteydessä kohonneeseen haittatapahtumien riskiin sekä AT:a sairastavilla että vertailuhenkilöillä. Ennen bentsodiatsepiinien ja niiden kaltaisten lääkkeiden käytön aloitusta on tärkeää arvioida hoidon hyödyt ja haitat, sillä vakavien haittatapahtumien riski on kohonnut jo lyhytaikaisessa käytössä.

Luokitus: QV 56, QV 77.2, QV 77.9, WE 855, WT 155
Yleinen suomalainen asiasanasto: Alzheimerin tauti; bentsodiatsepiinit; psyykenlääkkeet; unilääkkeet; haitat; riskit; ilmaantuvuus; esiintyvyys; luunmurtumat; lonkka; kuolleisuus; kohorttitutkimus; pitkittäistutkimus; seurantatutkimus; epidemiologia; lääkkeet; rekisterit; Suomi

'D: It is written'

Slumdog Millionaire (2008)

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Kuopio, October 2018

Laura Saarelainen

List of the original publications

This dissertation is based on the following original publications:

I Saarelainen L, Taipale H, Koponen M, Tanskanen A, Tolppanen AM, Tiihonen J, Hartikainen S. The incidence of benzodiazepine and related drug use in persons with and without Alzheimer's disease. *Journal of Alzheimer's Disease 49(3): 809–818, 2016.*

II Saarelainen L, Tolppanen AM, Koponen M, Tanskanen A, Sund R, Tiihonen J, Hartikainen S, Taipale H. Risk of hip fracture in benzodiazepine users with and without Alzheimer's Disease. *Journal of the American Medical Directors Association 18(1): 87.e15–87.e21, 2017.*

III Saarelainen L, Tolppanen AM, Koponen M, Tanskanen A, Tiihonen J, Hartikainen S, Taipale H. Risk of death associated with new benzodiazepine use among persons with Alzheimer's disease – A matched cohort study. *International Journal of Geriatric Psychiatry 33(4): 583–590, 2018.*

Contents

Abbreviations

AD	Alzheimer's disease
ADL	Activities of daily living
aHR	Adjusted hazard ratio
aOR	Adjusted odds ratio
aRR	Adjusted relative risk
ATC	Anatomical Therapeutic Chemical
BPSD	Behavioral and psychological symptom of dementia
BRD	Benzodiazepine-related drugs
BZD	Benzodiazepines
BZDR	Benzodiazepine and related drug
CCI	Charlson comorbidity index
ChEI	Cholinesterase inhibitor
CI	Confidence interval
CO	Community
COPD	Chronic obstructive pulmonary disease
DDD	Defined daily dose
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th edition
GABA	Gamma amino butyric acid
HR	Hazard ratio
I	Interview
IADL	Instrumental activities of daily living
ICD	International Classification of Diseases
IQR	Interquartile range
IR	Incidence rate
IRR	Incidence rate ratio
ITT	Intention to treat
LA	Long-acting
M	Medical records

MCI	Mild cognitive impairment
MEDALZ	Medication Use and Alzheimer's Disease
MX	Community and institutional
NMDA	N-methyl-D-aspartate receptor
OR	Odds ratio
PB	Population-based
PRE2DUP	From prescription drug purchases to drug use periods
Q	Questionnaire
R	Register-based
RR	Relative risk
SA	Short-acting
SII	Social Insurance Institution
SSRI	Selective serotonin reuptake inhibitor
WHO	World Health Organization

1 Introduction

Benzodiazepines and related drugs (BZDR) are used in the treatment of anxiety disorders, sleep disturbances, delirium, and alcohol withdrawal symptoms (Dell'Osso and Lader 2013). Initially, benzodiazepines were introduced in 1960s and they have become widely utilized drugs since then. However, the risk-benefit ratio of BZDR use remains questionable and other effective pharmacological treatment options have become available. BZDRs are frequently used by older persons (Rikala et al. 2011, Hwang et al. 2017), although these older individuals are more sensitive to the adverse effects of these drugs due to age-related changes in pharmacodynamics and pharmacokinetics (Greenblatt et al. 1991, Hämmerlein et al. 1998). In Finland, older persons are defined as persons aged ≥75 years but in this thesis, the literature includes studies on persons aged ≥65 years.

Older persons are often excluded from randomized clinical trials due to their advanced age or comorbidities such as cognitive disorders (Hilmer et al. 2012, Sherman et al. 2016). Therefore, there is a lack of knowledge on adverse outcomes resulting from the adverse effects of the use of BZDRs in an older population. On the other hand, certain adverse outcomes are so rare that they are not possible to examine in clinical trials. Instead, some adverse outcomes associated with BZDR use among older persons have been found in real-world settings in observational studies (Xing et al. 2014, Islam et al. 2016, Seppälä et al. 2018). The real-world effectiveness of drug use can be investigated with large, unselected population-based data such as administrative data collected in registers (Hilmer et al. 2012, Sherman et al. 2016). The nationwide registers in the Nordic countries represent a unique data source for studying the real-world effectiveness and the safety of drug use (Furu et al. 2010). These registers include information on dispensed drugs and hospital stays in conjunction with diagnoses, and all information has been collected systematically for all residents for many decades.

Despite the availability of large data sources, studies investigating BZDR use patterns and associated adverse outcomes among community-dwelling persons with Alzheimer's disease (AD) are mostly lacking. BZDRs may be used in the symptomatic treatment of AD (Azermai et al. 2012, Finnish Medical Society Duodecim 2017c). The appropriate treatment of AD is especially important as the number of persons with this disease is on the increase (Alzheimer's Disease International 2015) and the disease is associated with a patient and caregiver burden as well as increasing social and health care costs (Finnish Medical Society Duodecim 2017c).

This thesis aimed to investigate the incidence of BZDR use among community-dwelling older persons with and without AD utilizing a nationwide, register-based dataset. Furthermore, the risk of hip fracture associated with BZDR use was investigated among persons with and without AD and the associated risk of death among persons with AD.

2 Literature review

2.1 ALZHEIMER'S DISEASE

AD is a progressive neurodegenerative disease impairing cognition and functioning and altering behavior (Alzheimer's Association 2017). It is the most common cause of cognitive disorders, accounting for between 60% to 80% of cases. Aging is the greatest risk factor and, therefore, the number of persons with AD will increase due to the aging of the population (Alzheimer's Association 2017, Finnish Medical Society Duodecim 2017c).

In 2015, in global terms, the estimated number of new cases of any cognitive disorder was 9.9 million, and 46.8 million persons were estimated to have these disorders (Alzheimer's Disease International 2015). It has been estimated that the number of persons with any cognitive disorder will double every 20 years and approximately 132 million persons will have any cognitive disorder in 2050.

In Finland there are approximately 14,500 incident cases of some type of cognitive disorder every year (Finnish Medical Society Duodecim 2017c). According to recent estimates, 190,000 Finnish persons have a cognitive disorder (National Institute for Health and Welfare 2018). The number of persons with a moderate or severe cognitive disorder increases from 114,000 to 131,000 between 2015 and 2020 (Ministry of Social Affairs and Health 2012). Cognitive disorders are mainly diagnosed among persons aged ≥60 years, and less than 10% of cases are under the age of 60 years (Zhu et al. 2015, Alzheimer's Disease International 2015). The average age of Finnish persons at diagnosis of AD is 80 years (Tolppanen et al. 2016).

The exact etiology causing AD remains uncertain (Sperling et al. 2011, Alzheimer's Association 2017). The progressive accumulation of beta amyloid plaques and tau tangles in the brain are considered as key events in the pathophysiological process of AD. The development of AD begins with a presymptomatic phase, during which both beta amyloid and tau accumulate. This phase may begin decades before the first clinical symptoms can be observed. Neuronal loss, resulting in brain atrophy, is the main pathological finding among persons with AD (Minati et al. 2009, Alzheimer's Association 2017).

Initially, the brain can compensate for the neuronal loss, but once the loss is extensive enough, clinical symptoms emerge (Figure 1, Alzheimer's Association 2017). The neuronal damage typically occurs first in the entorhinal cortex and hippocampus, leading to impairments in episodic memory, for example in remembering recent events and new information (Minati et al. 2009). As the cognitive decline progresses, semantic memory and implicit memory are impaired as well. Additionally, other cognitive abilities, including language, visual processing, executive function, attention, and motor skills, are gradually impaired.

The phase of early clinical findings of cognitive disorders is referred to as mild cognitive impairment (MCI, Figure 1). MCI with AD pathology is associated with impairments in episodic memory, which are greater than expected for the subject's age, or impairments in other cognitive abilities, while no considerable functional decline is present (Dubois and Albert 2004, Albert et al. 2011). It is important to note that MCI with AD pathology does not invariably progress to AD: the annual conversion rate is 12% (Petersen et al. 1999).

The diagnosis of AD requires an assessment of the cognitive and functional decline (McKhann et al. 2011, Finnish Medical Society Duodecim 2017c). The diagnostic process also includes brain imaging with computed tomography scan or magnetic resonance imaging, and exclusion of alternative causes for the symptoms. The specific diagnostic criteria applied in Finland for special reimbursement of antidementia drugs will be described more thoroughly in Section 4.1.

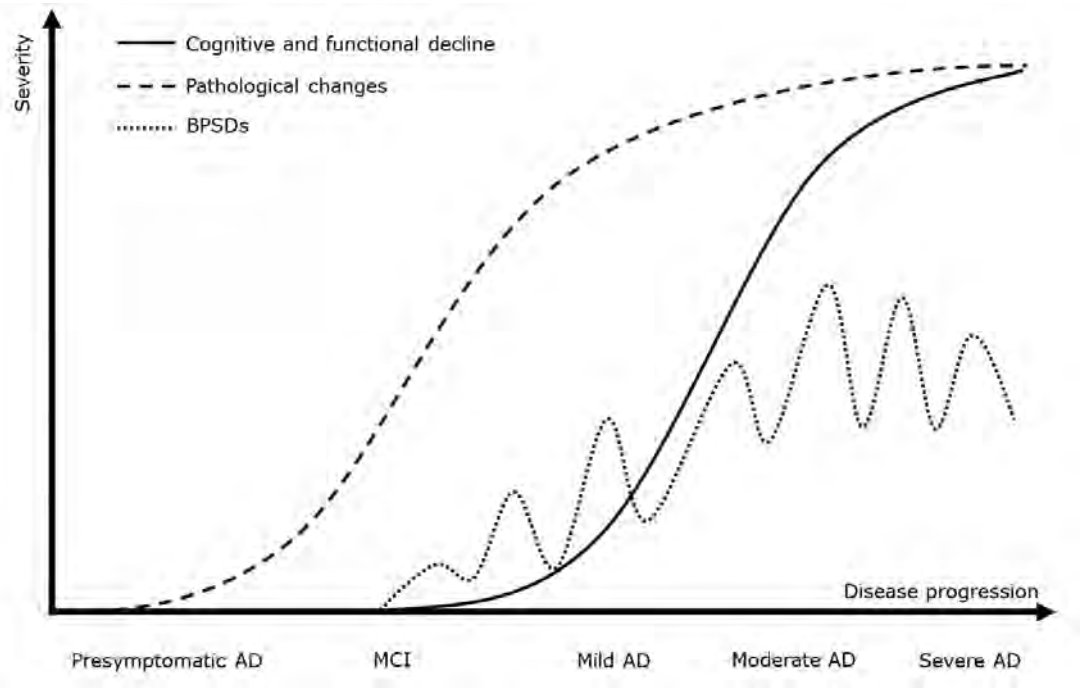

Figure 1. Progression of Alzheimer's disease (Gauthier et al. 2010, Sperling et al. 2011, Gallagher et al. 2017, Finnish Medical Society Duodecim 2017c). AD=Alzheimer's disease, BPSD=behavioral and psychological symptoms of dementia, MCI=mild cognitive impairment

The progression from the mild stage to moderate and severe stages of AD (Figure 1) is defined by the worsening memory and overall cognition, and a continuing decline in functioning (Finnish Medical Society Duodecim 2017c). The functional decline includes impairments in both activities of daily living (ADL) and instrumental activities of daily living (IADL), resulting in the need for help and the loss of independence. Behavioral and psychological symptoms of dementia (BPSD) are present in all stages of the disease, including MCI (Figure 1). BPSDs will be elaborated further in Section 2.1.1.

Persons with cognitive disorders can suffer from comorbid conditions, such as cardiovascular diseases, diabetes, Parkinson's disease, psychiatric diseases, and respiratory diseases, more frequently than those with intact cognition (Malone et al. 2009, Bauer et al. 2014). AD is associated with increased mortality in all age groups (Lönnroos et al. 2013), and the mean time from the diagnosis until death is 4–8 years (Alzheimer's Association 2017). Persons with AD use more health care services than other older persons, including inpatient care and long-term care (Tolppanen et al. 2015, Alzheimer's Association 2017). Most of the increasing costs result from the increased need for long-term care (Schaller et al. 2015, Alzheimer's Association 2017).

A timely diagnosis of cognitive disorders is promoted both in Finland and internationally (Alzheimer's Disease International 2011, Ministry of Social Affairs and Health 2012). 'Timely diagnosis' emphasizes the acknowledgement of the earliest clinical findings related to cognitive disorders (Alzheimer's Disease International 2011, Dubois et al. 2016). The benefits of a timely diagnosis include planning of individualized living conditions and care together with the patient, optimizing medical treatment, and earlier access to social support. Furthermore, there is a consensus that there are improved clinical outcomes and a delay in institutionalization resulting from a timely diagnosis (Alzheimer's Disease International 2011).

There is no pharmacotherapy available which could stop or slow down the progression of AD (Alzheimer's Association 2017). The current pharmacological treatment options can be considered as symptomatic, as the drugs do not affect the underlying pathology. Instead, a reduced availability of acetylcholine, resulting from the neuronal loss, is the main target of current antidementia drug treatment (Minati et al. 2009). Cholinesterase inhibitors (ChEI), i.e. donepezil, rivastigmine, and galantamine, inhibit the breakdown of acetylcholine, increasing its availability and resulting in symptom relief (Rodda and Carter 2012). Another approach in the treatment of AD is to target glutamate N-methyl-D-aspartate (NMDA) receptors which are overactivated in AD, resulting in neurodegeneration (Minati et al. 2009). Memantine is the drug currently used to antagonize the overactivated NMDA receptors.

The ChEIs are the first-line treatment of mild and moderate AD, unless there are contraindications (Rabins et al. 2007, Herrmann et al. 2013, Finnish Medical Society Duodecim 2017c). Potential contraindications include sick sinus syndrome and having gastrointestinal bleeding or other gastrointestinal disorders during the preceding six months (Rabins et al. 2007, Finnish Medical Society Duodecim 2017c). ChEI use for ≥6 months exerts a modest efficacy against cognition, functioning and global clinical state in all stages of the disease (Rodda and Carter 2012).

Memantine is the second-line treatment of AD and it is recommended for moderate and severe AD, or if the ChEIs are contraindicated (Rabins et al. 2007, Herrmann et al. 2013, Finnish Medical Society Duodecim 2017c). The effects of memantine use on cognition, functioning, and BPSDs are more evident in the moderate and severe stages of the disease than in the mild stage (Di Santo et al. 2013, Kishi et al. 2017). However, the overall efficacy is smaller than the efficacy of ChEI use. The efficacy of memantine use on cognition and behavior in the moderate and severe stages of the disease was affirmed in a recent meta-analysis of trials with a mean follow-up of seven months (Kishi et al. 2017). A combination of ChEI and memantine use, which is utilized in the moderate and severe stages of the disease, might provide additional benefits in cognition and functioning (Rabins et al. 2007, Herrmann et al. 2013, Finnish Medical Society Duodecim 2017c).

In clinical practice, the efficacy of pharmacological treatment on the symptoms can be evaluated after six months of use (Finnish Medical Society Duodecim 2017c). There is considerable variation in terms of efficacy between individuals (Alzheimer's Association 2017).

The use of antidementia drugs is more frequent and prolonged in Finland than in other countries (Maxwell et al. 2014). Among Finnish community-dwelling persons with AD, the median duration of the first treatment period was 860 days with ChEIs and 605 days with memantine (Taipale et al. 2014b). During a four-year period, 84% were using ChEIs and 47% were taking memantine, whereas 22% used these drugs concomitantly. Most (95%) ChEI users initiated the use during the first year after AD diagnosis, with the corresponding rate among memantine users being 50%.

2.1.1 Behavioral and psychological symptoms of dementia

BPSDs have been defined as 'disturbed emotions, mood, perception, thought, motor activity, and altered personality traits' (Cerejeira et al. 2012). As BPSDs are commonly correlated, they have been classified in symptom groups in various ways (Cerejeira et al. 2012). The specific BPSDs during MCI and AD are listed in Table 1, according to the grouping applied by Aalten et al. (2003).

Mood/apathy symptom group represents changes in emotions, sleeping, and eating (Table 1). Depressive symptoms are expressed as a decreased ability to experience pleasure and as fears and social isolation, whereas apathy refers to a lack of motivation without feelings of melancholy (Cerejeira et al. 2012, Wang et al. 2014). Sleep pattern changes include, for example, sleep-wake cycle reversal, fragmented sleep, insomnia and

hypersomnia (Cerejeira et al. 2012). Eating disturbances may include both appetite loss and hyperphagia, as well as selective eating due to changes in taste.

Table 1. Prevalent behavioral and psychological symptoms of dementia, categorized according to Aalten et al. (2003), during mild cognitive impairment and Alzheimer's disease (Apostolova and Cummings 2008, Gauthier et al. 2010, van der Linde et al. 2016, Gallagher et al. 2017).

	MCI*	**AD**
Mood/apathy symptoms		
Apathy	x	x
Depression	x	x
Eating disturbances		x
Sleep pattern changes		x
Hyperactivity symptoms		
Agitation	x	x
Disinhibition		x
Irritability, aggression	x	x
Motor hyperactivity		x
Psychotic symptoms		
Delusions		x
Hallucinations		x
Anxiety	x	x

AD=Alzheimer's disease; BPSD=behavioral and psychological symptoms of dementia; MCI=mild cognitive impairment.
* not restricted to AD pathology

Symptoms of hyperactivity (Table 1) result from an increased energy level (Cerejeira et al. 2012). Motor hyperactivity may include frequent movements or accelerated speech, whereas agitation has been defined in various ways: the symptoms include increased motor or vocal activity, but may also include aggression, wandering or disinhibition (Rabins et al. 2007, Cerejeira et al. 2012, Wang et al. 2014). Disinhibition refers to inappropriate behavior such as undressing in public. Persons with cognitive disorders may also have a lower threshold for hostility (Cerejeira et al. 2012).

Hallucinations among persons with cognitive disorders are visual or auditory (Wang et al. 2014) whereas delusional thoughts include suspiciousness, paranoia, and misidentification (Cerejeira et al. 2012). Symptoms of anxiety may represent independent symptoms or a component of depression (Seignourel et al. 2008, Wang et al. 2014). These symptoms are expressed as excessive worrying together with other symptoms such as muscle tension, respiratory complaints, restlessness, and irritability (Seignourel et al. 2008, Cerejeira et al. 2012).

BPSDs may represent prodromal symptoms of the cognitive disorder among persons with MCI (Rosenberg et al. 2013, Gallagher et al. 2017). Up to 85% of persons with MCI (Monastero et al. 2009, Gallagher et al. 2017) have these symptoms, and they might be the first clinical findings eventually leading to the diagnosis of a cognitive disorder (Gallagher et al. 2017). Further, practically all persons with AD experience BPSDs during the course of the disease (Gauthier et al. 2010).

The presentation of the symptoms varies considerably between persons (Cerejeira et al. 2012, van der Linde et al. 2016). The highest incidence and persistence have been reported for symptoms of hyperactivity: for example, in nearly 80% of cases, symptoms of agitation may persist for two years. On the other hand, a lower incidence and persistence have been reported for sleep pattern changes: over two years, these symptoms emerge in one-third of persons with cognitive disorders, but the symptoms persist in fewer than 10% of cases. Consequently, the prevalence of BPSDs varies over time (van der Linde et al. 2016). Based on cross-sectional assessments, the prevalence of symptoms of anxiety and apathy has ranged between 20% and 50% in most studies. The prevalence of agitation varied between 20% and 30% whereas sleep disturbances and hallucinations were observed in 20% of persons (van der Linde et al. 2016).

The neurobiology of BPSDs is related to brain atrophy and neurotransmitter imbalance in those brain regions associated with emotion and cognition (Cerejeira et al. 2012, Kales et al. 2015). Consequently, persons with cognitive disorders are more sensitive to the triggers for BPSDs, including factors related to the patient, caregiver, and environment. For example, pain and other undiagnosed conditions may predispose the patient to BPSDs (Kales et al. 2015). Additionally, previous psychiatric disorders may increase the risk of having BPSDs. The inability to express feelings and needs may result in affective symptoms (Wang et al. 2014). Further, misunderstandings related to communication challenges between the patient and the caregiver may result in frustration (Kales et al. 2015). Other caregiver-related factors potentially increasing the risk of having BPSDs include stress and depression. Environment-related factors include over- or under-stimulation, changes in daily routines or in physical or social environment (Cerejeira et al. 2012, Kales et al. 2015).

BPSDs represent a major burden for the patient and the caregiver. BPSDs are associated with a shorter time to disease progression, institutionalization, and death (Peters et al. 2015, Toot et al. 2017). Further, a lower quality of life has been observed among persons with BPSDs and among their caregivers (Conde-Sala et al. 2016). BPSDs have also been associated with a higher caregiver burden (Chiao et al. 2015).

Non-pharmacological treatment is the first-line treatment for BPSDs, according to the Finnish and international treatment guidelines of cognitive disorders (Azermai et al. 2012, Finnish Medical Society Duodecim 2017c). Non-pharmacological treatment involves investigating the underlying causes of symptoms and planning the treatment with the patient and caregivers (Gitlin et al. 2012). Non-pharmacological treatment options may target the patient, caregiver, or the environment (Kales et al. 2015). Interventions targeting caregivers, for example education in identifying and addressing causes of BPSDs, have shown the best efficacy in relieving BPSDs and caregiver distress in a community setting. Several studies investigating the efficacy of non-pharmacological interventions have had small sample sizes and they have focused on persons living in institutional care.

Pharmacological treatment can be initiated when non-pharmacological treatment has been insufficient (Rabins et al. 2007, Azermai et al. 2012, Kales et al. 2015, Finnish Medical Society Duodecim 2017c). In general, pharmacological treatment can be used in severe BPSDs, especially if there is a risk of self-harm or harm to others. However, the pharmacological options are not effective on wandering, hypersexuality, hoarding, inappropriate behavior, shouting, ingesting items, and self-harm such as people scratching or hitting themselves (Kales et al. 2015, Finnish Medical Society Duodecim 2017c). The drug groups used in the treatment of BPSDs include antidementia drugs which are the first-line option but also psychotropic drugs (BZDRs, antipsychotics, and antidepressants), antiepileptics, and beta-blockers (Table 2).

The efficacy of different drug groups in BPSD treatment is modest (Kales et al. 2015, Wang et al. 2015) and the risk of adverse outcomes, including falls, cerebrovascular events, and death, is considerable (Hartikainen et al. 2007, Rabins et al. 2007, Álamo et al. 2014, Ma et al. 2014). Treatment with antidementia drugs should be preferred because it is also effective in the long-term treatment of BPSDs, in addition to their effects cognition and

functioning (Wang et al. 2014, Wang et al. 2015). However, the evidence on the efficacy of antidementia drug treatment is scarce for example, in comparison to that of atypical antipsychotics (Wang et al. 2015). It has been postulated that any use of drugs that could further impair cognition, including psychotropic drugs (Rabins et al. 2007), should be minimized (American Geriatrics Society Beers Criteria Update Expert Panel 2015, Gallagher et al. 2017). Discontinuation of psychotropic drug treatment of BPSDs should be considered regularly as the symptoms resolve over time (van der Linde et al. 2016, Finnish Medical Society Duodecim 2017c).

Table 2. Drug groups used in the treatment of severe behavioral and psychological symptoms of dementia (Rabins et al. 2007, Azermai et al. 2012, Herrmann et al. 2013, Rabins et al. 2014, Wang et al. 2014, Kales et al. 2015, Finnish Medical Society Duodecim 2017c).

Drug group	Targeted symptoms
Antidementia drugs	
Cholinesterase inhibitors	Agitation, apathy, depression, psychotic symptoms, all BPSDs
Memantine	Agitation, depression, psychotic symptoms, all BPSDs
Benzodiazepines and related drugs	
Benzodiazepines	Agitation, anxiety, sleep pattern changes
Benzodiazepine-related drugs	Insomnia
Antipsychotics	
Atypical	Aggression, agitation, psychotic symptoms, sleep pattern changes
Typical	Aggression, agitation, psychotic symptoms
Antidepressants	
SSRIs	Agitation, aggression, anxiety, depression
Tricyclic	Depression
Others	Agitation, aggression, anxiety, insomnia, depression
Antiepileptics	Agitation, anxiety, psychotic symptoms
Beta blockers	Agitation, anxiety

BPSD=behavioral and psychological symptoms of dementia; SSRI=selective serotonin reuptake inhibitors

2.2 BENZODIAZEPINES AND RELATED DRUGS

2.2.1 Pharmacology

BZDRs bind to a specific site on the gamma-aminobutyric acid A ($GABA_A$) receptor (Baldwin et al. 2013, Griffin et al. 2013), inducing a conformational change in the receptor. This increases the receptor affinity for gamma-aminobutyric acid, which is the primary inhibitory neurotransmitter in the central nervous system. Consequently, the main pharmacological properties of BZDRs are sedative/hypnotic, anxiolytic, anticonvulsive, and muscle relaxing effects (Figure 2).

Tolerance to the sedative effects can develop already after two weeks of use (Buffett-Jerrott and Stewart 2002, Dell'Osso and Lader 2013). Development of tolerance results from the decreasing sensitivity of $GABA_A$ receptors (Ashton 2005). As a result, increased dosages are needed to obtain any response (Buffett-Jerrott and Stewart 2002, Baldwin et al. 2013). This is especially important among older persons, as insomnia is the main indication for

BZDR use in these individuals (Finnish Medical Society Duodecim 2017b). On the other hand, the anxiolytic and amnestic effects are less subject to tolerance, or tolerance might not develop at all (Buffett-Jerrott and Stewart 2002, Baldwin et al. 2013).

Dependence can develop during prolonged BZDR use (Baldwin et al. 2013, Dell'Osso and Lader 2013). Withdrawal symptoms may emerge if there is a too rapid dose decrease or abrupt discontinuation. For example, rebound anxiety and insomnia may appear (Dell'Osso and Lader 2013, Soyka 2017). Therefore, BZDR use should be discontinued by decreasing the dose gradually over a period ranging from several weeks to several months, depending on the duration of drug use (Soyka 2017). Among older persons, discontinuation of use might be challenging already after four weeks of use, and a systematic review found that up to 80% of BZDR users were able to discontinue use (Reeve et al. 2017).

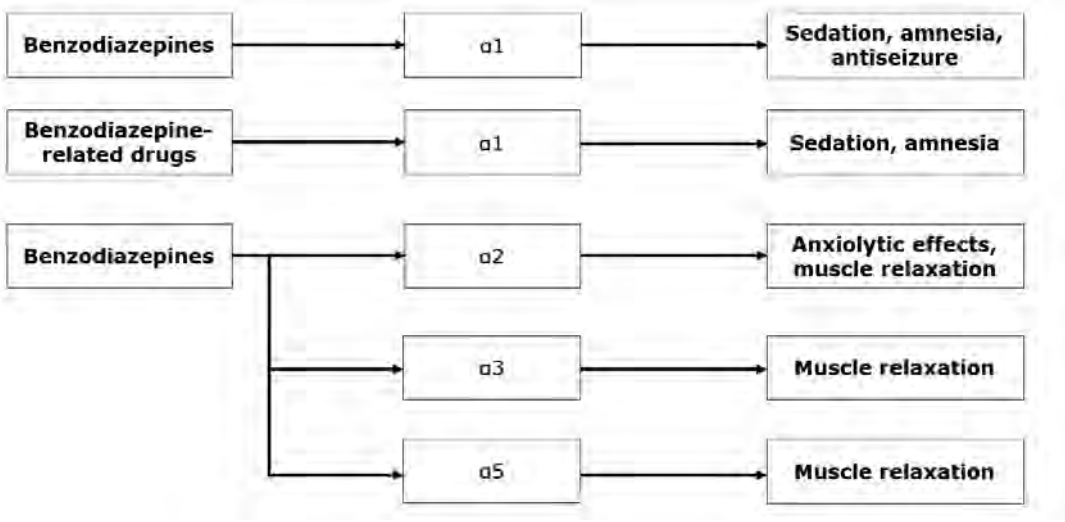

Figure 2. The pharmacological effects of benzodiazepines and related drugs according to specificity to $GABA_A$ receptor subunits (α1–3, α5) (Möhler et al. 2002, Gunja 2013).

Benzodiazepines, including drugs such as oxazepam and diazepam, and benzodiazepine-related drugs, including zolpidem, zopiclone, and zaleplon, have a similar pharmacological mechanism of action, although their structures and pharmacokinetic properties differ (Baldwin et al. 2013) and their affinity for different $GABA_A$ receptor subtypes varies (Figure 2). Benzodiazepines interact with all receptor subtypes, while benzodiazepine-related drugs interact only with the $\alpha 1$ subtype, mostly mediating the sedative and hypnotic effects (Möhler et al. 2002, Gunja 2013). BZDRs are classified according to their elimination half-lives among adults as short-, intermediate-, and long-acting drugs (Table 3).

Aging affects the pharmacokinetics and pharmacodynamics of BZDRs (Greenblatt et al. 1991, Hämmerlein et al. 1998). The proportion of adipose tissue of the total body weight increases with aging (Hämmerlein et al. 1998, Ruiz et al. 2015). As all BZDRs are lipophilic drugs, this results in an increased volume of distribution and, consequently prolongation of their elimination half-lives. Further, clearance is reduced for drugs metabolized by oxidation (Table 3) (Greenblatt et al. 1991, Hämmerlein et al. 1998). As some of these drugs, i.e. chlordiazepoxide, clobazam, diazepam, and zopiclone, have active metabolites, the total elimination half-life may be considerably extended (Greenblatt et al. 1981, Gunja 2013). The clearance of drugs metabolized by conjugation or nitroreduction is not considerably altered by aging (Greenblatt et al. 1991, Hämmerlein et al. 1998). Due to the age-dependent

alterations in pharmacokinetics, there is a risk of accumulation of BZDRs when they are administered frequently.

Table 3. Benzodiazepines and related drugs available in Finland, according to their elimination half-life and metabolic pathway (Greenblatt et al. 1981, Greenblatt et al. 1991, Gunja 2013, Finnish Medicines Agency and Social Insurance Institution 2017).

Short-acting	**Intermediate-acting**	**Long-acting**
Metabolized by oxidation:	*Metabolized by oxidation:*	*Metabolized by oxidation:*
Midazolam	Alprazolam	Chlordiazepoxide
Triazolam	Zopiclone	Clobazam
Zolpidem	*Metabolized by conjugation:*	Diazepam
	Lorazepam	*Metabolized by nitroreduction:*
	Oxazepam	Nitrazepam
	Temazepam	

The reasons for age-dependent changes in pharmacodynamics are less known (Hämmerlein et al. 1998, Ruiz et al. 2015). Potential reasons include neuronal loss, increased sensitivity of receptors, and the increased permeability of the blood-brain barrier (Ruiz et al. 2015). Further, the decreased ability to maintain homeostasis after a stimulus alters the effects of several drugs, including those affecting the central nervous system, among older persons. These changes might be more pronounced among persons with cognitive disorders due to the associated neuronal loss (Minati et al. 2009, Alzheimer's Association 2017).

Due to the changes occurring in their pharmacokinetics and pharmacodynamics, older persons are more sensitive to the adverse sedative and cognitive effects of BZDRs (Griffin et al. 2013), which increases the risk of adverse outcomes. The acute sedative and cognitive effects are listed in Table 4.

Table 4. Acute cognitive and sedative effects of benzodiazepine and related drug use (Buffett-Jerrott and Stewart 2002).

Sedation	**Impaired attention**	**Impaired long-term memory**
Drowsiness, relaxation	Reaction to an external stimulus	Explicit memory - Episodic memory
Slower performance - Cognitive processing - Psychomotor performance	Ability to maintain focus	Implicit memory
	Ability to focus on several stimuli in turn	
	Problem solving skills	

The use of sedative drugs has been associated with muscle weakness (Taipale et al. 2011), poor balance, and impaired mobility among older persons (Taipale et al. 2012). Sedative drug use was also associated with an increased risk of frailty, including symptoms such as muscle weakness, lower physical activity, slower walking speed, and weight loss (Peklar et al. 2015). These findings may result from muscle relaxation and impairment of psychomotor performance (Hindmarch 1980). BZDR use has been associated with

impairments in IADLs (Peron et al. 2011) which may result from adverse effects impacting on muscle strength and balance (Hairi et al. 2010, de Groot et al. 2013).

BZDR use might impair the episodic memory shortly after drug administration (Buffett-Jerrott and Stewart 2002). As a matter of fact, long-term use of benzodiazepines has been associated with impairments in attention and in both verbal and nonverbal memory (Barker et al. 2004a). The cognitive decline may persist for months after the discontinuation of long-term benzodiazepine use (Barker et al. 2004b).

In Finland, lorazepam, oxazepam, temazepam, and zopiclone are recommended to be used with caution among older persons, while the other BZDRs should be avoided (Finnish Medicines Agency 2018). However, in the classification by the American Geriatrics Society (American Geriatrics Society Beers Criteria Update Expert Panel 2015), all BZDRs are classified as drugs to be avoided by older persons. These classifications emphasize the considerable risk of adverse effects which may outweigh any potential benefits.

2.2.2 Implications for benzodiazepine and related drug use among older persons

General older population

The short-term (2–4 weeks) treatment of temporary primary insomnia is an important indication for BZDR use among older persons (Schroeck et al. 2016, Finnish Medical Society Duodecim 2017b). In Finland, 17% of men and 20% of women aged ≥75 years report difficulties in falling asleep or having fragmented sleep during a week (National Institute for Health and Welfare 2012). However, BZDR use should be restricted to the treatment of insomnia that is severe, distressing, and disabling (Baldwin et al. 2013), and non-pharmacological treatment options should be attempted first (Finnish Medical Society Duodecim 2017b). The dosage of BZDRs among older persons should be lower than that prescribed for younger people. BZDR use seems to improve sleep quality and prolong sleep duration among older persons (Alessi and Vitiello 2011, Schroeck et al. 2016). Other effects include reductions in both sleep onset latency and the number of night time awakenings. However, the effects have been modest, for example, sleep onset latency was reduced by 12 minutes after benzodiazepine use and by up to 20 minutes after benzodiazepine-related drug use (Alessi and Vitiello 2011). Total sleep duration was increased by up to 44 minutes after benzodiazepine use and by up to one hour after benzodiazepine-related drug use. Cognitive-behavioral therapy, including relaxation techniques and stimulus control, has been recommended as the first-line treatment of insomnia among older persons (Finnish Medical Society Duodecim 2017b).

In addition, benzodiazepines are used in the short-term treatment (up to a few weeks) of severe and distressing anxiety disorders, including generalized anxiety disorder and panic disorder (Lenze and Wetherell 2011, Baldwin et al. 2013). Among community-dwelling older persons, the six-month prevalence of any anxiety disorder is up to 10%, mostly due to generalized anxiety disorder (Lenze and Wetherell 2011). Benzodiazepines can be used as adjunctive treatment for prompt symptom relief among older persons. However, it should be noted that the prompt relief with benzodiazepines might result in neglecting long-term treatment options with better risk-benefit ratios, including relaxation training. As with insomnia treatment, the dose should be lower than among younger adults and avoidance of long-term use is emphasized. The currently available benzodiazepines have been studied only in two four-week trials; it was found that alprazolam had considerable efficacy and oxazepam exerted moderate efficacy on symptoms of anxiety or anxiety disorders among older persons (Pinquart and Duberstein 2007).

Persons with cognitive disorders

BZDRs can be used in the treatment of certain BPSDs if non-pharmacological options have not been effective enough and the symptoms are disturbing (Rabins et al. 2007, Finnish Medical Society Duodecim 2017c). Benzodiazepines can be used to relieve both acute or

severe symptoms of anxiety (Rabins et al. 2007, Wang et al. 2014). Further, benzodiazepines can also be used in occasional episodes of agitation, especially if there is a risk of self-harm or harm to others. Both benzodiazepines and benzodiazepine-related drugs can be used in the treatment of sleep disturbances (Rabins et al. 2007, Finnish Medical Society Duodecim 2017c). However, it is important to first recognize and relieve any symptoms and comorbidities potentially interrupting sleep, and a non-pharmacological approach, such as improving sleep hygiene, should be implemented before pharmacological options. If the sleep disturbances persist after other treatment approaches and if the benefits outweigh the potential risks, then pharmacological treatment such as BZDRs can be considered.

The use of BZDRs in the treatment of BPSDs should be short-term and infrequent (Rabins et al. 2007, Azermai et al. 2012, Finnish Medical Society Duodecim 2017c) with intermediate-acting drugs being preferred (Finnish Medical Society Duodecim 2017c) and with an initial dose which is half of the dose considered normal for adults (Wang et al. 2014). Further, discontinuation of BZDR use should be assessed on a regular basis. On the other hand, some recommendations state that benzodiazepine use should be totally avoided among persons with cognitive disorders (Sink et al. 2005, American Geriatrics Society Beers Criteria Update Expert Panel 2015).

The efficacy of benzodiazepine use in the treatment of BPSDs has been rarely studied. A systematic review (Tampi and Tampi 2014) including five randomized controlled trials indicated that benzodiazepine use has some benefits in the treatment of symptoms of anxiety or agitation. The efficacy of benzodiazepine use was similar with that of antipsychotic use in three studies, while antipsychotics were superior in a fourth study. Alprazolam use was compared with lorazepam use in the fifth study, and their efficacy in relieving the symptoms of agitation was found to be equal.

2.2.3 Incidence of use

The incidence of BZDR use among older persons has been investigated in six studies focusing on community-dwelling persons and in additional seven studies focusing on persons living in the community or in institutions (Table 5). The study populations ranged between 700 and 1,014,891 persons. The proportion of persons with cognitive disorders in the study populations was 9–24% but no study investigated the incidence of BZDR use specifically among these individuals.

The incidence of BZDR use was 6% during an 8-month period in Canada (Metge et al. 2005) and 8–10% during a one-year period in France and Israel (Bénard-Laribière et al. 2017, Steinman et al. 2017) in studies including persons living in the community and/or institutions. Another Canadian study found that 11% of the study population had initiated benzodiazepine use during a two-year period (Halme et al. 2013). Persons living in institutions or persons with cognitive disorders were not included in the above study. Further, in a Finnish study including the oldest study population and the highest proportion of persons with cognitive disorders, the incidence of BZDR use during a three-year period was 17% among community-dwelling persons (Rikala et al. 2011). Two Canadian studies reported that the five-year incidence of benzodiazepine use was 31–32% despite there being differences in the study populations and settings (Bartlett et al. 2009, Vozoris et al. 2013).

The separate incidence rates of benzodiazepine and benzodiazepine-related drug use were investigated during two time periods: 1996–1997 and 2011–2012 (Alessi-Severini et al. 2014). The annual incidence rate of benzodiazepine use declined from 55.5 to 30.3 incident users per 1000 persons between these time periods. On the other hand, the incidence rate of benzodiazepine-related drug use increased from 7.3 to 20.3 incident users per 1000 persons. This is the only study that has investigated the differences between the incidence of benzodiazepine and benzodiazepine-related drug use among older persons.

The initiation of benzodiazepine use after hospital discharge has been investigated in two studies (Bell et al. 2007, Scales et al. 2016). These found that approximately 3% of the

study population had initiated benzodiazepine use within 7 days and 5% within one month after their discharge. Additionally, in the sub-analyses of the study of Steinman et al. (2017), 5% initiated BZDR use within two months after hospitalization. One study found that during a period ranging from three months before to three months after hospitalization, the incidence rate was more than six times higher among hospitalized persons than among matched non-hospitalized persons (Stuffken et al. 2005).

Most of the studies (11 out of 13) were register-based (Table 5). In these studies, the duration of the washout period, applied to exclude prevalent drug users, was 4–12 months. Incident use was defined as the first purchase after the washout period, and drug use was assumed to begin on the date of drug purchase. However, some registers did not include information about drug use during hospital care (Metge et al. 2005, Bartlett et al. 2009, Alessi-Severini et al. 2013, Alessi-Severini et al. 2014, Bénard-Laribière et al. 2017).

A baseline interview had been utilized to exclude prevalent users in two studies (Fourrier et al. 2001, Rikala et al. 2011). Incident use was defined as a report of drug use in any of the consequent interviews. Both studies assessed drug use during the two preceding weeks in each interview. The reported information was ascertained from drug packages in both studies and, additionally from prescriptions and medical records in the other study (Rikala et al. 2011). Thus, the obtained information can be considered to represent actual drug use at the time point of the interviews.

Additional findings

Women have been reported to be more likely to initiate BZDR use than men (Bartlett et al. 2009, Vozoris et al. 2013, Scales et al. 2016). High age was associated with both increased (Scales et al. 2016) and decreased (Bartlett et al. 2009) risks of initiating benzodiazepine use among the general older population. Among persons with chronic obstructive pulmonary disease (COPD), persons aged ≥75 years were less likely to initiate BZDR use than those aged 66–74 years (Vozoris et al. 2013).

A high number of comorbidities, including also diseases other than psychiatric diseases, has been associated with the initiation of BZDR use (Fourrier et al. 2001, Bartlett et al. 2009, Vozoris et al. 2013, Scales et al. 2016). On the other hand, among persons with COPD, those with cognitive disorders were less likely to initiate use (Vozoris et al. 2013). A higher number of drugs, excluding BZDRs, was also associated with incident BZDR use (Halme et al. 2013, Vozoris et al. 2013).

With regard to health care use, increasing the number of prescribing physicians was associated with incident benzodiazepine use (Bartlett et al. 2009). Persons admitted to a hospital were more likely to initiate BZDR use than those who had an ambulatory visit (Stuffken et al. 2005, Halme et al. 2013, Steinman et al. 2017) and persons living in institutional care were more likely to initiate BZDR use than their counterparts living in the community (Vozoris et al. 2013, Scales et al. 2016).

Among Canadian community-dwelling older persons, 18% of incident benzodiazepine users continued use for ≥90 days and 9% for ≥180 days (Bartlett et al. 2004). The mean duration of the first benzodiazepine use period was 70 days. In the studies investigating only discharged persons, 49% of the incident users purchased benzodiazepines again within six months (Bell et al. 2007) and 23% after 10–14 months (Scales et al. 2016).

In conclusion, the incidence of BZDR use has been investigated among older persons, but not specifically among persons with cognitive disorders. Hospitalization, female gender, and a high number of comorbid conditions and drugs in use were recognized as risk factors for initiating BZDR use.

Table 5. Studies investigating the incidence of benzodiazepine and related drug use in older persons.

Study, country	Data source, years	Setting	Study population	Mean age, % women	Included drugs	Time window (washout)	Result
<1-year incidence							
Scales et al. (2016), Canada	R, 2002–2012	MX	All persons discharged from hospital, n=1,014,891, ≥66 years, 17% with CD, 7% institutionalized	78 years, 54%	BZD	7 days 30 days (12 months)	3.3% 5.0%
Bell et al. (2007), Canada	R, 1992–2005	CO	All persons discharged from hospital, ≥66 years, n=405,128	median age 76 years, 53%	BZD	7 days (12 months)	3.1%
Metge et al. (2005), Canada	R, 1996–2000	MX	PB, ≥65 years, n=156,547	nr	BZD, BRD	8 months (4 months)	6.3%
Stuffken et al. (2005), Netherlands	R, 1998–2000	MX	Random sample, hospitalized persons (n=3,124) and matched persons not hospitalized (n=3,124), ≥65 years	nr	BZD, BRD	6 months (6 months)	26.9 / 100 patient-years
1-year to 3-year incidence							
Bénard-Laribière et al. (2017), France	R, 2006–2012	MX	PB, n=82,961, ≥65 years	nr	BZD, BRD	1 year (12 months)	Aged 65–79 years: 7.6% Aged ≥80 years: 7.8%
Steinman et al. (2017), Israel	R, 2013–2015	MX	Random sample, ≥65 years, n=56,808, 9% with CD	57%	BZD, BRD	1 year (12 months)	10%
Alessi-Severini et al. (2014), Canada	R, 1996–2012	MX	All persons aged ≥65 years in one province, during 1996–1997 n=154,890, during 2011–2012 n=176,498	nr	BZD, BRD	1 year (12 months)	During 1996–1997: BZD 55.5/1000 persons BRD 7.3/1000 persons During 2011–2012: BZD 30.3/1000 persons BRD 20.3/1000 persons

BRD=benzodiazepine-related drugs; BZD=benzodiazepines; CD=cognitive disorders; CO=community; MX=community and institutional; nr=not reported; PB=population-based sample; R=register-based data

(Continued)

Table 5. (Continued)

Study, country	Data source, years	Setting	Study population	Mean age, % women	Included drugs	Time window (washout)	Result
1-year to 3-year incidence							
Alessi-Severini et al. (2013), Canada	R, 1997–2009	CO	All persons aged ≥65 years in one province, n=153,189	nr	BZD, BRD	1 year (12 months)	1998: 13.14 / 1000 persons 2009: 13.66 / 1000 persons
Halme et al. (2013), Canada	R, 2005–2008	CO	Random, persons without CD, n=1,189, ≥65 years	73 years, 66%	BZD	2 years (12 months)	11.0%
Rikala et al. (2011), Finland	I and M, 2004–2007	CO	PB, n=700, ≥75 years, 24% with CD	81 years, 69%	BZD, BRD	3 years (baseline)	17%
Five-year incidence							
Vozoris et al. (2013), Canada	R, 2004–2010	MX	All persons with COPD, n=111,445, ≥66 years, 20% with CD, 13% institutionalized	46%	BZD	5 years (12 months)	31.7%
Bartlett et al. (2009), Canada	R, 1989–1994	CO	Random, n=252,811, ≥66 years	73 years, 52%	BZD	5 years (12 months)	31.0%
Fourrier et al. (2001), France	I, 1988–1994	CO	Random, n=2,792, ≥65 years, 24% with CD	60%	BZD, BRD	5 years (baseline)	5.37 / 100 person-years

BRD=benzodiazepine-related drugs; BZD=benzodiazepines; CD=cognitive disorders; CO=community; COPD=chronic obstructive pulmonary disease; I=interview; M=medical records; MX=community and institutional; nr=not reported; PB=population-based sample; R=register-based data.

2.2.4 Prevalence of use

Approximately every third community-dwelling older person in Finland (31%) and France (32%) had used BZDRs during a two-week period (Fourrier et al. 2001, Rikala et al. 2011). A lower annual prevalence was reported among community-dwelling Canadians, i.e., 23% of older women and 15% of older men used BZDRs (Weymann et al. 2017). Among persons living in the community or in institutions, the one-year prevalence of BZDR use varied considerably between countries. Lower annual prevalence (12%) was reported in Scotland (Johnson et al. 2016) and higher (32–43%) in Israel, Korea, and Taiwan (Cheng et al. 2008, Hwang et al. 2017, Steinman et al. 2017).

Among community-dwelling Finnish persons with mild AD, the one-year prevalence of BZDR use was 16% and this increased to 24% during the third follow-up year (Törmälehto et al. 2017). A higher prevalence was observed in a nationwide sample of Finnish persons with AD, as 20% used BZDRs during a six-month period (Orsel et al. 2018) and 29% during one year (Taipale et al. 2014a). The proportion was higher (45%) during a four-year period (Taipale et al. 2015).

Among community-dwelling persons with AD in other countries, a lower point prevalence (13%) of BZDR use was observed in the United Kingdom (Ellul et al. 2007) and higher values (54% and 34% among persons with and without arthritis/rheumatism, respectively) in Canada (Balfour and O'Rourke 2003). Among persons with AD living in community and/or institutions, 20% of French persons reported benzodiazepine use (Lagnaoui et al. 2003) and 12% of German persons reported BZDR use during a three-month period (Hessmann et al. 2018). Further, 25% had taken benzodiazepines during a 12-year period in the United States (Rosenberg et al. 2012).

Among population-based samples with any cognitive disorders, the one-year prevalence of BZDR use has been 26% in Canada (Sivananthan et al. 2015) and the three-year prevalence estimated as 35% in the United States (Fick et al. 2007).

2.3 ASSOCIATED ADVERSE OUTCOMES

BZDR use has been associated with several adverse health outcomes among older persons; these will be reviewed in this section with the emphasis placed on hip fractures and mortality.

2.3.1 Hip fractures

Falls are frequent among older persons, and more than every third older person will experience a fall each year (Tinetti 2003). AD is a considerable risk factor for falls because the impairments in executive function and motor skills result in gait disturbances and balance impairment (Sheridan and Hausdorff 2007). Falls result in various injuries (Kannus et al. 1999), with approximately 1% resulting in hip fractures (Friedman and Mendelson 2014). On the other hand, 90% of hip fractures result from falls (Friedman and Mendelson 2014, Finnish Medical Society Duodecim 2017a). After the age of 50 years, the risk of hip fracture doubles every decade (Friedman and Mendelson 2014). The risk of hip fracture in persons with AD is more than twice as high as in the general older population (Tolppanen et al. 2013, Liang and Wang 2017). In 2016, there were 7,716 hip fractures among persons aged ≥50 years in Finland; the mean age of women with hip fracture was 82 years, while the mean age of men was 77 years (Kannus et al. 2018).

BZDR use has been associated with an increased risk of falls among older persons (Hartikainen et al. 2007); this may result from the cognitive and sedative effects of these drugs (Buffett-Jerrott and Stewart 2002). A meta-analysis of 14 studies indicated that benzodiazepine use was associated with a 40% increase (odds ratio [OR] 1.42, 95% CI 1.22–1.65) in the risk of falls among older persons, while one study found a 2.6-fold risk (adjusted odds ratio [aOR] 2.59, 95% CI 1.16–5.81) associated with zolpidem use (Seppälä et

al. 2018). Further, a systematic review found that benzodiazepine use was associated with an up to 2.5-fold risk (relative risk [RR] 2.50, 95% CI 1.30–4.90) of any fractures among the general older population (Xing et al. 2014). Zolpidem use was associated with a 70% increase (aOR 1.72, 95% CI 1.37–2.16) (Kang et al. 2012).

Risk of hip fracture associated with benzodiazepine and related drug use

There are no studies investigating the risk of hip fracture associated with incident use of any BZDRs (Tables 6–7). Incident use of short-acting benzodiazepines has been associated with a 30% risk increase, while the risk increase associated with incident benzodiazepine-related drug use was 20% (Bakken et al. 2014). Among incident users of benzodiazepines, the associated risk was at its highest, i.e. doubled, during the first two weeks of use, and the risk still remained elevated after four weeks of use (Wagner et al. 2004). Further, incident zolpidem use was associated with a 2–3-fold increased risk of hip fracture (Finkle et al. 2011, Lin et al. 2014) and the incident use of alprazolam, lorazepam, or diazepam with a 46–105% risk increase (Finkle et al. 2011). The association between incident alprazolam use and hip fracture risk was suggestive of an increased risk (rate ratio 1.45, 95% CI 0.91–2.35). All these studies were register-based cohort studies (Table 6). The study populations ranged between 7,579 and 906,422 persons and the follow-up times from three months up to nine years (Table 6).

Prevalent BZDR use was associated with a 16–20% increase in the risk of hip fracture (Tables 6–7) in a cohort study (Bakken et al. 2014) and in a case-control study (Zint et al. 2010), while another case-control study (Pierfitte et al. 2001) could detect no such association. The study population included 906,422 persons in the cohort study (Bakken et al. 2014) and 1,062–103,188 persons in the case-control studies (Pierfitte et al. 2001, Zint et al. 2010). Drug exposure data was based on health care register information (Zint et al. 2010, Bakken et al. 2014) or interviews or medical records, including verification of the use of the drug from plasma samples (Pierfitte et al. 2001).

When investigated separately, the prevalent use of benzodiazepines or benzodiazepine-related drugs has been associated with a similar (20–24%) risk increase in two cohort studies (Wagner et al. 2004, Bakken et al. 2014), while one cohort study found no association (adjusted hazard ratio [aHR] 1.20, 95% CI 0.72–2.00) between prevalent benzodiazepine use and the risk of hip fracture (Ensrud et al. 2003). Additionally, two case-control studies observed a 46–70% risk increase associated with prevalent benzodiazepine use (Wang et al. 2001, Chang et al. 2008). With regard to the elimination half-lives of benzodiazepines (Ensrud et al. 2003, Wagner et al. 2004, Chang et al. 2008, Bakken et al. 2014), the use of short- to intermediate-acting drugs was associated with a higher risk increase (27–80%) than long-acting drugs (20%). Only one study found a risk increase (standardized incidence ratio 1.2, 95% CI 1.2–1.3) associated with the use of long-acting benzodiazepines (Bakken et al. 2014), while several other studies observed no association (Pierfitte et al. 2001, Ensrud et al. 2003, Wagner et al. 2004, Chang et al. 2008, Zint et al. 2010).

A dose-response-relationship was observed in two case-control studies (Chang et al. 2008, Zint et al. 2010). Additionally, one study (Pierfitte et al. 2001) found an increased risk (OR 2.10, 95% CI 1.14–3.87) associated with the use of several BZDRs concomitantly, in comparison to the use of 0–1 drugs. The other study investigating concomitant use (Wagner et al. 2004) did not find an association with the use of several benzodiazepines in comparison to non-use, although the result was suggestive of an increased risk (adjusted incidence rate ratio [IRR] 1.53, 95% CI 0.92–2.53).

The statistical power has not been sufficient for analyses in most of the studies investigating specific BZDRs (Pierfitte et al. 2001, Zint et al. 2010, Tang et al. 2015, Tom et al. 2016). However, prevalent zolpidem use has been widely studied and it did seem to be associated with a 26–95% risk increase in three studies (Wang et al. 2001, Zint et al. 2010,

Tom et al. 2016), although two other studies could not detect any association (Pierfitte et al. 2001, Tang et al. 2015).

Methodological considerations

The new user design (Ray 2003) was applied in the register-based cohort studies (Wagner et al. 2004, Finkle et al. 2011, Bakken et al. 2014, Lin et al. 2014). The rationale for performing new user analyses is to minimize survival bias by excluding prevalent users from the analyses (Ray 2003). The risk of acute adverse outcomes, such as falls, is expected to be highest at the beginning of drug use and therefore, prevalent users are those who are more likely to be able to tolerate drug use. However, one study (Bakken et al. 2014) did not observe any difference in the risk associated with incident and prevalent use of short-acting benzodiazepines or benzodiazepine-related drugs.

In the cohort studies, the exposure was defined either in a baseline measurement (Ensrud et al. 2003, Finkle et al. 2011) or in a time-dependent manner from register-based data (Wagner et al. 2004, Bakken et al. 2014, Lin et al. 2014). The assumption that baseline exposure (use/non-use) remains the same during the follow-up, i.e., the intention to treat (ITT) approach, is susceptible to an exposure misclassification bias as baseline drug users may have discontinued drug use and, on the other hand, baseline non-users may have initiated use during the follow-up (Ray et al. 2002, Stricker and Stijnen 2010). Therefore, the studies applying time-dependent exposure data can be considered less biased.

The risk associated with drug use was compared with non-use in all cohort studies (Table 6). However, non-use was defined in different ways. In two studies, the non-users may have been in a better state of health: zolpidem users were compared with those who had never used zolpidem (Lin et al. 2014) and benzodiazepine users were compared with those who had no benzodiazepine, antidepressant, antiepileptic, nor opioid use at baseline (Ensrud et al. 2003). This potentially led to an overestimation of the hip fracture risk associated with drug use. Periods of drug use and non-use during the follow-up were compared in two studies (Wagner et al. 2004, Bakken et al. 2014) and, therefore, there was less selection related to non-use. However, as the applied register in the study of Bakken et al. (2014) did not contain drug purchase information during institutional care although persons in institutional care were included in the study, non-use may have been misclassified. This misclassification may have also contributed to the non-differential results between incident and prevalent drug use. Finally, rates of hip fractures before and after initiation of drug use were compared in one study (Finkle et al. 2011). The rate during non-use may have been underestimated as the investigators did not have complete data for all persons from the period before drug use initiation.

In the case-control studies, drug use and non-use were measured at the date of hip fracture (Pierfitte et al. 2001, Wang et al. 2001, Chang et al. 2008) or during the two preceding weeks (Zint et al. 2010). Several register-based studies (Wang et al. 2001, Chang et al. 2008, Zint et al. 2010) utilized information on drug purchases and dispensed amounts, and an association was detected between BZDR use and the risk of hip fracture. However, the risk estimates may have been overestimated in the study indicating the highest relative risk increase (Chang et al. 2008), as controls were selected from a sample that was not allowed to have any hip fractures during the study period. No association was presented in the study utilizing information from interviews and plasma samples (Pierfitte et al. 2001).

In the case-crossover studies investigating the hip fracture risk (Table 7), persons with hip fracture acted as their own controls. This study design is suitable when the exposure is transient and the outcome is acute (Delaney and Suissa 2009) and therefore it was applicable to this research question. The risk of hip fracture was investigated by comparing exposure status immediately before the outcome with prior time windows. The length of the time windows was either one day (Tang et al., 2015) or 30 days (Tom et al., 2016). The drug use data was obtained from register-based information on dispensed amounts of drugs and therefore the 30-day periods accounted better for the uncertainty related to

actual drug use. The main advantage of this study design is the possibility to account for unmeasured confounders which would be expected to remain stable over time (Delaney and Suissa 2009).

The information on hip fractures was based on claims data or discharge diagnoses in the register-based studies (Tables 6–7). In addition, clinical data was utilized to define hip fractures from medical records in the other studies (Pierfitte et al. 2001, Ensrud et al. 2003). These definitions of hip fractures are considered to be accurate as practically all hip fractures require hospitalization and surgical treatment. In addition, most studies investigated the risk of first hip fracture, whereas hip fracture rates before and after drug initiation were compared in one study (Finkle et al. 2011). Focusing on the first hip fracture provided less biased estimates, as an individual who has experienced a previous fracture has an increased risk of suffering fractures in the future (Friedman and Mendelson 2014).

To conclude, the association between an increased risk of hip fracture and BZDR use in older persons is now well established, although there has been considerable variation in the applied methodology. No study has investigated this association in persons with cognitive disorders living in the community.

Post-hip fracture outcomes

A hip fracture is a serious event, for example, persons with hip fracture are at increased risk of experiencing a decline in functioning and mobility, future fractures, and mortality (Haentjens et al. 2010, Friedman and Mendelson 2014, Dyer et al. 2016). Thus, one-third of patients will not regain their pre-fracture functioning, and 10–20% are institutionalized within six months after the hip fracture (Dyer et al. 2016). Among Finnish persons who lived at home independently and who had a hip fracture, more than one third needed more support in living at one year after hip fracture (Pajulammi et al. 2015). In addition, a hip fracture increases the need for health care services and persons with a hip fracture have more in-patient hospital days for at least two years, compared with those without a hip fracture (Lönnroos et al. 2009). Mortality remains elevated for years after the hip fracture, compared with persons without a hip fracture (Haentjens et al. 2010, Finnish Medical Society Duodecim 2017a).

Post-hip fracture outcomes, including the need for hospital care, institutionalization, and mortality, are even worse among persons with cognitive disorders (Seitz et al. 2014). Community-dwelling persons with cognitive disorders were initially hospitalized for seven days longer after a hip fracture in comparison to persons without cognitive disorders. Further, the risk of institutionalization was 2.5-fold higher and the risk of death was nearly 50% higher among persons with cognitive disorders during a three-year follow-up after a hip fracture.

A Swedish study evaluating 2,043 older persons found that the association between benzodiazepine use and one-year mortality after hip fracture was suggestive of an increased (OR 1.27, 95% CI 0.99–1.64) risk (Ekstam and Elmståhl 2016). However, benzodiazepine use may have been measured inadequately in this study as exposure was defined as having one or more benzodiazepine purchases during the six months before the hip fracture.

More studies investigating the association between BZDR use and post-hip fracture outcomes are needed. For example, the potential effects of BZDR use on post-fracture functioning remains unknown, although BZDR use might impair functioning due to the sedative effects of the drugs (Buffett-Jerrott and Stewart 2002).

Table 6. Cohort studies investigating the risk of hip fracture associated with benzodiazepine and related drug use, in comparison to non-use (unless otherwise stated), among older persons.

Study, country	Data source, years	Setting	Study population (follow-up)	n (% exposed)	Mean age, % women	Included drugs	Risk of hip fracture (95% CI)
Bakken et al. (2014), Norway	R, 2004–2010	MX	Nationwide cohort of persons aged ≥70 years (6 years)	906,422 (23.0)	73 years 56%	BZD, BRD	**Prevalent use:** BZDR: SIR 1.2 (1.2–1.2) SA BZD: SIR 1.5 (1.4–1.6) LA BZD: SIR 1.2 (1.2–1.3) BRD: SIR 1.2 (1.1–1.2) **Incident use:** SA BZD: SIR 1.3 (1.0–1.7) BRD: SIR 1.2 (1.0–1.5)
Lin et al. (2014), Taiwan	R, 1997–2008	MX	Random sample, ≥65 years (9 years)	7,579 (20.2)	nr	BRD	**Incident use:** Zolpidem: aIRR 2.08 (1.39–3.11)
Finkle et al. (2011), United States	R, 1999–2009	CO	Population-based, ≥65 years (90 days)	89,738 (100.0)	nr	BZD, BRD	**Incident use:** Zolpidem: rate ratio 3.11 (1.96–4.91) Alprazolam: rate ratio 1.46 (0.91–2.35) Lorazepam: rate ratio 2.05 (1.58–2.66) Diazepam: rate ratio 2.03 (1.03–4.00)
Wagner et al. (2004), United States	R, 1987–1990	MX	Population-based, ≥65 years, 32% in institutional care, 11% with CD (3.5 years)	125,203 (24.5)	75%	BZD	**Prevalent use:** BZD: aIRR 1.24 (1.06–1.44) SA BZD: aIRR 1.27 (1.01–1.59) LA BZD: aIRR 1.13 (0.82–1.55) >1 BZD type: aIRR 1.53 (0.92–2.53) **Incident use:** 1–2 weeks: aIRR 2.05 (1.28–3.28) 3–4 weeks: aIRR 1.88 (1.15–3.07) >4 weeks: aIRR 1.18 (1.03–1.35)
Ensrud et al. (2003), United States	I, 1994–1999	CO	Random sample, women, ≥65 years (6.7 years)	8,127 (7.7)	77 years	BZD	**Prevalent use*:** BZD: aHR 1.20 (0.72–2.00) SA BZD: aHR 1.17 (0.61–2.26) LA BZD: aHR 1.12 (0.49–2.56)

* In comparison to persons with no benzodiazepine, antidepressant, antiepileptic, or narcotic use; a=adjusted; BRD=benzodiazepine-related drugs; BZD=benzodiazepines; BZDR=benzodiazepines and related drugs; CI=confidence interval; CO=community; HR=hazard ratio; I=interview; IRR=incidence rate ratio; LA=long-acting; MX=community and institutional; nr=not reported; R=register-based data; SA=short-acting; SIR=standardized incidence ratio.

Table 7. Case-control and case-crossover studies investigating the risk of hip fracture associated with benzodiazepine and related drug use, in comparison to non-use, among older persons.

Study, country	Data source, years	Setting	Study population	n (% exposed)	Mean age, % women	Included drugs	Risk of hip fracture (95% CI)
Case-control studies							
Zint et al. (2010), United States	R, 1994–2005	CO	Population-based, ≥65 years	cases n=17,198 (16.5); controls n=85,990 (13.3)	cases: 84 years, 89% controls: 80 years, 82%	BZD, BRD	**Prevalent use:** Any use: aRR 1.16 (1.10–1.22) LA: aRR 1.05 (0.94–1.16) SA: aRR 1.19 (1.13–1.26) 1–14d: aRR 2.05 (1.52–2.77) 15–30d: aRR 1.42 (1.03–1.96) 31–60d: aRR 1.34 (1.02–1.77) 61–90d: aRR 1.05 (0.86–1.28) 91–180d: aRR 1.21 (0.99–1.48) 181–270d: aRR 1.53 (1.31–1.78) 271–360d: aRR 1.10 (1.04–1.17) <0.5DDD/d: aRR 1.09 (1.02–1.17) 0.5–1DDD/d: aRR 1.21 (1.11–1.31) >1 DDD/d: aRR 1.32 (1.17–1.48)
Chang et al. (2008), Taiwan	R, 2001–2004	MX	Random sample of persons aged ≥65 years, 4–8% with CD	cases: n=217 (26.3); controls: n=1,214 (15.2)	cases: 78 years, 68% controls: 78 years, 68%	BZD	**Prevalent use:** Any use: aOR 1.7 (1.2–2.5) SA: aOR 1.8 (1.3–2.7) LA: aOR 1.0 (0.4–2.5) 0.1–3mg/d: aOR 1.1 (0.4–3.0) 3,1–6mg/d: aOR 1.8 (1.1–3.1) >6 mg/d: aOR 1.8 (1.1–2.9) 1–30d: aOR 5.6 (2.7–11.8) 31–90d: aOR 1.4 (0.7–2.8) >90d: aOR 1.3 (0.8–2.1)

a=adjusted; BRD=benzodiazepine-related drugs; BZD=benzodiazepines; CD=cognitive disorders; CI=confidence interval; d=day; CO=community; DDD=defined daily dose; LA=long-acting; mg=milligrams; MX=community and institutional; OR=odds ratio; R=register-based data; RR=relative risk; SA=short-acting.

(Continued)

Table 7.(Continued)

Study, country	Data source, years	Setting	Study population	n (% exposed)	Mean age, % women	Included drugs	Risk of hip fracture (95% CI)
Case-control studies							
Pierfitte et al. (2001), France	Q and M, 1996–1997	MX	PB, ≥65 years, patients admitted to emergency departments	cases n=245 (33–36); controls n=817 (29–36)	nr	BZD, BRD	**Prevalent use:** Q: OR 1.00 (0.92–1.09) M: OR 1.19 (0.88–1.63) Plasma sample: OR 1.06 (0.78–1.43) SA BZDR: OR 1.06 (0.77–1.46) LA BZDR: OR 1.17 (0.70–1.96) ≥2 BZDRs vs. 0–1 BZDRs: OR 2.10 (1.14–3.87)
Wang et al. (2001), United States	R, 1993–1995	MX	PB, ≥65 years, 20–32% in institutional care	cases n=1,222 (BZD 16.2, zolpidem 1.6); controls n=4,888 (BZD 10.7, zolpidem 0.7)	cases: 82 years, 84%; controls: 82 years, 84%	BZD, BRD	**Prevalent use:** BZD: aOR 1.46 (1.21–1.76) Zolpidem: aOR 1.95 (1.09–3.51)
Case-crossover studies							
Tom et al. (2016), United States	R, 2007–2009	MX	Random sample, ≥65 years, 37% with CD	37,833 (3.2 at hazard period)	83 years, 78%	BRD	**Prevalent use:** Zolpidem: OR 1.59 (1.41–1.79) Eszopiclone: OR 1.12 (0.83–1.50) Zaleplon: OR 0.92 (0.40–2.13)
Tang et al. (2015), Taiwan	R, 2002–2010	MX	PB, persons with sleep disturbances, ≥65 years, 5% with CD	6,010 (nr)	68%	BZD, BRD	**Prevalent use:** BZD: aOR 0.99 (0.75–1.30) Zolpidem: aOR 1.25 (0.83–1.87)

a=adjusted; BRD=benzodiazepine-related drugs; BZD=benzodiazepines; BZDR=benzodiazepines and related drugs; CD=cognitive disorders; CI=confidence interval; LA=long-acting; M=medical records; MX=community and institutional; nr=not reported; OR=odds ratio; PB=population-based; Q=questionnaire; R=register-based data; SA=short-acting.

2.3.2 Mortality

Mortality associated with BZDR use has been evaluated in only a few studies among community-dwelling older persons or among those with cognitive disorders. The study populations, designs, and methodologies have varied, resulting in contradictory findings (Table 8).

Community-dwelling older persons

Mortality associated with BZDR use among community-dwelling older persons has been investigated in four cohort studies (Table 8). Two studies found no association between BZDR use and mortality, with the point estimates ranging from 1.01 to 1.21 (Gisev et al. 2011, Wauters et al. 2016). In one study (Jaussent et al. 2013), the association between benzodiazepine use and mortality (aHR 1.11, 95% CI 0.94–1.30) was suggestive of an increased risk, while no association was observed with benzodiazepine-related drug use (aHR 0.92, 95% CI 0.71–1.20). The fourth study reported lower mortality (hazard ratio [HR] 0.89, 95% CI 0.85–0.94) associated with benzodiazepine use (Patorno et al. 2017). The ITT approach was utilized in all studies. There was extensive variation in the follow-up times (from six months to 12 years) and in the sizes of study populations (from 503 to 184,546 persons). Health care register data was utilized in two studies (Gisev et al. 2011, Patorno et al. 2017), and the other two studies utilized data from interviews, questionnaires, or medical records (Jaussent et al. 2013, Wauters et al. 2016). Death dates had been obtained from registers in most studies (Gisev et al. 2011, Jaussent et al. 2013, Patorno et al. 2017), while Wauters et al. (2016) collected dates of death from questionnaires sent to general practitioners.

The new-user design (Ray 2003), with a six-month washout period, was utilized in the study demonstrating a decreased risk (HR 0.89, 95% CI 0.85–0.94) associated with benzodiazepine use (Patorno et al. 2017). Although the follow-up was restricted to six months, this study was susceptible to an exposure misclassification bias (Ray et al. 2002, Stricker and Stijnen 2010) because the exposure was defined only at baseline. The observed decrease in the risk of death may result from selected study population. Only persons with private health insurance policy were included, resulting in exclusion of the unemployed and the most vulnerable persons.

Drug use was defined at baseline, and both prevalent and incident users were included in the other three studies (Gisev et al. 2011, Jaussent et al. 2013, Wauters et al. 2016). Drug use was measured during the month (Jaussent et al. 2013) or the year (Gisev et al. 2011) preceding the study follow-up. The third study did not report the time window for defining drug exposure (Wauters et al. 2016). The follow-up times ranged from 18 months to 12 years in these studies (Table 8) and consequently they were subject to an exposure misclassification bias (Ray et al. 2002, Stricker and Stijnen 2010).

Persons with cognitive disorders in different settings

The risk of death associated with BZDR use among persons with cognitive disorders has been investigated in three cohort studies (Table 8). One study reported a risk increase associated with both benzodiazepine use (13% increase) and benzodiazepine-related drug use (11% increase), in comparison to non-use, in a population including persons living in the community or in institutions (Jennum et al. 2015). Another study found no association (IRR 1.21, 95% CI 0.87–1.68), when compared with atypical antipsychotic use, among persons admitted to institutional care (Huybrechts et al. 2011). The third study compared BZDR use with non-use; no association (aHR 1.13, 95% CI 0.86–1.47) during the first follow-up year was found, while a 28% risk decrease was observed during the second follow-up year among persons living in the community or in institutions (Brännström et al. 2017). The sizes of study populations ranged between 1,037 up to 26,821 persons, and the follow-up times were also highly variable, i.e. between 180 days and 12 years. Health care register

data was utilized in two studies (Huybrechts et al. 2011, Jennum et al. 2015), whereas the third study utilized data from interviews and medical records (Brännström et al. 2017). Death dates were obtained from registers.

There is only one study that applied the new-user design and a time-dependent drug exposure, and this study was performed among persons with cognitive disorders recently admitted to institutional care (Huybrechts et al. 2011). No association between BZDR use and mortality was found, but in the whole study population including older persons with and without cognitive disorders (n=4,887), BZDR use was associated with an increased risk of death (IRR 1.28, 95% CI 1.04–1.58). Therefore, the statistical power may not have been sufficient to detect a potential association in the subgroup of 1,354 BZDR users with cognitive disorders. The washout period was six months before the study and BZDR exposure during the six-month follow-up was modelled from the available information on drug dispensings, including the dispensed duration. Exposure misclassification bias was further reduced by censoring the follow-up at discontinuation of BZDR use. In the sub-analyses with the ITT approach, the risk estimate among persons with cognitive disorders was attenuated (IRR 0.98, 95% CI 0.77–1.25). Time-dependent BZDR use was compared with time-dependent atypical antipsychotic use, which might also explain why this study found no association between BZDR use and mortality among persons with cognitive disorders. A meta-analysis of randomized controlled trials found that atypical antipsychotic use is associated with an increased risk (OR 1.52, 95% CI 1.06–2.18) of death among persons with cognitive disorders (Ma et al. 2014) and BZDR use may not further elevate the risk of death in this population.

BZDR use and non-use were defined at baseline in the other studies (Jennum et al. 2015, Brännström et al. 2017). These studies included both incident and prevalent users of BZDRs. The decreased risk of death observed during the second year of one of the studies (Brännström et al. 2017) may have resulted from an exposure misclassification bias (Ray et al. 2002, Stricker and Stijnen 2010), as the exposure was not measured separately at the beginning of that year. In the other study (Jennum et al. 2015), drug use was defined from the year before the follow-up, whereas non-use was defined as non-use of any psychotropic drug during a two-year period. This selection of the comparison group may have resulted in a comparison of BZDR users with non-users who were in a better state of health. As a consequence, the risk associated with BZDR use may have been overestimated.

To conclude, the observations in the previous studies raise the question of whether BZDR use, depending on duration of use, would be associated with an increased risk of death, if compared with non-use. In addition, more studies will be needed to confirm the risk associated with the separate use of benzodiazepines and benzodiazepine-related drugs, as the previous studies have reported conflicting results. The risk of death associated with different durations of BZDR use has not been studied in older persons with or without cognitive disorders. Additionally, no study has investigated if there is a dose-response relationship or whether the risk varies according to elimination half-lives of the drugs. Finally, it is not known whether the risk of death associated with BZDR use is specifically present in community-dwelling persons with cognitive disorders.

Table 8. Cohort studies investigating mortality associated with benzodiazepine and related drug use, in comparison to non-use (unless otherwise stated), among the general older population and persons with cognitive disorders.

Study, country	Data source, years	Study population (follow-up)	n (% exposed)	Mean age, % women	Included drugs	Risk of death (95% CI)
Studies among community-dwelling older persons						
Patorno et al. (2017), United States	R, 2004–2013	PB, ≥65 years (180 days)	184,546 (50.0)	nr	BZD	**Incident use:** BZD: HR 0.89 (0.85–0.94) *
Wauters et al. (2016), Belgium	Q and M, 2008–2009	PB, persons with no CD, ≥80 years (18 months)	503 (35.4)	84 years, 61%	BZD, BRD	**Prevalent use:** BZDR: HR 1.21 (0.66–2.19)
Jaussent et al. (2013), France	I and M, 1999–2012	Random sample of persons without CD at baseline, ≥65 years (12 years)	6,696 (20.8)	median age 73 years, 59%	BZD, BRD	**Prevalent use:** BZD: aHR 1.11 (0.94–1.30) BRD: aHR 0.92 (0.71–1.20)
Gisev et al. (2011), Finland	R, 2000–2008	PB, all persons living in one community, 3% with AD, ≥65 years (9 years)	2,224 (14.6)	Users: 76 years, 67%; Non-users: 74 years, 57%	BZD, BRD	**Prevalent use:** BZDR: aHR 1.01 (0.84–1.21)
Studies among persons with cognitive disorders in community and institutional settings						
Brännström et al. (2017), Sweden/Finland	I and M, 2000–2012	Random sample, persons in community and institutional care, 52% with AD, ≥65 years (2 years)	1,037 (39.0)	89 years, 74%	BZD, BRD	**Prevalent use:** 1st year mortality BZDR: aHR 1.13 (0.86–1.47); 2nd year mortality BZDR: aHR 0.72 (0.54–0.96)
Jennum et al. (2015), Denmark	R, 1997–2009	Nationwide population of persons diagnosed with CD (12 years)	26,821 (BZD 11.1, BRD 16.4)	79 years, 60%	BZD, BRD	**Prevalent use:** BZD: aHR 1.13, SD 0.039 BRD: aHR 1.11, SD 0.031
Huybrechts et al. (2011), Canada	R, 1995–2006	PB, recently institutionalized, ≥65 years (180 days)	2,446 (55.4)	84 years	BZD, BRD	**Incident use:** BZDR: IRR 1.21 (0.87–1.68) †

* Propensity score-matched; † In comparison to atypical antipsychotic use

a=adjusted; AD=Alzheimer's disease; BRD=benzodiazepine-related drugs; BZD=benzodiazepines; BZDR=benzodiazepines and related drugs; CD=cognitive disorder; CI=confidence interval; HR=hazard ratio; I=interview; IRR=incidence rate ratio; M=medical records; nr=not reported; PB=population-based; Q=questionnaire; R=register-based; SD=standard deviation

2.3.3 Other associated adverse outcomes

Since BZDR use exerts effects on cognition, benzodiazepine use has been associated with a 40% increase (aOR 1.43, 95% CI 1.28–1.60) in the risk of developing AD among the general older population (de Gage et al. 2014). A considerably smaller relative risk increase (aOR 1.06, 95% CI 1.04–1.06) associated with BZDR use was reported in a recent nationwide study performed in Finland (Tapiainen et al. 2018). In both studies, a lag time of five years was utilized in the definition of BZDR exposure. In the study of de Gage et al. (2014), the period for exposure measurement was up to six years whereas in the study of Tapiainen et al. (2018), the period was 5–11 years. Use of long-acting and short- to intermediate-acting drugs was associated with a risk increase in both studies. De Gage et al. (2014) found that the associated risk was elevated during long-term BZDR use (>180 days), whereas Tapiainen et al. (2018) found that the associated risk was elevated throughout the use.

Among persons with AD, BZDR use has been associated with a worsening clinical condition (aOR 2.62, 95% CI 1.04–6.60), defined via cognition, functioning and behavior, during a one-year period (Ellul et al. 2007). In another study, benzodiazepine use was associated with declining cognition (B -2.67, 95% CI -4.10 to -1.23) and increasing disease severity (B 1.89, 95% CI 0.74–3.05), but not with a change on BPSDs (B 1,53, 95% CI -1.13 to 4.19) during a follow-up of several years (mean 3.7 years) (Rosenberg et al. 2012). Further, BZDR use was associated with a slight decline in functioning (aOR 1.02, 95% CI 1.01–1.03) and a slight increase in symptoms of depression (aOR 1.03, 95% CI 1.01–1.03) in a study with a three-year follow-up (Törmälehto et al. 2017).

The association between BZDR use and hospitalization and institutionalization was investigated in one study conducted in a community-dwelling general older population (Wauters et al. 2016). BZDR use was associated with an increase (aHR 1.62, 95% CI 1.01–2.60) in the risk of institutionalization. This association might reflect confounding by indication related to prescribing of BZDRs for persons with an increased risk of institutionalization, or the association might result from the effects of BZDRs on cognition and functioning (Buffett-Jerrott and Stewart 2002, Peron et al. 2011). No association was found between BZDR use and hospitalization (HR 1.11, 95% CI 0.81–1.54).

The effects of BZDR use on attention might impair performance in traffic. A meta-analysis published in 2011 was suggestive of an increased risk (OR 1.13, 95% CI 0.97–1.31) of motor vehicle crashes associated with benzodiazepine use among the general older population (Dassanayake et al. 2011). More recent studies have confirmed the association. Zolpidem use was associated with a doubled (adjusted rate ratio 2.35, 95% CI 1.20–4.61) risk (Booth et al. 2016), and benzodiazepine use with a five-fold risk (OR 5.3, 95% CI 3.6–7.8) of motor vehicle crashes (Meuleners et al. 2011). In contrast, another study found no association between benzodiazepine use (aOR 0.71, 95% CI 0.15–3.34) or zolpidem use (aOR 1.42, 95% CI 0.66–3.00) and the risk of motor vehicle crashes (Rudisill et al. 2016).

Other associated outcomes include adverse pulmonary outcomes and stroke, but it is not known whether these associations are biologically plausible or whether they represent confounding. Prevalent BZDR use was not associated (aOR 1.08, 95% CI 0.80–1.47) with a risk of pneumonia among community-dwelling older persons (Dublin et al. 2011). However, among community-dwelling older persons with COPD, incident benzodiazepine use was associated with an increased risk of COPD exacerbation (RR 1.45, 95% CI 1.36–1.54) and emergency room visits due to COPD or pneumonia (RR 1.92, 95% CI 1.69–2.18) (Vozoris et al. 2014). Further, among community-dwelling persons with AD, incident BZDR use has been associated with an increased risk (HR 1.22, 95% CI 1.05–1.42) of pneumonia (Taipale et al. 2017b). Benzodiazepine use was associated with an increased risk for the first 30 days of use, while no association was observed with benzodiazepine-related drug use. Incident BZDR use has also been associated with an increased risk (adjusted HR 1.21, 95% CI 1.04–1.40) of stroke among persons with AD (Taipale et al. 2017a). Benzodiazepine and benzodiazepine-related drug use were associated with similar risk increases.

3 Aims

The overall purpose of this thesis was to describe incident BZDR use and to investigate the associated major adverse outcomes in community-dwelling persons with AD in Finland. The specific aims of this thesis were to investigate:

1) The incidence of BZDR use from two years before to three years after the diagnosis of AD and to compare it with the corresponding incidence among persons without AD (Study I),

2) The association between incident BZDR use and the risk of hip fracture among persons with AD and persons without AD (Study II).
    - The association between BZDR use and one-year post-hip fracture mortality and long-term hospital stay after hip fracture in secondary analyses,

3) The association between incident BZDR use and the risk of all-cause mortality in persons with AD (Study III).

4 Materials and methods

4.1 STUDY COHORT

All studies in this thesis were based on the nationwide Medication Use and Alzheimer's Disease (MEDALZ) cohort which is based on Finnish health care registers (Tolppanen et al. 2016). Persons with AD were identified from the Special Reimbursement Register, and the cohort includes all community-dwelling persons who received entitlement to special reimbursement for antidementia drugs during 2005–2011 (n=70,719). One person died before the entitlement was recorded in the register and therefore, 70,718 newly-diagnosed persons were included in this study. The date of entitlement to the special reimbursement for antidementia drugs was considered as the date of clinically verified diagnosis of AD, and later in this thesis, it will be referred to as the date of AD diagnosis.

In Finland, the treatment guideline of cognitive disorders states that all persons with AD should be treated with antidementia drugs unless there are any contraindications (Finnish Medical Society Duodecim 2017c). To fulfill the criteria for the special reimbursement of antidementia drugs set by the Social Insurance Institution (SII), AD had to be in either a mild or moderate stage. However, the reimbursement is not withdrawn when the disease progresses. All diagnoses had to be confirmed by a neurologist or a geriatrician (Tolppanen et al. 2016). The diagnostic process of AD included obtaining information from the patient and family members or caregivers. Further, a clinical examination and assessment of symptoms, cognition, and ADL was included. Laboratory tests and computer tomography or magnetic resonance imaging scans were performed to identify AD-related changes and to exclude alternative diagnoses. The diagnosis statement was sent to the SII which granted the entitlement for the special reimbursement if the criteria were fulfilled. The diagnosed persons could also have mixed pathology, as long as AD pathology was the main contributor to the clinical findings. The positive predictive value of the AD diagnoses in the Special Reimbursement Register is 97.1 (95% CI 84.7–99.9) (Solomon et al. 2014). AD diagnoses were made according to the 'National Institute of Neurologic and Communicative Disorders and Stroke and the Alzheimer's disease and Related Disorders Association' (NINCDS-ADRDA) and the 'Diagnostic and Statistical Manual, Fourth Edition' (DSM-IV) criteria (McKhann et al. 1984, American Psychiatric Association 1994).

In addition to persons with AD, the cohort also includes persons without any previous AD diagnosis recorded in the Special Reimbursement Register, or antidementia drug purchases recorded in the Prescription Register. These persons without AD were identified from a register including all residents in Finland, maintained by the SII. Persons without AD have been matched with persons with AD for age, gender, and region of residence at the date of AD diagnosis (Taipale et al. 2014a). Further, these persons were not allowed to receive the entitlement to special reimbursement for antidementia drugs or to have an antidementia drug purchases on the matching date or during the following year. Additionally, the persons had to be alive and not in institutional care during the month of the corresponding AD patient's diagnosis date.

The matching was conducted with incidence density sampling (Matthews and Brill 2005) without replacement. This means that each person without AD could be selected multiple times to ensure a sufficient number of matched persons for the smallest age groups. Up to four persons without AD were matched for each person with AD. If these persons received an entitlement to special reimbursement for antidementia drugs later, their status was updated as an AD case and up to four persons without AD were matched as previously described. Once the matched person was diagnosed with AD, their follow-up as a person without AD was censored.

4.2 DATA SOURCES

The register data obtained for the MEDALZ cohort is summarized in Table 9. Persons could be identified from all registers with personal identification numbers (PIN). The PINs were replaced with research IDs by the register maintainers before submission to the research group. Thus, only pseudonymized data was utilized in these studies.

The Special Reimbursement Register includes the person's entitlement to special reimbursement of drugs due to chronic diseases, and data since 1972 is available (Table 9, Tolppanen et al. 2016). All diagnoses in the register are clinically verified and they are based on the prespecified criteria of the disease which are managed by the SII.

The Prescription Register includes information on reimbursed drug purchases for all community-dwelling persons in Finland since 1995 (Table 9, Furu et al. 2010). The register data does not include drugs used during stays at hospitals or public nursing homes because these drugs are provided by the facility during the stay. The Prescription Register data included purchase dates, the Anatomical Therapeutic Chemical (ATC) classification code of the drug, package size, strength, dosage form, purchased amount of drug in defined daily doses (DDD), and the Nordic article number (Vnr number) which identifies each package (Furu et al. 2010).

The Hospital Discharge Register includes information on inpatient hospital stays since 1972 (Table 9). The obtained data included admission and discharge dates, related discharge diagnoses (according to ICD-8, ICD-9, and ICD-10 classifications), and procedures (according to the Finnish version of the Nordic Medico-Statistical Committee Classification [NOMESCO] for Surgical Procedures). The Hospital Discharge Register also includes a variable related to the reason for admission. This variable was utilized to identify persons with substance abuse.

Data on decisions on long-term institutional care were received from the SII and they were utilized in defining periods of long-term institutional care. Additionally, data on the highest middle age occupational socioeconomic position and information on the date of death were obtained from Statistics Finland (Table 9).

Table 9. The data sources utilized in the MEDALZ dataset relevant to this thesis.

Register, data maintainer	**Data collected (years)**	**Register validity**
Prescription Register, SII	All reimbursed drug purchases (1995–2012)	Good validity of BZDR purchase data found among older persons (Rikala et al. 2010)
Special Reimbursement Register, SII	Comorbidities (1972–2012)	All diagnoses entitled for special reimbursements verified by physician and managed by SII
Hospital Discharge Register, THL	Hospital stays, hip fractures, comorbidities (1972–2012)	High quality data especially on common diseases (Sund 2012), excellent validity of data about first hip fractures (Sund et al. 2007)
Death Register, Statistics Finland	Mortality (2005–2012)	Complete coverage (Statistics Finland 2018)
Statistics Finland	Occupational socioeconomic position	

AD=Alzheimer's disease; ATC=Anatomical Therapeutic Chemical classification; BZDR=benzodiazepine and related drug; SII=Social Insurance Institution; THL=National Institute for Health and Welfare

4.3 BENZODIAZEPINES AND RELATED DRUGS

BZDRs included benzodiazepines (ATC classes N05BA and N05CD) and benzodiazepine-related drugs (ATC class N05CF). Oxazepam, lorazepam, and temazepam were classified as intermediate-acting whereas diazepam, chlordiazepoxide, alprazolam, and nitrazepam were classified as long-acting benzodiazepines (Table 10). Short-acting benzodiazepines, i.e., midazolam (N05CD08) and triazolam (N05CD05), were not included in this thesis as they did not have reimbursement status during the study period and, thus, the purchases of these drugs were not available in the Prescription Register. Further, the focus of this thesis was on drugs used in BPSD treatment and, therefore, clobazam (N05BA09) was excluded because it is indicated only for epilepsy and seizures. Benzodiazepine-related drugs included zopiclone and zolpidem (Table 10). Zaleplon (N05CF03) was not included because it did not have the reimbursement status during the study period.

Table 10. Benzodiazepines, classified according to elimination half-life, and benzodiazepine-related drugs (with ATC codes) included in this thesis (Greenblatt et al. 1981, Gunja 2013).

Intermediate-acting benzodiazepines	**Long-acting benzodiazepines**	**Benzodiazepine-related drugs**
Oxazepam (N05BA04)	Diazepam (N05BA01)	Zopiclone (N05CF01)
Lorazepam (N05BA06)	Chlordiazepoxide (N05BA02)	Zolpidem (N05CF02)
Temazepam (N05CD07)	Alprazolam (N05BA12)	
	Nitrazepam (N05CD02)	

ATC=Anatomical Therapeutic Chemical classification

4.4 DRUG EXPOSURE

4.4.1 Overview

The purchase data in the Prescription Register was not readily applicable for the analyses as the purchase dates do not provide information on the duration of drug use. Continuous information on drug use was needed to decrease exposure misclassification (Ray et al. 2002, Stricker and Stijnen 2010). Therefore, the 'From prescription drug purchases to drug use periods' (PRE2DUP) modelling method was applied when transforming the drug purchase data into drug use data (Tanskanen et al. 2015). This method calculates drug use periods, i.e. when each drug use started and ended. The modeling is based on computing sliding averages of daily dose between purchases and where applicable, joining consecutive purchases. The method also accounts for individual purchasing patterns, hospital stays, and potential stockpiling of drugs. Drug use periods have been constructed for each person and for each drug. The overall functioning of the method is described in Figure 3.

4.4.2 Parameters for modeling

Global parameters, concerning all drug use periods, defined general limits for modelling (Tanskanen et al. 2015). A global parameter restricted the joining of two consecutive purchases if there was ≥300 days between them. Another global parameter restricted the maximum duration of use after a single purchase to 150 days. Further, if the last purchase of a drug use period was followed by a hospital stay of ≥30 days, the drug use period was ended at the beginning of that hospital stay.

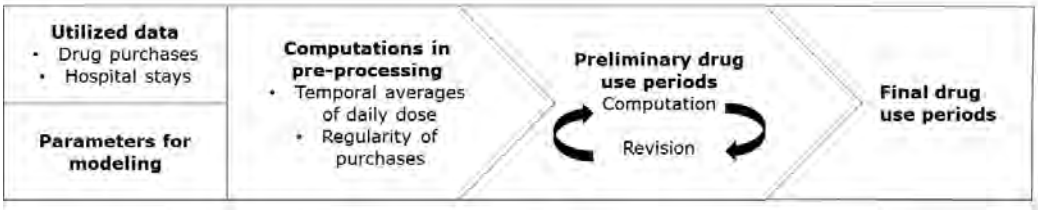

Figure 3. An overview of the drug use modeling procedure, modified from Tanskanen et al. (2015).

Specific parameters concerning the highest, lowest, and typical dosage options were defined for each drug, i.e. each separate ATC code (Tanskanen et al. 2015). However, BZDR use periods were modelled with parameters assigned to each separate package, identified with the Vnr numbers, instead of the less specific ATC level. These expert-defined parameters included maximum, minimum, and typical refill lengths, as well as the corresponding daily dosages as DDDs, calculated from the package information. Minimum daily dosage was defined for each package as the lowest possible dose in continuous use. The minimum daily dosage was based on the properties of the drug formulation and different use patterns, as the same drug may be used for various indications. Maximum daily dosage was defined to identify stockpiling. Additionally, the typical refill length was based on assumed patterns of drug use in older persons, by considering the amount of drug and dosage form.

4.4.3 Preprocessing the data

Based on each person's purchases of a drug, temporal averages of daily doses (Equation 1) were calculated from the purchase data (Tanskanen et al. 2015). The averages of daily doses ($DDDAVG_i$) were determined separately between each drug purchase (i), while considering the refill lengths (T) between them. However, if a person had less than three purchases of a drug, the average doses were not calculated. Hospital days were excluded from the dose computations. Additionally, a variable describing the variability of refill lengths and the purchased amounts was calculated for each person and each drug.

$$DDDAVG_i = \frac{DDD_{i-1} + 4DDD_i + DDD_{i+1}}{T_{i-1} + 4T_i + T_{i+1}}$$

Equation 1. Computation of temporal averages of daily drug dose between purchases (Tanskanen et al. 2015).

4.4.4 Drug use modeling

The first round of drug use period modeling applied the expert-defined parameters and the temporal averages of the daily dose (Tanskanen et al. 2015). The consequent modeling rounds included a revision of the drug use periods. The most common refill length was used in the revision, and it was calculated for each package of each drug included in the data, utilizing results from previous modeling rounds. The most common refill length was based on the distribution of refill lengths, which were computed from drug use periods involving at least six purchases. For each package with at least ten observations of refill lengths, the most common refill length was defined as the joined mode of these observations. Hospital days were included in computing the refill lengths.

Single purchases included cases in which a person had purchased the particular drug only once during the follow-up or in which the purchase was too far away from other purchases to be joined (Tanskanen et al. 2015). If the person had a drug use period of the

same drug, the duration of single purchase was calculated from the purchased amount with the dose that was used in the closest period. Otherwise, the most common refill length was assigned as the duration of the single purchase.

In case of several purchases, joining the consecutive purchases was considered, unless they were too far away from each other (see 4.4.2). An expected refill length was calculated to determine whether the current purchase reached the next one (Tanskanen et al. 2015). The expected refill length was based on the purchased amount of drug, calculated daily dose (Equation 1), and individual purchase pattern. However, if the calculated daily dose was below the daily minimum defined for that package, the minimum daily dose was used, instead of the calculated dose. Similarly, if the calculated dose exceeded the upper limit, the parameter for minimum refill length was assigned as the expected refill length. If the expected refill length reached the next purchase, these purchases were joined.

If the purchases could not be joined, the model performed a test for stockpiling (Tanskanen et al. 2015), which was based on a temporary drop in the pre-calculated dose. If stockpiling was observed, the purchased amounts in the current and the previous purchases were combined, and the expected refill length was calculated from the combined amount of drug.

The drug use period was ended if the expected refill length did not reach the next purchase, or if the purchase in question was the person's last purchase of the drug (Tanskanen et al. 2015). The expected refill length was used as a base for calculating the duration of last purchase, assuming the dosage remained constant after the previous purchase.

4.4.5 Constructing benzodiazepine and related drug use periods

As described, each separate drug (ATC) belonging to BZDRs was modelled separately. To retrieve continuous use time for any BZDR, the overlapping drug use periods of separate drugs were combined (Figure 4). The same was done when defining time for any benzodiazepine and benzodiazepine-related drug separately. Therefore, persons could switch drug during BZDR use, as long as the use was continuous. Similarly, during separate benzodiazepine use periods and benzodiazepine-related drug use periods, persons could switch to another drug as long as it was in the same group.

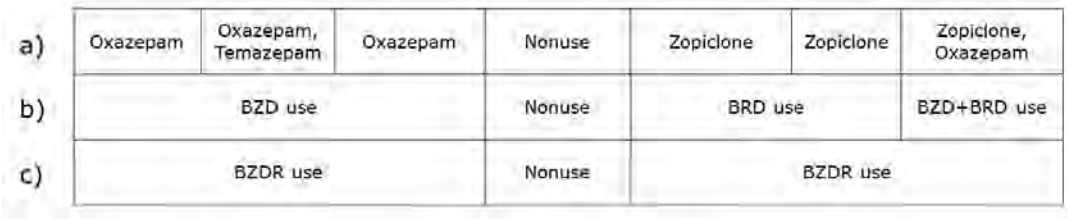

Figure 4. An example of joining separate benzodiazepine and related drug (BZDR) use periods (a) into combined periods (b) of benzodiazepines (BZD) and benzodiazepine-related drugs (BRD) and any use (c) of BZDRs (Tanskanen et al. 2015).

BZDR use periods modelled with the PRE2DUP method were utilized in all studies in this thesis. However, as the modeling method only reports the dose as an average over the entire drug use period, the actual dosages of drug use were not considered because doses may vary during the use. Where feasible, BZDR polypharmacy, i.e., concomitant use of ≥2 BZDRs, was taken into consideration.

The validity of the BZDR use periods modelled with the PRE2DUP method has been measured by investigating the agreement between drug use periods and interview data of 569 community-dwelling persons aged ≥75 years in Finland (Taipale et al. 2016b). The

study indicated that the agreement between BZDR use periods and interview data, utilizing a two-week time window, was good (Cohen's kappa value 0.70, 95% CI 0.64–0.77).

4.5 OUTCOMES

In Study II, the main outcome was the first hip fracture after the diagnosis of AD or the corresponding matching date in persons without AD. Incident hip fracture was defined according to the following ICD-10 codes: S72.0 (fracture of neck of femur), S72.1 (pertrochanteric fracture), and S72.2 (subtrochanteric fracture). When investigating incident hip fractures, all persons with a previous hip fracture were excluded. A previous hip fracture was defined as having a hip fracture after 1972 and before the AD diagnosis or the corresponding matching date. The corresponding ICD-9 (820) and ICD-8 (82000, 82010, 82090, 82001, 82011, and 82091) codes were utilized in defining previous hip fractures.

A secondary research outcome in Study II was the duration of uninterrupted post-fracture hospital stay, including acute care and in-patient rehabilitation. Longer than four-month hospital stay after a hip fracture was defined as long-term hospital care (Sund et al. 2011). Another secondary outcome in this Study was one-year post-fracture mortality.

In Study III, the outcome was 180-day all-cause mortality.

4.6 STUDY DESIGNS

4.6.1 New-user design

The new-user design (Ray 2003) was applied in all studies in this thesis. Incident BZDR use was defined as initiating drug use after a one-year washout period without any BZDR use. Prevalent users, i.e. those who used BZDRs during the washout period, were excluded. The new-user design was chosen because it minimizes the survival bias related to the inclusion of tolerant drug users. Further, all analyses were restricted to the first BZDR use period. The timing of the washout period was different in the studies because the study periods were different as well (Table 11).

Table 11. Timelines and included persons in each Study.

	Washout period	Study population	Start of follow-up	End of follow-up at latest
Study I	3 to 2 years before AD diagnosis or the corresponding matching date	Persons with AD, persons without AD	2 years before AD diagnosis or the corresponding matching date	3 years after AD diagnosis or the corresponding matching date
Study II	1 year before AD diagnosis or the corresponding matching date	Persons with AD, matched[a] persons without AD	AD diagnosis or the corresponding matching date	5 years after AD diagnosis or the corresponding matching date
Study III	1 year before AD diagnosis	Incident BZDR users with AD, matched[b] non-users with AD	The first BZDR purchase after AD diagnosis or, for non-users, the corresponding matching date	6 months after the first BZDR purchase or the corresponding matching date

AD=Alzheimer's disease; BZDR=benzodiazepines and related drugs
[a] Two persons without AD matched for each person with AD on the basis of age and gender;
[b] Two non-users matched for each incident user on the basis of time since AD diagnosis, age, and gender

In addition to excluding prevalent BZDR users, persons who were hospitalized/institutionalized for more than six months during the washout period were excluded. Further, those individuals who had an ongoing ≥90 days' hospital/institutional stay at the end of the washout period were also excluded. The exclusions based on long hospital/institutional stays decreased the potential for an immeasurable time bias related to the unknown exposure status during the stays (Palmaro et al. 2017).

4.6.2 Reasons for ending the follow-up

Reasons for ending the follow-up in all studies included death, beginning of ≥90 days' hospitalization/institutionalization, or the end of the study follow-up (31 December 2012). Additional reasons for ending the follow-up (Table 12) were utilized in the studies due to different study questions and designs. The maximum duration of follow-up was five years in Studies I and II and 6 months in Study III. In all studies, the follow-up ended at the first occurrence of any of the pre-defined reasons for ending the follow-up.

Table 12. Reasons for ending the follow-up included in the Studies.

	Application		
Reason	**Study I**	**Study II**	**Study III**
Reasons utilized in all Studies			
Death	x	x	x
End of study follow-up (31 December 2012)	x	x	x
Initiation of the first BZDR use period[a]	x	x	x
Start of long-term (≥90 days) hospital and/or institutional stay	x	x	x
Study-specific reasons			
Two years before AD diagnosis[b]	x		
First hip fracture		x	
AD diagnosis[b]		x	
End of the first BZDR use period[c]		x	x
Initiation of concomitant use of BZDs and BRDs[d]		x	x

[a] For incident BZDR users in Study I and for non-users in Studies II and III; [b] For persons without AD; [c] For incident BZDR users; [d] In analyses regarding the separate effects of BZD use and BRD use in comparison to non-use.
AD=Alzheimer's disease; BRD=benzodiazepine-related drugs; BZD=benzodiazepines; BZDR=benzodiazepines and related drugs.

4.6.3 Incident benzodiazepine and related drug use

Description of all incident BZDR users

Additional analyses were performed outside Studies I–III to describe the characteristics of all incident BZDR users with and without AD in the MEDALZ cohort. A one-year washout period before the AD diagnosis or the corresponding matching date in persons without AD was utilized. Altogether, 22,660 persons with AD and 140,530 persons without AD were excluded due to BZDR use or long hospital/institutional stay during the washout period, or due to the lack of matched persons after exclusions. The characteristics of the remaining persons with AD (n=48,058) and persons without AD (n=142,328) were examined. Further, the reasons for ending the follow-up, i.e., death, long-term

hospitalization/institutionalization, AD diagnosis, or 31st December 2012, were investigated among these persons.

Incidence of benzodiazepine and related drug use

In Study I, the initiation of BZDR use in relation to AD diagnosis or the corresponding matching date was investigated among persons with and without AD (Table 11). Additionally, the duration of the first BZDR use period, initial drugs, and prevalence of BZDR polypharmacy (concomitant use of ≥2 BZDRs) for ≥60 days was investigated among the incident BZDR users. The cutoff of ≥60 days was selected in this study to distinguish actual concomitant use from switching between drugs. The follow-up started at two years before the AD diagnosis or the corresponding matching date, and the washout period was defined as the year preceding the follow-up. All exclusion criteria were applied separately to persons with and without AD. In order to retain the matching, persons with AD who had no matched persons without AD, and vice versa, were excluded (Table 13). As a result, each person with AD had up to four matched comparison persons without AD.

In total, 7,802 persons without AD were diagnosed with AD during the follow-up. The follow-up for these persons ended at two years before the diagnosis to prevent overlap between the follow-up times. Otherwise, the follow-up ended after five years at latest (Table 12).

4.6.4 Risk of hip fracture

In Study II, persons with and without AD were investigated separately.

First, the exclusion criteria were applied to persons with AD. The washout period was the year preceding the AD diagnosis (Table 11). All persons with a hip fracture since 1972 until the date of AD diagnosis were excluded (Table 13). Further, persons who were hospitalized / institutionalized throughout the follow-up were excluded.

After the exclusions, two persons without AD were matched for each person with AD on the date of AD diagnosis based on age (±2 years) and gender with incidence density sampling (Matthews and Brill 2005). The same exclusion criteria were applied to persons without AD at the matching date (Table 13). Each person without AD was only selected once in the matching process. Those persons with AD who could not be matched with two persons without AD were excluded.

The follow-up began at the date of AD diagnosis or the corresponding matching date. The follow-up ended after 5 years at the latest (Table 12). In the sub-analyses comparing the risk between the use of different drug groups (benzodiazepines, benzodiazepine-related drugs), the follow-up ended at the initiation of concomitant use of these drug groups.

In the secondary analyses, the frequency of hospital stays longer than four months and one-year mortality were investigated in all persons with a hip fracture. In these analyses, the follow-up started at the date of the hip fracture and ended at death, after one year, or on 31st December 2012.

4.6.5 Risk of death

In Study III, the risk of death associated with incident BZDR use was investigated among persons with AD. The washout period was the year before the AD diagnosis (Table 11). Persons initiating BZDR use after the AD diagnosis were matched with two persons not using BZDRs on the same day. The matching was performed on the basis of time since the AD diagnosis (±90 days), age (±2 years), and gender, with the incidence density sampling (Matthews and Brill 2005). Each non-user was only selected once in the matching. Users who could not be matched with non-users and those who were hospitalized/institutionalized throughout the follow-up were excluded (Table 13).

The follow-up started at the initiation of BZDR use or the corresponding matching date in non-users. Persons with long-term (≥90 days) hospital/institutional stays before BZDR initiation were only considered as potential non-users in this study (until the hospitalization/institutionalization date). The follow-up was up to 180 days (Table 12) due to the high overall mortality in this population (Lönnroos et al. 2013). In the sub-analysis on the use of different drug groups, the follow-up ended at the initiation of concomitant use of benzodiazepines and benzodiazepine-related drugs.

Table 13. Formation of study samples in Studies I–III.

	Study I		Study II		Study III
Exclusion criteria	**Persons with AD (n=70,718), n**	**Persons without AD (n=282,858), n**	**Persons with AD (n=70,718), n**	**Matched persons without AD (n=209,355), n**	**Persons with AD (n=70,718), n**
BZDR use during washout	18,194	68,155	20,438	55,128	20,438
Retaining matching	--	53,788	--	--	--
Long hospital/institutional stay during washout[a]	271	135	1,834	225	1,834
Retaining matching	--	806	--	--	--
Previous hip fracture	--	--	2,043	4,161	--
Hospitalization/institutionalization throughout follow-up	--	--	13	41	17
Matching	--	--	Each person with AD was matched with two persons without AD		Two non-users matched for each BZDR initiator
Retaining matching	272 persons with no matched persons left	--	17 persons with AD could not be matched	57,054	121 persons initiating BZDR use could not be matched
Final study sample	n=51,981	n=159,974	n=46,373	n=92,746	Incident BZDR users n=10,380, matched non-users n=20,760

AD=Alzheimer's disease; BZDR=benzodiazepines and related drugs

[a] Either hospital/institutional stay for ≥6 months during the washout period or ≥90 days stay at the end of the washout period

4.7 COVARIATES

The covariates obtained from Special Reimbursement Register, Hospital Discharge Register and Prescription Register are presented in Tables 14–16.

A modified Charlson Comorbidity Index (CCI) was utilized to describe overall morbidity in all Studies (Charlson et al. 1987, Taipale et al. 2014b). Additionally in Study III, the modified CCI score was utilized as a covariate in the statistical analyses because it has been developed to predict mortality (Charlson et al. 1987). Any history of chronic heart failure, coronary artery disease, diabetes, asthma/COPD, and disseminated connective tissue diseases, rheumatoid arthritis, and other comparable conditions (later: rheumatic diseases) was assigned a score of 1 whereas any history of severe renal failure and cancer was assigned a score of 2. The CCI was based on granted special reimbursements (Table 14), with cancer being the only exception. In Studies I and II, cancer was defined as having a special reimbursement for any of the following cancers: leukemia and other malignant diseases of blood and bone marrow including malignant diseases of the lymphatic system, breast cancer, prostate cancer, gynecologic cancer, and malignant neoplasms. In Study III, cancer was defined as having active cancer treatment during one year before the start of the follow-up. Active cancer treatment was defined as having diagnoses or procedures related to cancer in the Hospital Discharge Register data (Table 15) or the use of anticancer drugs (Table 16) modelled with the PRE2DUP method (Hamina et al. 2017).

Further, to describe general comorbidity, data on epilepsy, hypothyroidism, and chronic cardiovascular diseases were also collected from the Special Reimbursement Register (Table 14).

In all studies and analyses, a history of psychiatric diseases was determined from the Hospital Discharge Register data (Table 15). The history was defined from 1972 until five years before the AD diagnosis or the corresponding matching date in persons without AD to exclude hospital care due to prodromal symptoms of AD (Gallagher et al. 2017). This variable was used as a covariate in Studies II and III because psychiatric diseases have been associated with an increased risk of falls (Finkelstein et al. 2007) and death (Kriegbaum et al. 2015).

In addition, data on occupational socioeconomic position was obtained from Statistics Finland. This data was based on the highest position recorded for study persons in their middle age (45–55 years old) in the population census. The position was categorized as high (entrepreneurs and higher clerical workers), medium (lower clerical workers and employees), low (unemployed, retired, students), or unknown (unknown or missing; data was missing for approximately 5% of the original MEDALZ cohort). Occupational socioeconomic position was used as a covariate in Studies II and III because previous studies have found an association between low socioeconomic position and an increased risk of fractures (Brennan et al. 2009) and death (Kriegbaum et al. 2015).

<u>Covariates specific for Study I</u>

The description of the study population included CCI and somatic chronic comorbidities based on special reimbursement data, and these were determined from the beginning of data availability and until the date of AD diagnosis or the corresponding matching date (Table 14). In addition, the history of psychiatric disorders was assessed (Table 15).

<u>Covariates specific for Study II</u>

Covariates were defined by the start of follow-up. In the main analyses, the follow-up started at the date of the AD diagnosis or the corresponding matching date, whereas in the secondary analyses, the follow-up started at the date of hip fracture.

BZDR use is a recognized risk factor for falls (Hartikainen et al. 2007, Seppälä et al. 2018) and benzodiazepines are prescribed more frequently for persons with pre-existing risk

factors for injurious falls (Bartlett et al. 2009). Therefore, the covariates in Study II included previously identified risk factors for falls and injurious falls. The statistical analyses included adjustment for chronic somatic comorbidities (Table 14) due to their clinical relevance for general health or risk of falls. Other covariates associated with a risk of falling included histories of any hospital-treated fractures (Pohl et al. 2014), stroke (Deandrea et al. 2010), and substance abuse (Finkelstein et al. 2007).

Drug use covariates were measured on the basis of their assumed exposure time windows, i.e., whether the drugs were expected to have acute or long-term effects on the risk of falls or hip fractures. The use of antipsychotics, antidepressants, and opioids was utilized as a covariate due to their association with an increased risk of falls and hip fractures (Hartikainen et al. 2007, Finnish Medical Society Duodecim 2017a) but also as they can be considered as proxies of BPSDs (Finnish Medical Society Duodecim 2017c, Hamina et al. 2018). The use of antidepressants and antipsychotics was measured from the five-year period before the start of follow-up. Opioid use was defined as baseline use, i.e. within two weeks before the start of follow-up, due to the expected acute effects on fall risk. BZDR use has been associated with concomitant use of other psychotropic drugs (Abbing-Karahagopian et al. 2015) and, therefore, the sensitivity analyses included adjustment for the time-dependent use of antipsychotics, antidepressants, and opioids during the follow-up.

Use of urinary antispasmodics and antiparkinson drugs, which have been associated with an increased risk of falls (Kouladjian O'Donnell et al. 2017), were also defined as baseline use, i.e., within two weeks before the start of follow-up. Further, osteoporosis is a risk factor for hip fractures (Finnish Medical Society Duodecim 2017a), and previous use of systemic estrogen (including oral and transdermal formulations), bisphosphonates, and calcitonin, were adjusted for as they served as proxies for osteoporosis (Delmas 2002, Finnish Medical Society Duodecim 2014). The use of these drugs was defined as having any purchases in the register data before the start of follow-up. Previous long-term use of oral corticosteroids was utilized as a marker of possibly decreased bone mass density and it was defined as having a period of ≥1 year continuous use before the start of follow-up (Finnish Medical Society Duodecim 2014).

In the secondary analyses, the time between AD diagnosis or the corresponding matching date and the date of hip fracture was utilized as a covariate to account for progression of AD and aging.

Covariates specific for Study III

All covariates, except for the history of psychiatric diseases, were measured until the start of the follow-up, i.e. the initiation date of BZDR use or the corresponding matching date for non-users (Tables 14–16). Covariates were selected due to their association with BZDR use and the risk of death. The risk factors identified from the previous literature included any history of stroke (Ingall 2004, Taipale et al. 2017a), hip fractures (Hartikainen et al. 2007, Haentjens et al. 2010), and substance abuse (Wu and Blazer 2011, Kriegbaum et al. 2015). Additionally, antipsychotic, antidepressant, and opioid use have been associated with incident benzodiazepine use (Bartlett et al. 2009) and an increased risk of death (Schneider et al. 2005, Dhalla et al. 2009, Álamo et al. 2014). The use of these drugs was defined from the one-year period before the matching date. Similar to Study II, the use of these drugs was considered as a proxy of having BPSDs (Finnish Medical Society Duodecim 2017c, Hamina et al. 2018). In the sensitivity analyses, time between AD diagnosis and initiation of BZDR use was utilized as a covariate.

Additional cohort description

To describe the incident users of BZDRs in the MEDALZ cohort, additional analyses were conducted for this thesis. Comorbidities obtained from Special Reimbursement Register, bisphosphonate use, calcitonin use, long-term oral corticosteroid use, stroke, hip fractures, other fractures, and substance abuse were measured until the date of AD diagnosis or the corresponding matching date among persons without AD (Tables 14–16). The use of urinary antispasmodics, opioids, estrogens, and antiparkinson drugs was measured during the two weeks before the AD diagnosis or the matching date. The use of antipsychotics and antidepressants and active cancer treatment were measured during one year before AD diagnosis or the matching date.

Table 14. Covariates obtained from the Special Reimbursement Register and their measurement in the studies.

		Measurement time windows		
Variable	**Special Reimbursement code(s)**	**Study I**	**Study II ***	**Study III**
Any cardiovascular diseases	201 (heart failure), 205 (hypertension), 206 (coronary artery disease), or 207 (arrhythmias)	D	F	F
Asthma/COPD	203	D	F	F
Cancer	115 (breast cancer), 116 (prostate cancer), 117 (leukemia and other malignant diseases of blood and bone marrow including malignant diseases of the lymphatic system), 128 (gynecological cancer), or 130 (other malignant neoplasms)	D	F	na
Diabetes	103	D	F	F
Epilepsy	111	D	F	na
Hypothyroidism	104	D	na	na
Rheumatic diseases	132 (sarcoidosis), 202 (disseminated connective tissue diseases, rheumatoid arthritis and other comparable conditions)	D	F	F
Severe renal failure	137 (uremia requiring dialysis) or 138 (severe anemia in connection with chronic renal failure)	D	F	F

* In Study II, the follow-up in main analyses began at AD diagnosis or the corresponding date, whereas in the secondary analyses, the follow-up began at hip fracture date.

COPD=chronic obstructive pulmonary disease; D=until AD diagnosis or corresponding matching date; F=until start of follow-up; na=not applied

Table 15. Covariates obtained from the Hospital Discharge Register and their measurement in the studies.

		Measurement time windows		
Variable	**Definitions and applied classification(s)**	**Study I**	**Study II***	**Study III**
Cancer treatment	Discharge diagnoses related to malignant neoplasms ICD-10: C00–C97 or procedures related to cancer NOMESCO: AAG50, AX, HA0, PJO, QA0, QB0, QC0, QD0, QW0, QX0, WA, WB, WC, WD, WE, WF0, WFO, ZX0	na	na	One year before start of follow-up
Hip fractures	ICD-10: S72.0, S72.1, S72.2, ICD-9: 820 ICD-8: 82000, 82001, 82010, 82011,82090, 82091	na	na	F
Other fractures	ICD-10: S02, S12, S22, S32, S42, S52, S62, S82, S92, T02	na	F	na
Psychiatric disorders	Includes schizophrenia, schizotypal or delusional disorders, bipolar disorder, and severe depression ICD-10: F20–F39 ICD-9: 295, 297, 298, 2961–2964, 2967, 2968, 3004, 3010–3012 ICD-8: 295, 297, 298, 29600, 29610, 29620, 29630, 29688, 29699, 29999, 30100, 30110, 30120, 30040, 30041	≥5 years before AD diagnosis or matching date in persons without AD	≥5 years before AD diagnosis or matching date in persons without AD	≥5 years before AD diagnosis
Stroke	ICD-10: I60–I64 ICD-9: 430–432, 4330A, 4331A, 4339A, 4340A, 4341A, 4349A, 4360 ICD-8: 430–434	na	F	F
Substance abuse	Discharge diagnoses related to drug abuse or alcoholic pancreatitis ICD-10: F10–F19, K86.0 ICD-9: 291*, 292*, 303*, 304*, 305* ICD-8: 291*, 303*, 304* or hospital admission reasons related to alcohol/drug/narcotic abuse or addiction (33, 71–75)	na	F	F

* In Study II, the follow-up in main analyses began at AD diagnosis or the corresponding date whereas in the secondary analyses, the follow-up began on the date of hip fracture.

F=until start of follow-up; ICD=International Classification of Diseases; na=not applied; NOMESCO=Nordic Medico-Statistical Committee Classification of Surgical Procedures

Table 16. Covariates obtained from the Prescription Register and their measurement in the studies.

		Measurement time windows		
Variable	**Anatomical Therapeutic Chemical classification code(s)**	**Study I**	**Study II ***	**Study III**
Antidepressants	N06A	na	5 years before F§	year before F
Anticancer drugs	L01, L02, L03AA, L03AB01, L03AB04, L03AB05, L03AC, L03AX (excluding L03AX13), L04AA10, L04AA18, L04AA34, L04AX02, L04AX03, L01BA01	na	na	year before F
Anti-parkinson drugs	N04	na	2 weeks before F	na
Antipsychotics	N05A (excluding N05AN01 and N05AB04)	na	5 years before F§	year before F
Bisphosphonates	M05BA and M05BB	na	F	na
Calcitonin	H05BA	na	F	na
Estrogen, systemic and transdermal drug forms	G03C and G03F	na	2 weeks before F	na
Opioids	N02A	na	2 weeks before F§	year before F
Oral corticosteroids	H02AB	na	Long-term (≥1 year) use period before F	na
Urinary antispasmodics	G04BD	na	2 weeks before F	na

* The follow-up in main analyses began at AD diagnosis or the corresponding date, whereas in the secondary analyses, the follow-up began at the date of hip fracture.
§ In addition, time-varying antipsychotic, antidepressant, and opioid use during follow-up was applied as a covariate in sensitivity analyses

F=until start of follow-up; na=not applied

4.8 STATISTICAL ANALYSES

4.8.1 Descriptive statistics

In order to describe the characteristics of incident BZDR users and non-users, continuous variables were reported with mean, range, standard deviation (SD), median, and interquartile range (IQR). They were compared between incident BZDR users and non-users with the Mann-Whitney U test and presented with p values. Categorical variables were reported with proportions, and comparison was made between BZDR users and non-users with p values, calculated with the chi square test.

4.8.2 Incidence of benzodiazepine and related drug use

To describe the initiation patterns of BZDR use in Study I, six-month incidence rates (IR) per 100 person-years were computed for BZDR use throughout the follow-up. Additionally, separate IRs of benzodiazepine and benzodiazepine-related drug use were computed for those initiating drug use with one BZDR. The IRs were compared between persons with and without AD with the Poisson regression (Frome and Checkoway 1985) to obtain IRRs with 95% confidence intervals (CI). The IRR reported the IR among persons with AD in relation to the IR among those without AD.

The initial drugs (Table 10) were examined among the incident BZDR users who started drug use with one BZDR. In addition, the median modelled duration of first BZDR use period and the prevalence of having BZDR polypharmacy for ≥60 days was investigated among the incident users. Finally, the proportion of BZDR use initiations with recent (≤10 days) hospital discharge was calculated.

4.8.3 Associated adverse outcomes

In Studies II and III, the drug exposure status was categorized as BZDR use or non-use, and further categorized into drug groups (benzodiazepines, benzodiazepine-related drugs) and according to duration of use.

The absolute risks of the adverse outcomes were reported as age-adjusted event rates per 100 person-years with 95% CIs (Schechtman 2002). The absolute risk provides information on the magnitude of the risk. Event rates were reported in all analyzed drug exposure categories and in non-use. An age adjustment was conducted for these rates; age was categorized as <65, 65–69, 70–74, 75–79, 80–84, 85–89, 90–94, and ≥95 years.

The relative risk of a first hip fracture (Study II), post-fracture mortality (Study II), and all-cause mortality (Study III) was investigated with Cox proportional regression (Stricker and Stijnen 2010). As the health care registers include daily data, it was feasible to utilize the time to event analysis in these research questions. In the main analyses (Studies II and III), the Cox regression was utilized for investigating the risk of the outcome associated with time-dependent BZDR use in comparison to non-use. In Study III, the feasibility of Cox proportional regression was verified by comparing Kaplan Meier curves. The sub-analyses included investigating the risk associated with different durations of BZDR use and the risk associated with use of the drug groups separately. In Study II, the time windows for duration of BZDR use were 1–30, 31–180, 181–365, and >365 days whereas in Study III, they were 1–30, 31–60, 61–90, 91–120, and 121–180 days. Persons who initiated BZDR use with concomitant use of benzodiazepines and benzodiazepine-related drugs were excluded from the sub-analyses regarding the use of the drug groups separately.

The risk of adverse outcomes associated with BZDR polypharmacy could not be investigated due to the low number of users.

In the secondary analyses of Study II, the association between BZDR use and one-year post-hip fracture mortality was investigated with the Cox regression. These analyses were performed utilizing the ITT approach and the exposure (use, non-use) was defined at the date of hip fracture. Time-dependent BZDR exposure could not be utilized in these

analyses because hip fractures lead to hospital stays during which the BZDR use was unknown.

The association between BZDR use during hip fracture and long-term (≥4 months) hospital stays after the hip fracture was investigated in a cross-sectional manner with the logistic regression (Schechtman 2002). Only persons surviving ≥4 months after the hip fracture were included in these analyses. Therefore, 289 persons with AD and 319 matched persons without AD were excluded due to dying within four months after the hip fracture.

Clinically relevant covariates, potentially confounding the association between BZDR use and the adverse outcome, were adjusted for in the multivariable analyses in Studies II and III (see Chapter 4.7). The CCI score was categorized as 0, 1, and ≥2. The time between the AD diagnosis or the corresponding matching date and hip fracture was categorized as ≤365, 366–730, 731–1095, 1096–1460, and 1461–1825 days. The results were reported as aHRs and aORs with 95% CIs.

Three sensitivity analyses were performed in Studies II and III. In Study II, time-dependent antipsychotic, antidepressant, and opioid use during the follow-up was utilized as a covariate in the multivariable analyses. These analyses were performed to investigate whether concomitant psychotropic drug use affected the risk estimate. Study III included ITT analyses in which the follow-up was not censored at the end of BZDR use or at the beginning of long-term hospital/institutional stay (Schneeweiss 2010). With these analyses, informative censoring related to discontinuation of BZDR use or hospitalization/institutionalization due to adverse outcomes was minimized. Further, the impact of varying durations between AD diagnosis and initiation of follow-up on the observed risk estimate was analyzed. Mortality is high among persons with AD (Lönnroos et al. 2013) and thus the interaction between the time since the AD diagnosis and initiation of BZDR use was analyzed with a Cox regression (Rothwell 2005). The time between the AD diagnosis and the initiation of follow-up was classified as <180, 180–364, 365–729, 730–1094, and ≥1095 days.

4.9 ETHICAL CONSIDERATIONS AND DATA PROTECTION

No ethics committee approval or informed consent was required by the legislation as only pseudonymized personal data from registers were used and the study participants were not contacted. Register maintainers approved the study protocol and provided permissions for data use. Only authorized persons had access to the data.

I received permission to use the MEDALZ data from the SII and the National Institute for Health and Welfare. I processed the data with a password-secured computer and I did not share the data with any unauthorized persons. All results were reported in an aggregated manner, ensuring that individuals could not be identified.

5 Results

5.1 CHARACTERISTICS OF INCIDENT USERS AND NON-USERS

There were 48,058 persons with AD and 142,328 persons without AD in the cohort after the exclusions due to previous BZDR use and long hospitalization/institutionalization before AD diagnosis or the corresponding matching date in persons without AD (Table 17). The median age was 80.2 (IQR 75.4–84.4) years among persons with AD and 79.6 (IQR 74.7–83.8) years among those without AD. Most persons were female (62.5% and 59.5% of persons with and without AD, respectively). After the AD diagnosis or the corresponding matching date, 22.3% (n=10,736) of persons with AD and 13.2% (n=18,826) of persons without AD initiated BZDR use.

Among persons either with or without AD, a history of psychiatric disorders and previous use of antipsychotics and antidepressants were more frequent among incident BZDR users than non-users (Tables 18–19).

Among persons with AD, incident BZDR users had less frequently hip or other fractures and diabetes in comparison to non-users, whereas a history of substance abuse was more frequent among the incident BZDR users (Tables 18–19).

Incident BZDR users without AD had more frequently asthma/COPD, cardiovascular diseases, and hypothyroidism, in comparison to those not initiating BZDR use (Tables 18–19). In addition, previous use of estrogens, bisphosphonate/calcitonin, and opioids was more frequent among incident BZDR users.

Among persons with AD, death and institutionalization were more common reasons for ending the follow-up than among those without AD (Table 17). Persons without AD reached the end of study follow-up more commonly than persons with AD.

Table 17. Description of incident benzodiazepine and related drug users and non-users with and without Alzheimer's disease.

Variable	Persons with AD				Persons without AD			
	All (n=48,058), n (%)	Users (n=10,736), n (%)	Non-users (n=37,322), n (%)	p	All (n=142,328), n (%)	Users (n=18,826), n (%)	Non-users (n=123,502), n (%)	p
Age				<0.0001				<0.0001
<75	11,224 (23.4)	2,892 (26.9)	8,332 (22.3)		37,119 (26.1)	4,575 (24.3)	32,544 (26.4)	
75–84	26,570 (55.3)	5,883 (54.8)	20,687 (55.4)		78,140 (54.9)	11,008 (58.5)	67,132 (54.4)	
≥85	10,264 (21.4)	1,961 (18.3)	8,303 (22.3)		27,069 (19.0)	3,243 (17.2)	23,826 (19.3)	
Gender								
Female	30,012 (62.5)	6,767 (63.0)	23,245 (62.3)	0.1581	84,676 (59.5)	12,309 (65.4)	72,367 (58.6)	<0.0001
Socioeconomic position				<0.0001				<0.0001
High	16,541 (34.4)	3,568 (33.2)	12,973 (34.8)		49,380 (34.7)	6,766 (35.9)	42,614 (34.5)	
Middle	27,942 (58.1)	6,257 (58.3)	21,685 (58.1)		78,505 (55.2)	10,666 (56.7)	67,839 (54.9)	
Low	3,017 (6.3)	777 (7.2)	2,240 (6.0)		8,155 (5.7)	1,117 (5.9)	7,038 (5.7)	
Unknown	558 (1.2)	134 (1.3)	424 (1.1)		6,288 (4.4)	277 (4.4)	6,011 (4.9)	
Reason for ending follow–up				<0.0001				<0.0001
Death	11,396 (23.7)	3,168 (29.5)	8,228 (22.1)		21,517 (15.1)	3,826 (20.3)	17,691 (14.3)	
Institutionalization	9,314 (19.4)	1,463 (13.6)	7,851 (21.0)		7,033 (4.9)	674 (3.6)	6,359 (5.2)	
AD diagnosis					8,771 (6.2)	747 (4.0)	8,024 (6.5)	
31 December 2012	27,348 (56.9)	6,105 (56.9)	21,243 (56.9)		105,007 (73.8)	13,579 (72.1)	91,428 74.0)	

AD=Alzheimer's disease

Table 18. Previous drug use among incident benzodiazepine and related drug users and non-users with and without Alzheimer's disease.

	Persons with AD				Persons without AD			
Variable	All (n=48,058), n (%)	Users (n=10,736), n (%)	Non-users (n=37,322), n (%)	p	All (n=142,328), n (%)	Users (n=18,826), n (%)	Non-users (n=123,502), n (%)	p
Antidepressant use	7,994 (16.6)	2,170 (20.2)	5,824 (15.6)	<0.0001	7,284 (5.1)	1,722 (9.2)	5,562 (4.5)	<0.0001
Antiparkinson drug use	895 (1.9)	231 (2.2)	664 (1.8)	0.0119	1,872 (1.3)	331 (1.8)	1,541 (1.3)	<0.0001
Antipsychotic use	3,542 (7.4)	1,045 (9.7)	2,497 (6.7)	<0.0001	2,742 (1.9)	554 (2.9)	2,188 (1.8)	<0.0001
Bisphosphonate or calcitonin use	6,940 (14.4)	1,507 (14.0)	5,433 (14.6)	0.1766	14,549 (10.2)	2,475 (13.2)	12,074 (9.8)	<0.0001
Opioid use	1,205 (2.5)	258 (2.4)	947 (2.5)	0.4330	3,821 (2.7)	663 (3.5)	3,158 (2.6)	<0.0001
Oral corticosteroid[a] use	1,924 (4.0)	390 (3.6)	1,534 (4.1)	0.0261	4,942 (3.5)	795 (4.2)	4,147 (3.4)	<0.0001
Systemic estrogen[b] use	750 (1.6)	211 (2.0)	539 (1.4)	0.0001	3,402 (2.4)	628 (3.3)	2,774 (2.3)	<0.0001
Urinary antispasmodic use	1,454 (3.0)	336 (3.1)	1,118 (3.0)	0.4747	2,044 (1.4)	357 (1.9)	1,687 (1.4)	<0.0001

[a] Long-term (≥1 year) use of oral corticosteroids.
[b] Systemic estrogen included oral and transdermal formulations.
AD=Alzheimer's disease

Table 19. Comorbidities among incident benzodiazepine and related drug users and non-users with and without Alzheimer's disease.

	Persons with AD				Persons without AD			
Variable	All (n=48,058), n (%)	Users (n=10,736), n (%)	Non-users (n=37,322), n (%)	p	All (n=142,328), n (%)	Users (n=18,826), n (%)	Non-users (n=123,502), n (%)	p
Any cardiovascular disease[a]	23,183 (48.2)	5,187 (48.3)	17,996 (48.2)	0.8609	65,749 (46.2)	9,740 (51.7)	56,009 (45.4)	<0.0001
Asthma/COPD	3,824 (8.0)	881 (8.2)	2,943 (7.9)	0.2794	11,447 (8.0)	1,789 (9.5)	9,658 (7.8)	<0.0001
Cancer[b]	971 (2.0)	199 (1.9)	772 (2.1)	0.1631	2,896 (2.0)	473 (2.5)	2,423 (2.0)	<0.0001
Diabetes	6,219 (12.9)	1,190 (11.1)	5,029 (13.5)	<0.0001	15,490 (10.9)	1,998 (10.6)	13,492 (10.9)	0.2011
Epilepsy	943 (2.0)	207 (1.9)	736 (2.0)	0.7724	1,826 (1.3)	254 (1.4)	1,572 (1.3)	0.3859
Hip fractures	2,024 (4.2)	363 (3.4)	1,661 (4.5)	<0.0001	3,799 (2.7)	476 (2.5)	3,323 (2.7)	0.1983
Hypothyroidism	2,088 (4.3)	476 (4.4)	1,612 (4.3)	0.6080	5,782 (4.1)	983 (5.2)	4,799 (3.9)	<0.0001
Other fractures [c]	7,659 (15.9)	1,613 (15.0)	6,046 (16.2)	0.0034	16,734 (11.8)	2,266 (12.0)	14,468 (11.7)	0.2017
Psychiatric disorder	2,780 (5.8)	790 (7.4)	1,990 (5.3)	<0.0001	7,296 (5.1)	1,249 (6.6)	6,047 (4.9)	<0.0001
Rheumatic diseases	2,024 (4.2)	413 (3.9)	1,611 (4.3)	0.0328	5,706 (4.0)	880 (4.7)	4,826 (3.9)	<0.0001
Severe renal failure	81 (0.2)	12 (0.1)	69 (0.2)	0.1037	316 (0.2)	54 (0.3)	262 (0.2)	0.0425
Stroke	4,218 (8.8)	890 (8.3)	3,328 (8.9)	0.0430	10,415 (7.3)	1,362 (7.2)	9,053 (7.3)	0.6390
Substance abuse	1,235 (2.6)	382 (3.6)	853 (2.3)	<0.0001	2,601 (1.8)	497 (2.6)	2,104 (1.7)	<0.0001

[a] Cardiovascular diseases included heart failure, coronary artery disease, hypertension, and arrhythmias.
[b] Cancer referred to active cancer treatment which was based on hospital discharge diagnoses or purchases of anticancer drugs
[c] Excluding hip fractures

AD=Alzheimer's disease; COPD=chronic obstructive pulmonary disease

5.2 INCIDENCE OF USE (STUDY I)

From two years before to three years after the AD diagnosis or the corresponding matching date, 25.7% (n=13,341) of persons with AD and 16.9% (n=27,028) of persons without AD initiated BZDR use. Among persons with AD, the incidence of BZDR use began increasing from one year before the diagnosis. There was a considerable peak in the IRR of BZDR (IRR 2.62, 95% CI 2.48–2.76) and benzodiazepine (IRR 4.49, 95% CI 4.13–4.88) use at six months after the AD diagnosis. At the same time, the IRR of benzodiazepine-related drug use was 1.58 (95% CI 1.46–1.71). The IRRs revealed the more frequent initiation of benzodiazepine use in persons with AD throughout the follow-up (Figure 5). The initiation of benzodiazepine-related drug use was more frequent in persons with AD from the diagnosis until 18 months after the diagnosis.

Persons with AD initiated drug use most commonly with intermediate-acting benzodiazepines (47.4%), whereas initiation with benzodiazepine-related drugs was most common (64.8%) in persons without AD. Long-acting benzodiazepines were the initial drugs for 6.6% of incident users with AD and 8.6% incident users without AD. The duration of first BZDR use period was longer in persons with AD (median 121 days, IQR 40–349) than in persons without AD (median 88 days, IQR 37–211, $p < 0.0001$). Among the incident BZDR users, persons with AD had a recent hospital discharge more frequently (20.3%, n=2,706) than persons without the disease (12.2%, n=3,289).

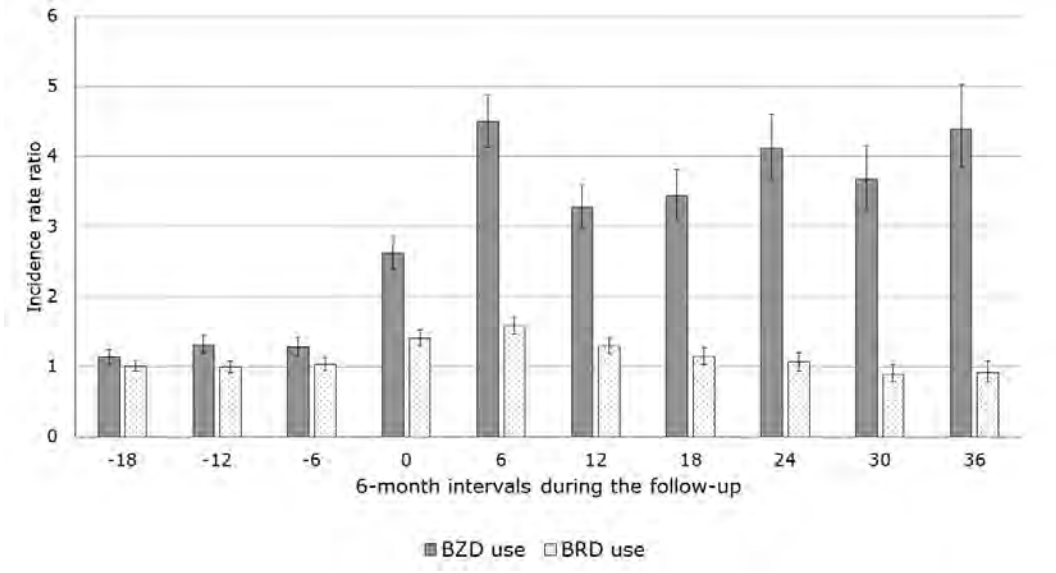

Figure 5. Six-month incidence rate ratios of benzodiazepine (BZD) use and benzodiazepine-related drug (BRD) use among persons with Alzheimer's disease (AD), in relation to persons without AD. The time point 0 represents the AD diagnosis date or the corresponding matching date in persons without AD.

5.3 ASSOCIATION WITH ADVERSE OUTCOMES

5.3.1 Hip fractures (Study II)

Among persons with AD and their matched persons without AD, 21.1% (n=9,782) and 12.8% (n=11.871), respectively, initiated BZDR use after the AD diagnosis or the matching date. The

median duration of the first BZDR use period was 121 days (IQR 41–359) in persons with AD and 72 days (IQR 37–172) in persons without AD. In total, 62.0% (n=6,062) of incident users with AD and 34.8% (n=4,135) of incident users without AD initiated drug use with benzodiazepines only. Additionally, 36.8% (n=3,604) and 64.6% (n=7,674) of persons with and without AD, respectively, initiated drug use with benzodiazepine-related drugs only. Finally, 1.2% (n=116) of persons with AD and 0.5% (n=62) of persons without AD initiated drug use with concomitant use of benzodiazepines and benzodiazepine-related drugs, and these persons were excluded from the sub-analyses regarding the use of different drug groups.

Incident hip fracture was experienced by 4.5% (n=2,075) of persons with AD and 2.3% (n=2,135) of matched persons without AD during the five-year follow-up. The age-adjusted hip fracture rate per 100 person-years was higher in persons with AD during both BZDR use and non-use (Figure 6). In persons with AD, the age-adjusted hip fracture rate per 100 person-years was 2.51 (95% CI 2.15–2.86) during BZDR use and 1.56 (95% CI 1.49–1.63) during non-use. In matched persons without AD, the corresponding rates were 1.35 (95% CI 1.08–1.60) and 0.64 (95% CI 0.62–0.67).

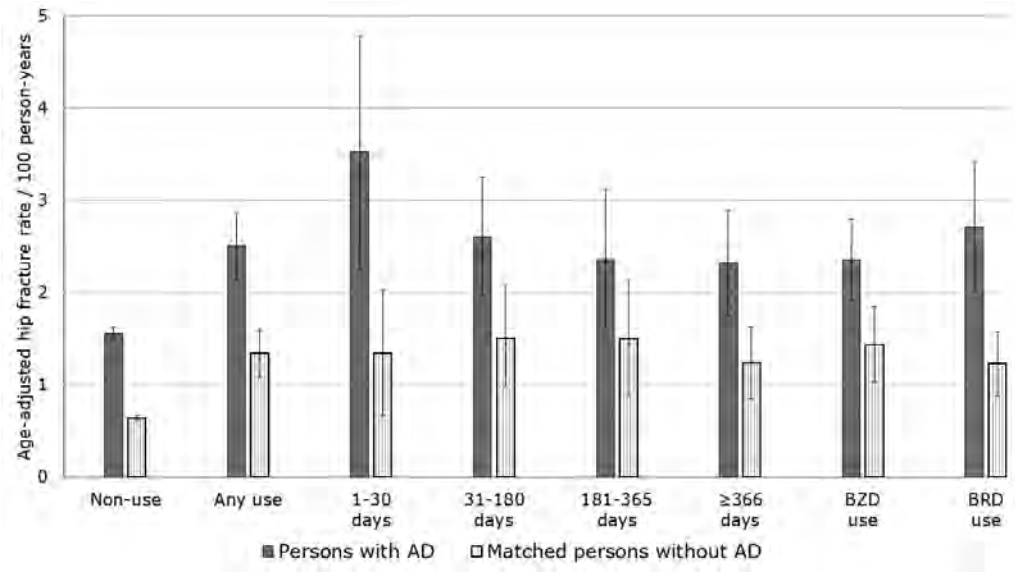

Figure 6. Age-adjusted hip fracture rates in persons with AD and matched persons without AD during benzodiazepine and related drug use and non-use. BRD=benzodiazepine-related drug, BZD=benzodiazepine.

Incident BZDR use, compared with non-use, was associated with an increased risk of hip fracture in persons with AD (aHR 1.43, 95% CI 1.23–1.66) and persons without AD (aHR 1.58, 95% CI 1.31–1.91). The results were not considerably altered in the sensitivity analysis (aHR 1.29, 95% CI 1.11–1.50 among persons with AD and aHR 1.47, 95% CI 1.22–1.79 among persons without AD). The associated risk remained elevated until 180 days in persons with AD and until 365 days in matched persons without AD (Figure 7). However, the risk estimates were suggestive of an increased risk throughout the duration of use among persons with and without AD. Both benzodiazepine use and benzodiazepine-related drug use were associated with an increased hip fracture risk in both persons with and without AD.

Among those who experienced a hip fracture, BZDR use at the time of the fracture was not associated with one-year post-fracture mortality in persons with AD (aHR 1.00, 95% CI 0.75–1.34) or in matched persons without AD (aHR 1.03, 95% CI 0.73–1.45). However, among

those persons with AD who survived for ≥4 months after the hip fracture, BZDR use was associated with a longer than 4-month post-fracture hospital stay (aOR 1.90, 95% CI 1.29–2.80). There was no such association among persons without AD (aOR 1.35, 95% CI 0.75–2.45).

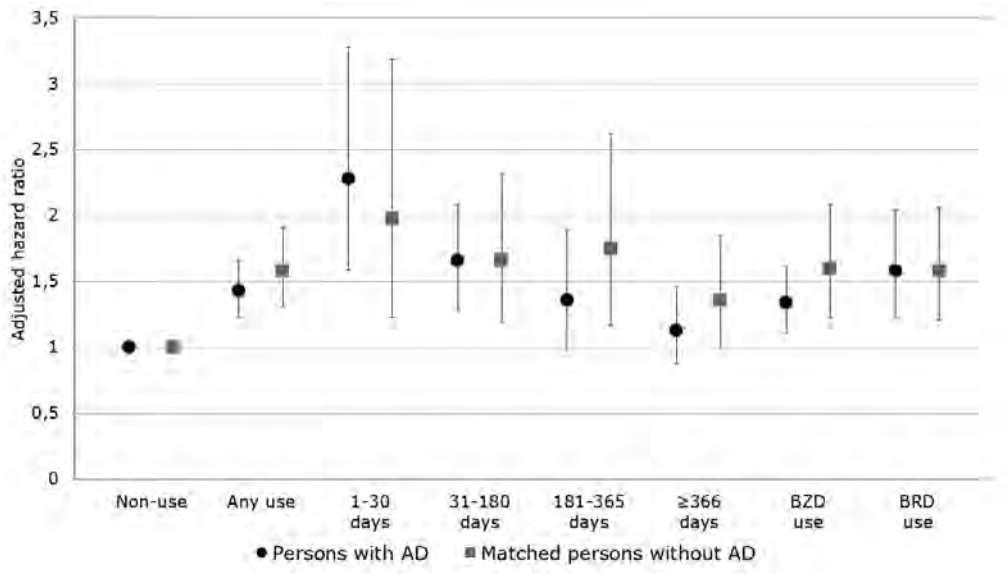

Figure 7. Relative risk of first hip fracture associated with incident benzodiazepine and related drug use in comparison to non-use among persons with Alzheimer's disease (AD) and matched persons without AD. The analyses were adjusted for age, gender, socioeconomic position, comorbidities, and previous use of drugs associated with a risk of fall or hip fracture (See Section 4.7 for further details). BRD=benzodiazepine-related drug; BZD=benzodiazepine

5.3.2 Mortality (Study III)

The median duration of first BZDR use period was 121 days (IQR 40–180) among incident BZDR users with AD during the 180-day follow-up. Among the 10,380 incident BZDR users, 62.0% (n=6,438) initiated drug use with benzodiazepines only and 36.9% (n=3,826) with benzodiazepine-related drugs only. In addition, 1.1% (n=116) initiated drug use with concomitant use of benzodiazepines and benzodiazepine-related drugs; these individuals were excluded from the sub-analyses regarding the use of different drug groups.

The median time from the AD diagnosis until BZDR use initiation was 445 days (IQR 166–903.5). In total, 440 persons died during BZDR use, while 785 persons died during non-use. The age-adjusted death rate per 100 person-years was 13.4 (95% CI 12.2–14.5) during BZDR use and 8.5 (95% CI 7.9–9.1) during non-use (Figure 8).

Incident BZDR use was associated with an increased risk of death (aHR 1.41, 95% CI 1.23–1.62) during the six-month follow-up, and the associated risk remained elevated until four months of BZDR use (Figure 9). Benzodiazepine use was associated with an increased risk (aHR 1.59, 95% CI 1.35–1.88) of death, while benzodiazepine-related drug use was not (aHR 1.06, 95% CI 0.83–1.35). The sensitivity analyses indicated that the observed association remained in the ITT analyses (aHR 1.40, 95% CI 1.25–1.57) and that there was no interaction between the risk of death and the time since AD diagnosis (p=0.9470).

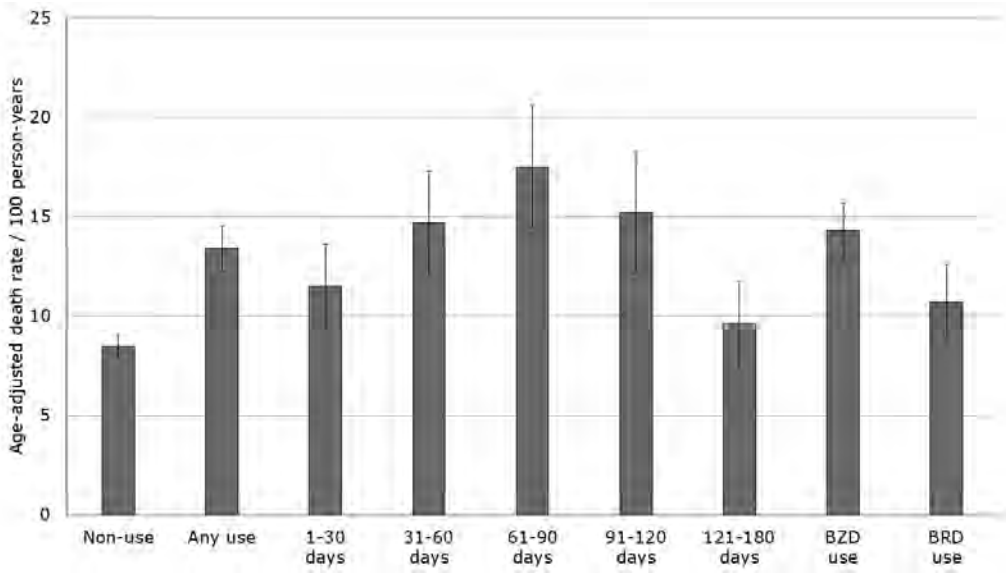

Figure 8. Age-adjusted death rates per 100 person-years during benzodiazepine and related drug use and non-use among persons with Alzheimer's disease. BRD=benzodiazepine-related drug, BZD=benzodiazepine.

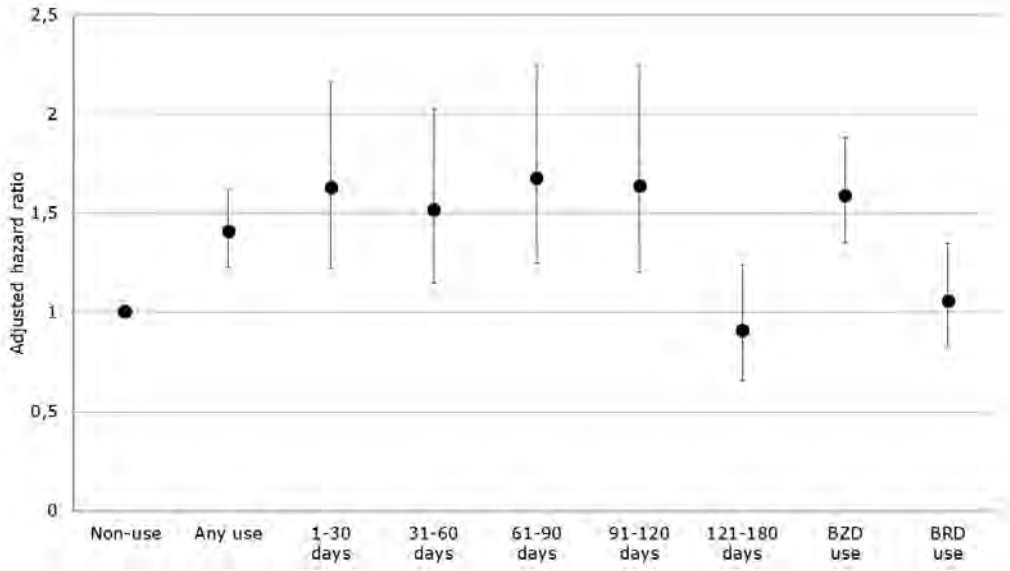

Figure 9. Relative risk of death associated with incident benzodiazepine and related drug use in comparison to non-use among persons with Alzheimer's disease. The analyses were adjusted for socioeconomic position, Charlson Comorbidity Index, previous diagnoses (hip fractures, psychiatric disorders, substance abuse, and stroke) and previous drug use (antidepressants, antipsychotics, and opioids). BRD=benzodiazepine-related drugs, BZD=benzodiazepines

6 Discussion

To summarize, every fourth community-dwelling person with AD initiated BZDR use during a time period from two years before to three years after the diagnosis of the disease. The corresponding incidence among persons without AD was considerably lower. Incident BZDR use was associated with a 43% increase in the hip fracture risk among persons with AD and with a 58% increase among persons without AD in a five-year study. BZDR use was associated with long-term post-hip fracture hospital stay among persons with AD but not among persons without AD. In addition, there was a 41% increase in the risk of death associated with incident BZDR use among persons with AD in a six-month study.

6.1 INCIDENCE OF BENZODIAZEPINE AND RELATED DRUG USE (STUDY I)

Every fourth community-dwelling individual with AD initiated BZDR use during the five-year study period. The incidence was considerably lower among persons without AD, as less than every fifth of these individuals initiated BZDR use during the same period. There are no previous studies examining the incidence of BZDR use among persons with cognitive disorders. However, a steady prevalence of BZDR use from five years prior to four years after the AD diagnosis has been reported in Finland, and the prevalence was similar among matched persons without AD (Orsel et al. 2018). Although the prevalence seems to remain stable, Study I indicated that the number of BZDR users varies extensively around the time of AD diagnosis.

The five-year incidence observed among persons without AD was similar to the three-year incidence of BZDR use among general older population in Finland (Rikala et al. 2011). In that trial, every fourth study individual had a cognitive disorder, which may have contributed to the relatively high incidence. On the other hand, Bartlett et al. (2009) observed that one-third of the general older population initiated benzodiazepine use during a five-year period. This higher incidence may have resulted from inclusion of persons living in institutional care, as they are twice as likely to initiate benzodiazepine use, in comparison with persons living in community (Vozoris et al. 2013, Scales et al. 2016).

Among persons with AD, the incidence of BZDR use began to increase one year before the diagnosis. This finding may reflect the treatment of the prodromal symptoms of AD (Apostolova and Cummings 2008, Gallagher et al. 2017). The actual indications for prescribing BZDRs remain unknown as the register-based data did not include this information. However, prodromal symptoms are frequent before the AD diagnosis (Apostolova and Cummings 2008, Gallagher et al. 2017) and the treatment of prodromal symptoms has also been suggested by other studies that found an increasing incidence of antipsychotic and antidepressant use before AD diagnosis (Koponen et al. 2015, Puranen et al. 2017). Therefore, when an older person starts to experience sleep disturbances or disturbances in emotions or behavior, the cause should be investigated thoroughly, and the possibility of an underlying cognitive disorder should be considered (Dubois and Albert 2004, Alzheimer's Disease International 2011). If BZDR use is deemed necessary while a cognitive disorder is suspected, it is important to note that BZDR use might even complicate the recognition of the disorder since these drugs are known to interfere with cognition (Buffett-Jerrott and Stewart 2002) and functioning (Peron et al. 2011).

The incidence of BZDR use among persons with AD was at its highest during the six months following the diagnosis and it remained elevated for at least until three years after the diagnosis. This observation might reflect the treatment of BPSDs (Rabins et al. 2007, Finnish Medical Society Duodecim 2017c). However, antidementia drug treatment is also initiated soon after the diagnosis and most Finnish persons diagnosed with AD are dispensed antidementia

drugs within one year after the diagnosis (Taipale et al. 2014b). Concomitant treatment with BZDRs might complicate the monitoring of efficacy and tolerability of antidementia drug treatment (Finnish Medical Society Duodecim 2017c) because BZDR use impairs cognition (Buffett-Jerrott and Stewart 2002) and functioning (Peron et al. 2011).

It is unlikely that the increasing incidence of BZDR use only results from an increasing frequency or severity of BPSDs initially after the diagnosis: for example, receiving the diagnosis of AD has not been associated with a considerable worsening of anxiety symptoms (Mormont et al. 2014). Instead, the stigma and discrimination associated with cognitive disorders might partially explain the increase in the incidence of BZDR use (Werner and Giveon 2008, Kaduszkiewicz et al. 2008, Jennings et al. 2018). Stigma and discrimination might be reflected in a paternalistic approach to pharmacological treatment and a pessimistic attitude towards treatment of BPSDs. On the other hand, physicians may feel pressurized to prescribe psychotropic drugs due to a perceived lack of feasible alternatives in BPSD treatment (Wood-Mitchell et al. 2008, Jennings et al. 2018). The increase in the incidence before the AD diagnosis may also reflect more frequent healthcare service use, as those individuals may have had fewer healthcare encounters previously due to pre-clinical symptoms. Further research is needed to elucidate the factors accounting for the evident increase in the incidence of BZDR use observed around the AD diagnosis.

One-fifth of the incident BZDR users with AD and one-tenth of those without AD had been recently discharged from hospital in the current study. Hospitalization rates are higher among persons with AD than among those without AD (Tolppanen et al. 2015) and, especially during the six months following the diagnosis, a considerable proportion of persons with AD are hospitalized (Taipale et al. 2016a). As hospitalization increases the risk of initiation of BZDR use by as much as 6.5-fold among older persons (Stuffken et al. 2005, Halme et al. 2013, Steinman et al. 2017), the difference in the initiation of BZDR use after hospital discharge may result from the different hospitalization rates between persons with and without AD.

The prescribing of BZDRs initially after hospital discharge may reflect the treatment of sleep disturbances or other BPSDs during the inpatient stay. In fact, a temporary increase in the prevalence of BZDR use has been observed among older persons during hospital care (Arnold et al. 2017). The frequency and severity of sleep disturbances and other BPSDs might increase during a hospital stay (Sampson et al. 2014) due to a new and confusing environment, non-familiar people, and generally stressful situation (Schnelle et al. 1993, Kales et al. 2015). However, the provision of psychotropic drugs, including benzodiazepines, during an inpatient stay has not been associated with any benefits in relieving BPSDs (Alanen et al. 2015). BZDR use may have been intended for short-term treatment during the inpatient stay in the MEDALZ cohort, but for unknown reasons, the use has continued after discharge.

In addition, the treatment of delirium during the inpatient stay might result in an outpatient prescription of BZDRs (Inouye et al. 2014). Cognitive disorders are the most significant risk factor for developing delirium, and factors such as infections and pain may further increase the risk. Delirium is highly prevalent among hospitalized persons with cognitive disorders (Fick et al. 2002). BZDR use may be initiated for the treatment of delirium, although it is not recommended due to the potential prolongation or worsening of the syndrome (Inouye et al. 2014).

Almost half of the incident BZDR users with AD initiated drug use with intermediate-acting benzodiazepines, while less than one-third of persons without AD initiated with these drugs. Further, the initiation of benzodiazepine-related drugs was more common among persons without AD (65%) than among those with AD (46%). These differences might reflect different indications for BZDR use between these persons. The effects of benzodiazepines are more diverse, including sedative and anxiolytic effects, while benzodiazepine-related drugs are used as hypnotics (Möhler et al. 2002, Gunja 2013). It seems that benzodiazepines are preferred for persons with AD due to their distinctive symptoms. Further, the rare initiation of BZDR use with long-acting benzodiazepines (less than 10% among persons with and without AD) was in

accordance with treatment guidelines (Azermai et al. 2012, Finnish Medical Society Duodecim 2017c, Finnish Medical Society Duodecim 2017b). Intermediate-acting benzodiazepines are recommended over their long-acting counterparts since these drugs carry a lower risk of accumulating (Greenblatt et al. 1991, Hämmerlein et al. 1998).

The median duration of the first BZDR use period among both persons with AD (17 weeks) and persons without AD (13 weeks) was considerably longer than the recommended 2–4 weeks (Rabins et al. 2007, Baldwin et al. 2013, Finnish Medical Society Duodecim 2017c, Finnish Medical Society Duodecim 2017b). Further, the durations of use in Study I were longer than the previously reported mean duration (10 weeks) of benzodiazepine use (Bartlett et al. 2004). Such prolonged use of BZDRs raises concerns because tolerance to the expected sedative effects can develop after two weeks (Dell'Osso and Lader 2013) and dependence can develop after use of 4–6 weeks (Soyka 2017). Further, the efficacy of BZDR use in symptomatic treatment among older persons has not been studied for longer than four weeks (Pinquart and Duberstein 2007, Alessi and Vitiello 2011, Tampi and Tampi 2014).

It is important to acknowledge that non-pharmacological treatment is the first-line option in the treatment of insomnia and other BPSDs (Rabins et al. 2007, Azermai et al. 2012, Finnish Medical Society Duodecim 2017c), whereas memantine and other antidementia drugs are the primary pharmacological options (Finnish Medical Society Duodecim 2017c). Treatment guidelines note that BZDR use might be provided as short-term treatment, but the current results on the duration of the first BZDR use period indicate that the use is prolonged in Finland. Prolonged BZDR use is concerning due to the potentially increased risk of adverse effects (Griffin et al. 2013) and because discontinuation might be challenging (Reeve et al. 2017). In the case of persistent symptoms, non-pharmacological options are feasible and effective (Lenze and Wetherell 2011, Finnish Medical Society Duodecim 2017b, Finnish Medical Society Duodecim 2017c).

6.2 ADVERSE OUTCOMES

6.2.1 Hip fractures (Study II)

In Study II, incident BZDR use was associated with a 40% increased risk of hip fracture among persons with AD, while the corresponding relative risk increase among persons without AD was nearly 60%. There are no previous studies investigating the risk of hip fracture associated with BZDR use among community-dwelling persons with cognitive disorders. The relative risks in persons with and without AD found in Study II were higher than in the previous studies conducted among general older population which have reported an approximately 20% increased risk (Zint et al. 2010, Bakken et al. 2014). This difference may result from somewhat younger study populations and inclusion of prevalent BZDR users, potentially resulting in survival bias, in the previous studies.

As persons with AD represent vulnerable persons with an increased risk of falls when compared to the general older population (Sheridan and Hausdorff 2007), the observation of a similar relative risk increase among persons with and without AD was not expected. However, persons with AD had a higher age-adjusted hip fracture rate also during non-use, in comparison to non-users without AD in Study II. This indicates that persons with AD had higher baseline risk of hip fractures, which has also been observed previously (Tolppanen et al. 2013). Due to the elevated baseline risk caused by AD, the relative risk in comparison to non-use of BZDRs may not increase as much as among persons without AD who have a lower baseline risk and fewer other risk factors for falls and fractures. Further, the heterogeneity in health status may be larger among persons without AD compared to those with AD and that might have also contributed towards a higher risk estimate among persons without AD.

In our study, the risk of hip fracture was doubled during the first 30 days of BZDR use which was in line with a previous report on incident use of benzodiazepines (Wagner et al. 2004).

Here, the associated risk remained elevated until six months of use among persons with AD and until 12 months among those without AD. The lower risk estimates with respect to the longer duration of use in our study may have resulted from a form of survival bias. The follow-up was censored at beginning of long-term hospital or institutional care since we did not have access to data about drugs used in these units. Every fifth person with AD but less than 10% of those without AD were admitted into the long-term hospital or institutional care. Persons who were not institutionalized may represent 'survivors' and they may be in a better state of health than those who were institutionalized. Therefore, no conclusions can be drawn on the long-term effects of BZDR use on the risk of hip fractures on the basis of this study.

In drug group analyses, benzodiazepine use was associated with a 30% increased risk of hip fracture among persons with AD and a 60% increased risk among persons without AD. The difference between persons with and without AD was similar as in the analysis of any BZDR use. Further, the magnitude of the increased risk of hip fracture in this study was similar to findings in the previous studies conducted among a general older population since they found increases of 20–50% (Wang et al. 2001, Wagner et al. 2004) and 70% (Chang et al. 2008) Further, the use of short-to-intermediate-acting benzodiazepines has been associated with a 20–50% (Wagner et al. 2004, Zint et al. 2010, Bakken et al. 2014) or an 80% (Chang et al. 2008) increased risk of a hip fracture. On the other hand, the use of long-acting benzodiazepines was associated with only a 20% increased risk in one study (Bakken et al. 2014). We could not determine separate risk estimates for long-acting drugs because less than 10% of incident BZDR users initiated drug use with long-acting benzodiazepines.

Our estimates for the relative risk increase associated with benzodiazepine-related drug use were somewhat higher (60%) than in the previous study which found a 20% increased risk in a general older population (Bakken et al. 2014). However, zolpidem use has been associated with a risk increase ranging from 60% increase to a 3-fold risk in several other studies (Wang et al. 2001, Finkle et al. 2011, Lin et al. 2014, Tom et al. 2016). Thus, it can be concluded that benzodiazepine-related drug use is associated with an increased risk of hip fracture as well.

The association between an increased hip fracture risk is plausible as BZDR use is a recognized risk factor for falls (Hartikainen et al. 2007, Seppälä et al. 2018). However, confounding by indication can also be present. Among persons with AD, the results might be confounded by BPSDs or by the increasing severity of the disease, as both are risk factors for falls (Fernando et al. 2017). Other cognitive disorders than AD might represent a source for confounding by indication among both persons with and without AD (Tinetti 2003). On the other hand, the analyses were adjusted for several comorbidities, such as cardiovascular diseases, and the use of other psychotropic drugs, which also are risk factors for falling (Tinetti 2003, Bartlett et al. 2009). However, these risk factors may not have been completely captured in the register-based data, and the possibility of residual confounding cannot be excluded. Residual confounding might also result from a lack of information on confounders such as functioning (Schneeweiss and Wang 2005), but this confounding is not likely to completely explain the observed risk increase.

BZDR use at the time of hip fracture was associated with long-term post-hip fracture hospital stay among those persons with AD who survived for ≥4 months after the fracture in Study II. This association might reflect the sedative effects of these drugs and the consequent impairments in muscle strength and balance (Taipale et al. 2011, Taipale et al. 2012). The adverse effects of BZDRs may have a greater impact on persons with AD as they already have impairments in gait, balance, and functioning (Finnish Medical Society Duodecim 2017c, Ries 2018). Therefore, the adverse effects of BZDRs might complicate post-surgery rehabilitation and prolong hospital stay among persons with AD (Finnish Medical Society Duodecim 2017a, Ries 2018). In addition, benzodiazepine use during hospital care has been associated with an increased risk of developing delirium (Clegg and Young 2011), which might also complicate rehabilitation (Morandi et al. 2014). On the other hand, confounding by indication may have

contributed to these results if BZDR users had more challenging BPSDs or more progressed disease stage (Ries 2018, Seematter-Bagnoud et al. 2018).

The results on post-hip fracture mortality contradict those reported in the previous study of Ekstam and Elmståhl (2016). The previous study was suggestive of an increased risk (aOR 1.27, 95% CI 0.99–1.64) of one-year post-fracture mortality associated with benzodiazepine use, while no association was found in Study II. Further studies with exposure information after the hip fracture are needed to clarify this association. Nonetheless, mortality is excessive after hip fracture (Haentjens et al. 2010), and even more elevated among persons with cognitive disorders (Seitz et al. 2014). Both pre-existing comorbidities and post-operative complications contribute to this excessive mortality (Roche et al. 2005). Therefore, having a hip fracture is a major event with regard to mortality, and BZDR use may not exert any additional impact.

Short-term and infrequent use of BZDRs among older persons with or without cognitive disorders has been emphasized in treatment guidelines (Rabins et al. 2007, Baldwin et al. 2013, Finnish Medical Society Duodecim 2017c, Finnish Medical Society Duodecim 2017b). However, the associated risk of hip fracture was at its highest, i.e. doubled, at the beginning of BZDR use. Therefore, it is especially important to consider other factors potentially increasing the risk of falls before initiating BZDR treatment (Finnish Medical Society Duodecim 2017a). In addition to increased age, older persons might have a higher risk of falls due to the use of several drugs, malnutrition, comorbidities such as cardiovascular diseases, reduced muscle strength, poor balance, and the decline in their cognitive abilities (Finnish Medical Society Duodecim 2017a). Assessing the risks and benefits of BZDR use before initiation of treatment and consideration of alternative treatment options is important when treating older persons with or without cognitive disorders.

6.2.2 Mortality (Study III)

A 40% increased risk of death associated with incident BZDR use was observed among persons with AD. This is a novel finding, as previous studies have not found any association between BZDR use and an increased risk of death among a community-dwelling general older population (Gisev et al. 2011, Wauters et al. 2016) or persons with cognitive disorders living in the community or in institutional care (Huybrechts et al. 2011, Brännström et al. 2017). Methodological issues, such as determining exposure only at baseline or comparison with antipsychotic use instead of BZDR non-use, may explain those previous findings. However, among older persons living in institutional care, BZDR use has been associated with an increased risk of death in comparison to antipsychotic use (Huybrechts et al. 2011). The magnitude of the risk increase (28%) was similar as detected here, despite the differences between the study populations and study designs.

The observed increase in the risk of death may result from the other adverse outcomes associated with BZDR use, including falls and consequent injuries (Seppälä et al. 2018), pneumonia (Taipale et al. 2017b), and stroke (Taipale et al. 2017a). These outcomes have been associated with increased mortality among older persons (Kannus et al. 1999, Ingall 2004, Kothe et al. 2008, Haentjens et al. 2010). As these adverse outcomes associated with BZDR use are not restricted to persons with AD (Wagner et al. 2004, Zint et al. 2010, Vozoris et al. 2014), it is plausible that BZDR use would also be associated with an increased risk of death among older persons without cognitive disorders. However, since there was a lack of information about causes of death, the exact mechanisms explaining the observed differences in mortality remain unclear. The increased risk of death might be partly explained by confounding by indication related to prescribing BZDRs to persons with more severe BPSDs or stage of the disease (Peters et al. 2015). Although several methodological approaches were utilized to minimize this confounding, residual confounding might have contributed to the results.

No previous study has investigated the risk of death according to the duration of BZDR use among older persons. We found that the associated risk of death was increased from the initiation of use and remained elevated until 4 months of use. This is in accordance with

previous findings on an elevated risk of falls for at least two months (Neutel et al. 1996), hip fractures for six months (Study II) and adverse respiratory outcomes for 30 days of use (Vozoris et al. 2014, Taipale et al. 2017b). The consequent decrease in the risk estimates after four months may reflect a survival bias and censoring the follow-up at the end of the first BZDR use period. The follow-up was censored before 180 days for most users due to the discontinuation of BZDR use. Those with a follow-up of more than four months might represent users who better tolerate the effects of BZDRs. Future studies with longer follow-up times are needed to investigate the risk of death associated with long-term BZDR use.

One previous study investigating persons with cognitive disorders found an approximately 10% increased risk of death associated with both benzodiazepine use and benzodiazepine-related drug use (Jennum et al. 2015). A higher risk increase, approximately 60%, associated with benzodiazepine use was observed, but no association with benzodiazepine-related drug use. Confounding by indication related to prescribing benzodiazepines to more severe symptoms might partially explain the observed difference. However, both benzodiazepines and benzodiazepine-related drugs exert sedative effects (Möhler et al. 2002, Gunja 2013) and both have been associated with an increased risk of major adverse outcomes in Study II and in other studies (Wang et al. 2001, Taipale et al. 2017a, Seppälä et al. 2018). Therefore, we cannot conclude that benzodiazepine-related drug use would represent a safer choice than benzodiazepine use with regard to risk of death.

These results further highlight the importance of treatment guidelines, stating that non-pharmacological treatments are the first-line option for the treatment of insomnia and other BPSDs, and BZDR use should be limited to the most disturbing symptoms (Rabins et al. 2007, Wang et al. 2014, Finnish Medical Society Duodecim 2017c). It is important to assess thoroughly potential risk factors for adverse outcomes before initiating the use of these drugs as the increased risk of death might be mediated by various outcomes. Further, if BZDR use is necessary, it is essential to plan early discontinuation strategies to prevent the emergence of adverse outcomes and prolongation of use.

6.3 STRENGTHS AND LIMITATIONS

6.3.1 Data sources

The main strength of this thesis was the utilization of the nationwide MEDALZ cohort. The cohort consisted of all persons who received a clinically verified diagnosis of AD, required for the entitlement to reimbursement of antidementia drugs, in Finland during 2005–2011. Various data were obtained from several decades and, due to the systematic data collection, complete follow-up was available for all persons in the cohort. Further, as the cohort was nationwide, there was no selection bias related to the socioeconomic position (Tolppanen et al. 2016). In addition to persons with AD, the cohort included up to four matched persons without AD for each person with AD (Taipale et al. 2014a).

AD diagnoses obtained from the Special Reimbursement Register were correct in 97% of cases (Solomon et al. 2014) due to a thorough assessment of the underlying pathology and clinical symptoms required for the special reimbursement (Finnish Medical Society Duodecim 2017c). However, the validation study may have captured some AD cases earlier than they would have been diagnosed in clinical practice as careful clinical examinations were performed (Solomon et al. 2014). Persons were diagnosed with AD at the mild or moderate stage of the disease, but the reimbursement for antidementia drugs was not withdrawn as the disease progressed (Tolppanen et al. 2016). Persons with AD could have other cognitive disorders as well, but they could not be accounted for.

The sensitivity of the AD diagnoses obtained from the Special Reimbursement Register is 64% (Solomon et al. 2014). This may indicate that all persons with very mild or mild AD pathology had not received the special reimbursement, although all antidementia drugs were

reimbursed only after receiving the right to special reimbursement (Virta 2013). Further, fulfilment of the special reimbursement criteria was not considered in the validation study (Solomon et al. 2014) and thus all persons diagnosed with AD in the careful clinical examinations may have not been eligible for the special reimbursement. This potentially decreased the sensitivity estimate. Although the mildest cases of AD were not eligible for the special reimbursement for antidementia drugs, they could enter the MEDALZ cohort after disease progression. In addition, the diagnostic process for the special reimbursement may have been prolonged in some cases. To account for these uncertainties, the matched persons without AD could not receive the special reimbursement or have antidementia drug purchases for 12 months after matching (Taipale et al. 2014a). The additional analyses conducted in this thesis indicated that, after excluding prevalent BZDR users, 8,771 (6.2%) persons without AD were diagnosed with AD by 31 December 2012. As this is a relatively small group of persons, the potential impact of, for example, delayed diagnostic process on the results in Studies I and II would have been small.

Valid information on hip fractures (Sund et al. 2007) and BZDR purchases (Rikala et al. 2010) were obtained from registers. The diagnoses obtained from the Hospital Discharge Register and the Special Reimbursement Register cover a variety of conditions (Tolppanen et al. 2016). The diagnoses obtained from the Hospital Discharge Register represented hospitalizations due to certain conditions whereas the diagnoses obtained from the Special Reimbursement Register included also diagnoses in the outpatient setting but in general, this register does not include the mildest cases.

6.3.2 Drug exposure

The time-dependent BZDR exposure was modelled with the PRE2DUP method from reimbursed drug purchases. This method avoids the pitfalls related with simplistic assumptions on drug use patterns by considering individual purchase patterns, hospital stays, stockpiling of drugs and, if necessary, the purchase pattern in the whole cohort (Tanskanen et al. 2015). Consideration of individual patterns of BZDR use is especially important in an older population because the dosage varies considerably between persons (Rikala et al. 2013). Therefore, PRE2DUP provides more accurate information on drug use periods compared with many other frequently used modeling methods (Tanskanen et al. 2017). The appropriateness of the utilized doses could not be studied from this register-based data.

The PRE2DUP method estimates BZDR use with good validity as the Cohen's kappa value was 0.70 (Taipale et al. 2016b). The modeling method identified 71% of BZDR use reported in interviews in the validation study, indicating that the method may not always capture infrequent use. On the other hand, the BZDR use periods modelled with the PRE2DUP were found in the interview data in 89% of cases. This may result from some overestimation of drug use by the PRE2DUP method, or due to discontinuation of use or non-reporting of drug use in the interviews. However, the overestimation concerns only 10% of cases. Therefore, misclassification of BZDR exposure due to an underestimation of drug exposure is the main reason why the kappa value could not be categorized as 'very good'. The investigation of infrequent drug exposure, for example by the use of only 1–3 tablets a week, is practically impossible in pure register-based studies as actual timing and frequency of drug use is not recorded in the administrative data.

In addition to infrequent drug use, BZDR exposure may have been underestimated also because all BZDR drugs and the smallest packages were not reimbursed and thus not included in the Prescription Register data. This may have led to a minor underestimation of the risk estimates and misclassification of non-users. However, it is much more likely that physicians have a preference to prescribe reimbursed packages to avoid extra costs to the patients. In addition, the consumption of the BZDRs excluded from this thesis (midazolam, triazolam, and zaleplon) is minimal in Finland (Finnish Medicines Agency and Social Insurance Institution 2017). Another source for misclassification of BZDR use in this thesis is drug use during

hospital or institutional care (Palmaro et al. 2017). The impact of this misclassification was decreased by censoring the follow-up to the beginning of long-term (≥90 days) hospital or institutional stay.

The application of the PRE2DUP for purchases since 1995 enabled exclusion of prevalent BZDR users from all analyses. Despite utilizing a washout period of one year, it is possible that all prevalent BZDRs users could not be excluded due to the potential underestimation of BZDR use resulting from infrequent use. However, this concerns only those persons who purchased BZDRs before the washout period and who did not have any purchases during the washout period, i.e. only a limited number of persons.

When investigating the incidence of BZDR use, the timing of drug use initiation may have been misclassified if the drug use was initiated with a small, non-reimbursed package. However, these users would have been included in the study with a delay if they continued BZDR use with a larger, reimbursed package. Therefore, it seems likely that this potential misclassification may have led to only a small underestimation of the incidence of BZDR use. Further, the time before AD diagnosis represents immortal time as the persons had to be alive on the AD diagnosis date. This may have lead to a minor bias in the results on BZDR incidence before AD diagnosis, because persons who were eligible for special reimbursement of antidementia drugs but who died before receiving the diagnosis could not be included.

The new user design (Ray 2003) was utilized in Studies II and III. The risk estimates in Study II were somewhat higher than in the previous studies investigating risk of hip fracture associated with BZDR use, highlighting the importance of minimizing the survival bias. The analyses were censored at discontinuation of the first BZDR use period to further minimize the impact of any survival bias related to re-initiation of drug use later. Additionally, in the sub-analyses, the follow-up was censored at the initiation of concomitant use of benzodiazepines and benzodiazepine-related drugs because adding another drug in the treatment indicates tolerance to BZDR use. Restriction of the analyses on new users and only the first drug use periods reduced the data available for analyses. Therefore, the number of persons using ≥2 BZDRs concomitantly or long-acting benzodiazepines was too small to permit any outcome analyses. The associated risk of hip fracture was investigated with a five-year follow-up and the risk of death with a six-month follow-up, and no conclusions can be drawn on the associations in longer time periods.

Time-dependent BZDR exposure was utilized in Study II (main analyses) and Study III to minimize exposure misclassification bias (Ray et al. 2002, Stricker and Stijnen 2010). The ITT approach, utilized in several other cohort studies (Ensrud et al. 2003, Finkle et al. 2011, Gisev et al. 2011, Jaussent et al. 2013, Jennum et al. 2015, Wauters et al. 2016, Patorno et al. 2017, Brännström et al. 2017) is susceptible to exposure misclassification bias (Ray et al. 2002). The utilization of time-dependent drug exposure contributed to the higher risk estimates in comparison to several previous studies. However, as a result of the potential underestimation of BZDR use, the risk of adverse outcomes may have been underestimated as well, if some outcomes occurred in fact during BZDR use instead of non-use. The ITT approach was utilized in secondary analyses in Study II because BZDR use during the hospital care after hip fracture was not recorded in the registers. Further, in Study III, the ITT approach was utilized to measure the impact of informative censoring (Schneeweiss 2010) and this did not change the results. Therefore, it seems that BZDR use was not discontinued purposely due to signs of approaching death and, additionally, BZDR users were not hospitalized initially before death within this study.

6.3.3 Confounding

Confounding results from systematic differences, in addition to the exposure status, between the exposed and unexposed persons (Psaty et al. 1999). A confounder is associated with both the exposure and the outcome, and an inability to account for the confounder results in biased observations. The indication for drug use is an important confounder in

pharmacoepidemiological research, because the symptom or disease being treated might also affect the risk of the outcome. The resulting confounding is referred to as confounding by indication.

Data in the nationwide registers have been collected for administrative purposes and therefore, they lack some important information about confounders. As in all other register-based studies, confounding by indication could not be completely ruled out in Studies II and III. An inability to account for the reasons for BZDR use might have resulted in biased risk estimates in Studies II and III. In fact, certain BPSDs, including symptoms of anxiety, have been associated with an increased risk of falls (Fernando et al. 2017). Further, symptom clusters of agitation/aggression and depression/anxiety/irritability and also sleep disturbances have been associated with an increased risk of death (Peters et al. 2015, Spalletta et al. 2015) among persons with cognitive disorders. Therefore, the results obtained in Studies II and III might be overestimated due to confounding by indication.

Several methodological approaches (Psaty et al. 1999) were utilized to minimize the impact of confounding in Studies II and III. With regard to confounding by indication, the use of psychotropic drugs was included in the multivariable analyses as they can be considered as proxies of symptoms for which BZDR use might be prescribed. Additionally, the concomitant use of BZDRs and other psychotropic drugs was accounted for in the sensitivity analyses performed in Study II (Abbing-Karahagopian et al. 2015). Confounding was minimized also by including age and gender in the multivariable analyses in Study II and as matching criteria, in addition to time since AD diagnosis, in Study III. Further, differences in comorbid conditions and socioeconomic position were taken into account in the multivariable analyses.

The severity of the disease was also a potential confounder in Studies II and III (Lönnroos et al. 2013, Fernando et al. 2017). In the sensitivity analyses conducted in Study III, the investigated persons were stratified according to time since AD diagnosis. As the progression of the disease process varies extensively between individuals, the time since the AD diagnosis could be utilized as a crude proxy of disease progression. The results were not changed, implying that the risk increase was not dependent on this proxy of disease progression. The other studies investigating the risk of death associated with BZDR use among persons with cognitive disorders did not account for the stage of the cognitive disorder or the progression of the disorder (Huybrechts et al. 2011, Jennum et al. 2015, Brännström et al. 2017). Information about the place of death was not available in the MEDALZ cohort. Less than 10% of Finnish persons with cognitive disorders die at home (Masuchi et al. 2018), and transitions between health care settings increase as death approaches (Aaltonen et al. 2017). As the follow-up was censored at the beginning of long-term hospitalization or at admission to long-term institutional care, a considerable proportion of persons in the need of the most demanding care were excluded. This reduced the potential for confounding by indication related to disease severity in this study. However, the study included persons living in intensive residential care.

7 Conclusions

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

1. There was a considerable increase in the incidence of benzodiazepine and related drug use around the time of the diagnosis of Alzheimer's disease when compared to persons without Alzheimer's disease. This increase might imply that these drugs are prescribed in the treatment of prodromal symptoms of Alzheimer's disease as well as behavioral and psychological symptoms of dementia.

2. Benzodiazepine and related drug use was associated with an increased risk of hip fracture among persons with and without Alzheimer's disease. The risk increase was highest at the initiation of the use of these drugs. These results do not support even short-term benzodiazepine and related drug use in the symptomatic treatment of AD which has been mentioned in several treatment guidelines.

3. Benzodiazepine and related drug use was associated with an increased risk of death among persons with Alzheimer's disease. The associated risk was elevated starting from the initiation of use. The increased mortality might result from consequences of other associated severe outcomes.

4. The results related to the risk of adverse outcomes are generalizable to community-dwelling persons with AD and the general older population. Nonetheless, the incidence of BZDR use might vary between countries due to differences in care practices, health care systems, and costs.

8 Implications

8.1 CLINICAL PRACTICE

1. Contrary to the treatment guidelines on the behavioral and psychological symptoms of dementia, even short-term use of benzodiazepines and related drugs should be avoided whenever possible because the risks of hip fracture and death were considerable, starting from the initiation of use.

2. If treatment with benzodiazepines and related drugs seems necessary, it is essential to carefully assess the potential benefits and risks, such as the risk factors for falling, before initiating the treatment.

3. The observed risks of severe adverse outcomes highlight the importance of non-pharmacological treatment options. These approaches are the first-line treatment for behavioral and psychological symptoms of dementia as well as for sleep disturbances in the general older population. It is important to first utilize non-pharmacological treatment options in order to reduce unnecessary benzodiazepine and related drug use among older persons.

4. When new disturbances related to emotions, behavior, or sleep emerge in an older person, the possibility of an underlying cognitive disorder should be considered.

8.2 FUTURE RESEARCH

1. Factors accounting for the increase in the incidence of benzodiazepine and related drug use at the time of diagnosis of Alzheimer's disease should be assessed in future studies.

2. More studies will be needed to establish whether there is a risk of death associated with benzodiazepine and related drug use among older persons with or without Alzheimer's disease.

3. The risk of hip fracture associated with the concomitant use of ≥2 benzodiazepines and related drugs as well as the risk associated with the use of different dosages should be investigated with larger datasets.

4. Potential causes of death associated with benzodiazepine and related drug use are an important topic for further research among persons with Alzheimer's disease.

5. Further research will be needed to clarify the association between benzodiazepine and related drug use and prolonged hospital stay after a hip fracture.

6. It will be important to conduct clinical studies to investigate whether benzodiazepine and related drug use has any impairing effects on rehabilitation outcomes after hip fracture among persons with Alzheimer's disease.

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LAURA SAARELAINEN

Benzodiazepines and related drugs are used in treatment of behavioral and psychological symptoms of dementia. This thesis examined the incidence of benzodiazepine and related drug use in a nationwide sample of persons with Alzheimer's disease and compared it with the incidence among matched comparison persons without the disease. The risk of hip fracture and death associated with the use of these drugs was also investigated.

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