SANNA TORVINEN-KIISKINEN

This register-based thesis was based on nationwide MEDALZ-cohorts including persons with Alzheimer's disease and their comparison persons. Thesis determined the prevalence and duration of concomitant use of acetylcholinesterase inhibitors and urinary antispasmodics. Furthermore, the risk of hip fracture associated with antidepressant, or proton pump inhibitor, use was investigated. The prevalence of use of these drugs before and after Alzheimer's diagnosis was also examined.
Risks Associated with Urinary Antispasmodics, Antidepressants and Proton Pump Inhibitors

The Medication Use and Alzheimer’s Disease Study
SANNA TORVINEN-KIISKINEN

Risks Associated with Urinary Antispasmodics, Antidepressants and Proton Pump Inhibitors

The Medication Use and Alzheimer’s Disease Study

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ABSTRACT

Alzheimer’s disease (AD) causes cognitive and non-cognitive symptoms, which are treated with a variety of drugs. These symptoms include not only disturbances in memory but also the behavioral and psychological symptoms of dementia as well as urinary incontinence. The pharmacotherapies for some of those symptoms, however, are associated with adverse events among older persons and persons with AD.

The aims of this thesis were to investigate I) the prevalence and duration of concomitant use of acetylcholine esterase inhibitors (AChEIs) and urinary antispasmodics (UAs) among persons with AD, II) the association between antidepressant use and hip fracture among persons with and without AD and III) the association between long-term and cumulative use of proton pump inhibitors (PPIs) and the risk of hip fracture among persons with AD. In addition, the prevalence of use of UAs, antidepressants and PPIs was investigated from three years before until three years after the diagnosis of AD.

The studies examined in this thesis are based on nationwide register-based MEDALZ-2005 and MEDALZ-cohorts, which include Finnish community-dwelling persons with AD identified from the Special Reimbursement Register (with persons diagnosed until December 31, 2005, N=28,093; and during 2005–2011, N=70,718; respectively) and their matched comparison persons without AD. Drug use periods were modelled from Prescription Register data by the PRE2DUP method. Hip fractures were identified from the Hospital Discharge Register. The studies were conducted with either cohort (studies I and II) or nested case-control (study III) designs.

The concomitant use of AChEIs and UAs was 7.3%, with the median duration of concomitant use being 7.9 months among persons with AD. Antidepressant use was associated with an increased risk of hip fracture among those with AD as well as in the persons without AD (adjusted HR 1.61, 95% CI 1.45–1.80 and 2.71, 2.35–3.14, respectively) as compared with nonuse of these drugs. No association was found between long-term (≥1 year) PPI use and the risk of hip fracture (adjusted OR 1.00; 95% CI 0.89–1.13). Short-term (<1 year) current PPI use was associated with an increased risk of hip fracture (adjusted OR 1.23; 95% CI 1.10–1.37) among persons with AD. The prevalence of antidepressant and PPI use, but not UA use, clearly increased after the diagnosis of AD in comparison to the time before the diagnosis.

In conclusion, persons with AD are susceptible to pharmacodynamic drug interactions and antidepressant users have an increased risk for suffering a hip fracture. The prescribing of UAs or antidepressants should be carefully considered in older persons, furthermore overall pharmacotherapy should be assessed on a regular basis.

National Library of Medicine Classification: QV 37.5, QV 77.5, QV 124, QV 132, WE 855, WT 155
Medical Subject Headings: Alzheimer Disease; Dementia; Antidepressive Agents; Drug Interactions; Parasympatholytics; Muscarinic Antagonists; Urological Agents; Cholinesterase Inhibitors; Proton Pump Inhibitors; Risk; Hip Fractures; Cohort Studies; Longitudinal Studies; Follow-Up Studies; Case-Control Studies; Pharmacoepidemiology; Drug Utilization; Registries; Finland
Alzheimerin tauti (AT) aiheuttaa kognitiivisia ja ei-kognitiivisia oireita, joiden hoitoon voidaan käyttää oireenmukaisia lääkeita. Näitä oireita ovat esimerkiksi dementiaan liittyvät tunne-elämän ja käytäntymisen oireet sekä virtsankarkailu. Oireenmukainen lääkehoito voi kuitenkin olla yhteydessä moniin haittatapauksiin.


AKE-lääkkeiden ja virtsatieantikolinenergian yhtäaikaista käyttöä esiintyi 7,3 %:lla AT:a sairastavilla, ja yhteiskäytön keston mediaani oli 7,9 kuukautta. Masennuslääkkeiden käyttö oli yhteydessä kohonneeseen lonkkamurtumariskiin sekä AT:a sairastavilla [vakioitu HR 1,61, 95 % luottamusväli (LV) 1,45–1,80], että vertailuhenkilöillä (vakioitu HR 2,71, 95 % LV 2,35–3,14). Pitkäaikaisen PPI-lääkekäytön (≥1 vuota), ja lonkkamurtumariskin välillä ei havaittu yhteyttä (vakioitu OR 1,00; 95 % LV 0,89–1,13), mutta alle 1 vuoden käyttö oli yhteydessä kohonneeseen lonkkamurtumariskiin (vakioitu OR 1,23; 95 % LV 1,10–1,37) AT:a sairastavilla. Masennus- ja PPI-lääkkeiden, muttei virtsatieantikolinenergian, käyttö lisäntyi selkeästi AT-diagnoosin jälkeen verrattuna aikaan ennen diagnoosia.

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This thesis was conducted in the School of Pharmacy, University of Eastern Finland, Kuopio, during 2014-2019. I am thankful for the financial support that I received from the University of Eastern Finland, the Finnish Cultural Foundation and the Olvi Foundation. I also want to thank the Finnish Pharmacists’ Association for a travel grant and a grant for printing this thesis.

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Lieksa, February 2019

Sanna Torvinen-Kiiskinen
List of the original publications

This dissertation is based on the following original publications:


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Contents

1 INTRODUCTION 1

2 REVIEW OF THE LITERATURE 2
  2.1 Alzheimer’s disease ................................................................. 2
     2.1.1 Behavioral and psychological symptoms of dementia .................. 4
     2.1.2 Urinary incontinence ......................................................... 5
  2.2 Hip fractures ................................................................. 6
  2.3 Urinary antispasmodics .......................................................... 8
     2.3.1 Concomitant use of acetylcholine esterase inhibitors and urinary antispasmodics ................................................. 9
  2.4 Antidepressants ........................................................................ 12
     2.4.1 Risk of hip fracture associated with antidepressant use .......... 13
  2.5 Proton pump inhibitors .......................................................... 17
     2.5.1 Risk of hip fracture associated with proton pump inhibitor use .... 18

3 AIMS OF THE STUDY 24

4 MATERIALS AND METHODS 25
  4.1 Study cohorts and data sources .................................................... 25
     4.1.1 Diagnostic criteria of Alzheimer’s disease ................................. 25
     4.1.2 MEDALZ-2005 (Study I) ......................................................... 25
     4.1.3 MEDALZ (Studies II and III) .................................................. 25
  4.2 Drug exposure ........................................................................... 28
     4.2.1 Modelling of drug use; PRE2DUP ........................................... 28
     4.2.2 Definition of the exposure in studies I-III ................................. 29
  4.3 Outcome measures .................................................................... 32
     4.3.1 Pharmacodynamic drug interaction (Study I) ............................ 32
     4.3.2 Hip fracture (Studies II and III) ................................................ 32
  4.4 Study designs ........................................................................... 32
     4.4.1 Descriptive cohort (Study I) .................................................... 32
     4.4.2 Cohort study (Study II) .......................................................... 33
     4.4.3 Nested case-control study (Study III) ....................................... 33
  4.5 Covariates ............................................................................... 34
  4.6 Statistical analyses ..................................................................... 38
  4.7 Ethical considerations and data protection ................................. 39
5 RESULTS

5.1 Concomitant use of acetylcholine esterase inhibitors and urinary antispasmodics (Study I)

5.2 Association between antidepressant use and risk of hip fracture among persons with and without Alzheimer’s disease (Study II)

5.3 Association between proton pump inhibitor use and risk of hip fracture among persons with Alzheimer’s disease (Study III)

5.4 Prevalence of urinary antispasmodics, antidepressants and proton pump inhibitors use before and after Alzheimer’s disease diagnosis

6 DISCUSSION

6.1 Discussion of results

6.1.1 Concomitant use of acetylcholine esterase inhibitors and urinary antispasmodics (Study I)

6.1.2 Antidepressant use and risk of hip fracture (Study II)

6.1.3 Proton pump inhibitor use and risk of hip fracture (Study III)

6.1.4 Prevalence of urinary antispasmodics, antidepressants and proton pump inhibitors use before and after Alzheimer’s disease diagnosis

6.2 Methodological considerations

7 CONCLUSIONS

8 IMPLICATIONS

8.1 Clinical implications

8.2 Suggestions for future research

9 REFERENCES

APPENDICES Original publications (I-III)
## Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AChEi</td>
<td>Acetylcholine esterase inhibitor</td>
</tr>
<tr>
<td>AD</td>
<td>Alzheimer’s disease</td>
</tr>
<tr>
<td>ATC</td>
<td>Anatomical Therapeutic Chemical</td>
</tr>
<tr>
<td>BPH</td>
<td>Benign prostatic hyperplasia</td>
</tr>
<tr>
<td>BPSD</td>
<td>Behavioral and psychological symptoms of dementia</td>
</tr>
<tr>
<td>BZDR</td>
<td>Benzodiazepines and related drugs</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence Interval</td>
</tr>
<tr>
<td>DDD</td>
<td>Defined Daily Dose</td>
</tr>
<tr>
<td>DSM-IV</td>
<td>Diagnostic and Statistical Manual of Mental Disorders, 4th edition</td>
</tr>
<tr>
<td>HR</td>
<td>Hazard Ratio</td>
</tr>
<tr>
<td>ICD</td>
<td>International Classification of Diseases</td>
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<tr>
<td>IQR</td>
<td>Interquartile range</td>
</tr>
<tr>
<td>MCI</td>
<td>Mild cognitive impairment</td>
</tr>
<tr>
<td>MEDALZ</td>
<td>Medication use and Alzheimer’s disease</td>
</tr>
<tr>
<td>NINCDS-ADRDA</td>
<td>National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association</td>
</tr>
<tr>
<td>OR</td>
<td>Odds ratio</td>
</tr>
<tr>
<td>OTC</td>
<td>Over the counter</td>
</tr>
<tr>
<td>PPI</td>
<td>Proton pump inhibitor</td>
</tr>
<tr>
<td>PRE2DUP</td>
<td>Prescriptions to drug use periods</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized controlled trial</td>
</tr>
<tr>
<td>SII</td>
<td>Finnish Social Insurance Institution</td>
</tr>
<tr>
<td>SNRI</td>
<td>Serotonin and noradrenaline reuptake inhibitor</td>
</tr>
<tr>
<td>SSRI</td>
<td>Selective serotonin reuptake inhibitor</td>
</tr>
<tr>
<td>THL</td>
<td>Finnish National Institute of Health and Welfare</td>
</tr>
<tr>
<td>UA</td>
<td>Urinary antispasmodics</td>
</tr>
<tr>
<td>UI</td>
<td>Urinary incontinence</td>
</tr>
<tr>
<td>WO</td>
<td>Washout period</td>
</tr>
</tbody>
</table>
1 Introduction

Alzheimer’s disease (AD) is commonly thought of as a disease characterized by cognitive symptoms. However, the disease also causes non-cognitive symptoms, such as behavioral and psychological symptoms of dementia (BPSD), mobility and balance problems, and urinary incontinence, and these symptoms can even dominate the symptom profile of AD (Memory disorders: Current Care Guideline 2017). Many persons with AD have also comorbid conditions and frequently are treated by drugs (Tolppanen et al. 2016a), although these drugs may cause adverse effects and drug interactions in these subjects.

Urinary incontinence may be an independent symptom, a symptom caused by AD or an adverse effect of acetylcholine esterase inhibitors (AChEIs) (Hashimoto et al. 2000, Hägglund 2010, Lampela et al. 2016). The pharmacotherapy of urinary incontinence has traditionally involved administration of anticholinergic urinary antispasmodics (UAs). However, these drugs have actions which are opposite to the AChEIs, the first-line antidementia drugs, and this can lead to a failure of the AChEI treatment.

BPSDs, such as aggression, agitation, apathy, depression, sleep disturbances and a variety of inappropriate behaviors, occur in nearly all persons with cognitive disorders at some point of the disease course (Kales et al. 2015, Memory disorders: Current Care Guideline 2017, Lyketsos et al. 2011). BPSDs may be treated with psychotropic agents including antidepressants. These are drugs which have been associated with several adverse events, such as an increased risk of injurious falls among older persons (Oderda et al. 2012).

Proton pump inhibitors (PPIs) are drugs for gastric acid-related diseases (Shi and Klotz 2008). Because of their gastro-protective properties, they are often co-prescribed with gastro-irritating drugs, such as non-steroidal anti-inflammatory drugs (NSAIDs), low-dose aspirin and oral corticosteroids (Lanza et al. 2009, Munson et al. 2012, Masclee et al. 2014, Juntunen et al. 2017). In previous studies examining the general older population, PPI use has been associated with increased risks of untoward events, such as pneumonia, infections and fractures (Leonard et al. 2007, Eom et al. 2011, Zhou et al. 2016).

Persons with cognitive disorders such as AD are often excluded from randomized controlled trials (RCTs) and thus it is important to assess the safety and effectiveness of pharmacotherapy in this vulnerable population (Hilmer et al. 2012). All of the above mentioned symptomatic pharmacotherapies are commonly used among persons with AD; for this reason, new information about risks of these therapies are urgently needed. This is important also from a public health perspective as the number of persons with AD or other dementias is increasing all around the world (Prince et al. 2016).

The extensive, nationwide register-based MEDALZ-2005 and MEDALZ cohorts (Tolppanen et al. 2013b, Tolppanen et al. 2016a) utilized in this thesis provide a unique opportunity to gather novel information on the risks associated with pharmacotherapies in persons with clinically verified diagnosis of AD, and their matched comparison persons. Due to the predefined criteria for AD diagnoses and nationwide coverage, the samples are representative and the results are generalizable to Finnish community-dwelling persons with AD. The findings can be utilized in medication assessments or for updating the care guidelines, especially those targeting persons with AD.
2 Review of the Literature

2.1 ALZHEIMER’S DISEASE

Alzheimer’s disease (AD) is a progressive neurodegenerative disease; it is the most common cause of dementia (accounts for approximately 60-80% of dementia cases) (Alzheimer’s Association 2016). Age is the greatest single risk factor for AD and thus the global prevalence of the disease is increasing due to aging of populations. The World Alzheimer report estimated that there were 46.8 million people living with dementia in 2015 and this number will reach 131.5 million in 2050 (Prince et al. 2016). In Finland, the overall incidence of cognitive disorders is estimated to be 14,500 persons every year (Memory disorders: Current Care Guideline 2017). It has been calculated that over 190,000 persons suffer from the early, moderate or severe stages of a cognitive disorder (National Institute of Health and Welfare 2018). Less than 5% of persons aged 65-75 years have the moderate to severe stage of cognitive disorder, approximately 10% of those aged 75-84 years, but every third person aged 85 years or over is affected either moderately or severely. Cognitive disorders of mixed pathology are common, especially among the oldest persons (Memory disorders: Current Care Guideline 2017).

Other known risk factors for AD are family history, cardiovascular diseases, carrying the ε4 allele form of the APOE gene, low education, and traumatic brain injury (Loy et al. 2014, Alzheimer’s Association 2016, Li et al. 2017). However, despite intensive research efforts, the etiological reasons behind the manifestation of AD remains unclear.

The pathological brain processes that characterize AD are believed to start several years or even decades before the appearance of any symptoms (Villemagne et al. 2013). There are some typical pathological changes observed in AD i.e. abnormal protein deposits, β-amyloid plaques and neuro-fibrillary tangles formed by hyperphosphorylated tau (Jack et al. 2010). Neurodegeneration manifests in several ways i.e. neuron loss, atrophy of brain tissue, and gliosis. The loss of synapses is significant for the clinical progression of AD. Acetylcholine is an important neurotransmitter for cognition and its levels decline in persons with AD due to a loss of cholinergic neurons (Martorana et al. 2010). Thus, current first-line pharmacotherapy of AD strives to elevate the concentration of acetylcholine by inhibiting the activity of its degrading enzyme, acetylcholine esterase.

According to the updated diagnostic criteria, there is mild cognitive impairment (MCI) which is characterized by changes differing from normal ageing (Albert et al. 2011). A person with MCI usually manages well in everyday living but may experience problems with the most complex tasks (Albert et al. 2011, Sanford 2017). Neuropsychiatric symptoms such as apathy, anxiety and depression, are common among persons with MCI, as most of these persons exhibit at least one of these symptoms (Apostolova and Cummings 2008). However, at the stage of MCI, the criteria for diagnosing a dementing disease are not met, and all persons with MCI do not inevitably develop AD (Petersen et al. 1997).

The progression of AD is typically divided into three stages: mild, moderate, and severe (Memory disorders: Current Care Guideline 2017). AD is a disease which causes many symptoms, including a decline of episodic memory, a difficulty to learn new skills, a decline of performance in daily living, communication problems and changes in mood and personality (Alzheimer’s Association 2016). As the disease is progressive, symptoms of the disease tend to gradually worsen with time. In the mild stage of AD, the disease’s impact on daily living presents as difficulties in managing money, taking care of medication and spatial orientation. Cognitive deficits lead to difficulties in problem solving, and finding words due to aphasia. In moderate AD, instrumental activities of daily living such as cooking or shopping become problematic, and the person needs to be reminded about
activities on daily living, such as bathing or dressing. In severe AD, assistance is needed in all aspects of daily living accompanied by an inability to communicate due to severe aphasia and agnosia. A person with severe AD is disoriented with respect to time and place. However, there are large variations in frequency, timing and severity of symptoms between individuals and it is impossible to draw a definite line between the different stages (Albert et al. 2011, McKhann et al. 2011). The most common symptoms of MCI and different stages of AD are described in Figure 1. BPSDs will be described in more detail in chapter 2.1.1.

<table>
<thead>
<tr>
<th>Mild cognitive impairment</th>
<th>Mild Alzheimer’s disease</th>
<th>Moderate Alzheimer’s disease</th>
<th>Severe Alzheimer’s disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Mild changes in cognition</td>
<td>• Moderate memory loss</td>
<td>• Severe memory loss</td>
<td>• Severe memory loss</td>
</tr>
<tr>
<td>• Problems with complex tasks, which have been performed previously</td>
<td>• Difficulties in planning and problem solving</td>
<td>• Aphasia</td>
<td>• Severe aphasia</td>
</tr>
<tr>
<td>• Apathy, depression, anxiety and irritability</td>
<td>• Difficulties in complex tasks</td>
<td>• Misplacing items</td>
<td>• Agnosia</td>
</tr>
<tr>
<td></td>
<td>• Difficulties in taking care of medication or money</td>
<td>• Getting lost in familiar places</td>
<td>• Apraxia</td>
</tr>
<tr>
<td></td>
<td>• BPSP such as apathy, anxiety, isolation and depression</td>
<td>• Difficulties to dress/undress or cook</td>
<td>• Disability to concentrate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• BPSP such as wandering, sleep disturbances, delusions, hallucinations depression and apathy</td>
<td>• Activities in daily living cannot be managed without assistance</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Urinary Incontinence</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• BPSP such as agitation, aggression and apathy</td>
</tr>
</tbody>
</table>

*Figure 1. The most common symptoms of mild cognitive impairment and Alzheimer’s disease at different stages of the disease. BPSD=behavioral and psychological symptoms of dementia. Adapted from Memory disorders: Current Care Guideline 2017, Apostolova and Cummings 2008 and Lyketsos et al. 2011*

**Pharmacotherapy of AD**

The currently available drugs are unable to prevent or even slow the progression of AD. As stated, the following AChEIs are the first-line pharmacotherapy of AD; donepezil, galantamine or rivastigmine (Memory disorders: Current Care Guideline 2017). Their use is associated with an improvement in activities in daily living and a reduction in BPSDs, as well as delay in the need for nursing home admission (Standridge 2004, Lopez et al. 2009). The Finnish Current Care Guideline on cognitive disorders recommends AChEI treatment for all patients suffering from mild or moderate stage of AD, if there is no contraindication for treatment (Memory disorders: Current Care Guideline 2017).

Another pharmacological option is memantine, which acts by partially antagonizing the glutamate N-methyl-D-aspartate (NMDA) receptors and thus blocking the neural toxicity associated with prolonged glutamate release (Danysz et al. 2000, Standridge 2004). Memantine exerts small beneficial effects on cognition, activities in daily living and behavior in moderate and severe stage of AD (McShane et al. 2006). It can be combined with AChEI in moderate to severe stage of AD or used as the first-line therapy if there is a contraindication for AChEI use (Memory disorders: Current Care Guideline 2017). The combination of AChEI and memantine has been reported to delay nursing home admission for a longer time when compared to AChEI monotherapy (Lopez et al. 2009).
2.1.1 Behavioral and psychological symptoms of dementia

BPSDs include symptoms of aggression, agitation, apathy, depression, repetitive questioning, psychosis, sleep disturbances, wandering, and a variety of inappropriate behaviors (Kales et al. 2015). Symptoms vary between patients and stage of the disease, but nearly all people with cognitive disorders experience one or more of these symptoms during the course of their disease (Memory disorders: Current Care Guideline 2017, Lyketsos et al. 2011). BPSDs are associated with adverse health outcomes, such as prolonged duration of hospital stays and early admission to institutional care (Yaffe et al. 2002, Wancata et al. 2003, Kales et al. 2005). Moreover, BPSD are a great burden to caregivers causing stress and depression in these persons (Clyburn et al. 2000, Kales et al. 2015).

In MCI and the early stage of AD, the most frequent BPSDs are depression and apathy, while verbal and physical agitation is common during all stages of MCI and AD (Lyketsos et al. 2011). Apathy is the most common BPSD throughout the whole course of the disease and it tends to worsen over time. As the disease progresses, episodically manifested delusions, hallucinations, and aggression become more common.

There are several factors increasing the risk of BPSDs (Kales et al. 2015). Factors related to the patient and the disease include neurobiological factors, acute or chronic medical illnesses or symptoms (for example, urinary tract infections or pain) and unmet needs (such as hunger or thirst). Thus, good care of comorbid diseases and symptoms is essential in the treatment of BPSD. Caregiver related factors behind BPSD include communication problems and stress, whereas environmental factors can involve changes in a familiar environment or apartment, and lack of activity or loss of established routines.

Non-pharmacological treatments are recommended as first-line options for relieving BPSD (Memory disorders: Current Care Guideline 2017). Examples of non-pharmacological treatments are cognitive training and rehabilitation, music therapy, exercise as well as the provision of communication training to caregivers (Kales et al. 2015, Memory disorders: Current Care Guideline 2017).

The recommended first-line pharmacotherapy of BPSDs is the appropriate pharmacotherapy for a cognitive disorder i.e. AChEIs, in the mild to moderate stage, and memantine in moderate to severe stage of the disease or their combination (National Institute for Health and Care Excellence 2016, Memory disorders: Current Care Guideline 2017). Any possible underlying causes, such as pain or infection, responsible for the BPSD should be treated properly.

In the most severe cases of BPSD, such as situations where a patient is at risk of causing harm to him/herself or to a caregiver, short-term psychotropic pharmacotherapy can be considered (Kales et al. 2015). Atypical antipsychotics are the most commonly used psychotropic agents in the treatment of severe BPSD, although their benefits have been questioned (Sink et al. 2005). It is known that antipsychotics, as with any other form of pharmacotherapy, are not efficacious for symptoms such as wandering, hoarding, yelling, hypersexual symptoms or dressing problems and thus, are not recommended for the treatment of those kinds of symptoms (Memory disorders: Current Care Guideline 2017). Moreover, antipsychotic treatment has been associated with severe adverse events, such as mortality, stroke, increased risk of hip fractures, anticholinergic effects, orthostatic hypotension and sexual dysfunction (Ballard and Waite 2006, Kales et al. 2015, Koponen et al. 2017a, Koponen et al. 2017b).

In cases of moderate or severe depression as a symptom of BPSDs, antidepressants are recommended; this is based on clinical experience, even though the evidence-based efficacy is limited (Sepehry et al. 2012, Memory disorders: Current Care Guideline 2017). Antidepressants are also used for the treatment of insomnia in adults, and agitation and psychosis in persons with dementia (Seitz et al. 2011, Everitt et al. 2018). Antidepressants will be described in more detail in section 2.4.
Benzodiazepines are only recommended for short-term treatment of anxiety and insomnia, due to the risk of several adverse events (Kales et al. 2015). However, the prevalence of benzodiazepines and related drugs (BZDRs) use is comparatively high (45%) and long-term use is also common among persons with AD, as many as 30% of them are using BZDRs for ≥180 days (Taipale et al. 2015). BZDRs are also initiated more frequently among persons with AD than in those not suffering from this disease (Saarelainen et al. 2016).

2.1.2 Urinary incontinence
Urinary incontinence (UI) refers to involuntary urinary leakage; it is divided into stress, urge, mixed and overflow incontinence (Urinary incontinence (women): Current Care Guideline 2017). The International Continence Society defines stress UI as leakage with effort or physical exertion, or on sneezing or coughing (Abrams et al. 2003). Urge UI refers to leakage with the sensation of a sudden, compelling desire to void that is difficult to defer (Haylen et al. 2010). In overflow UI, there is an inability to empty the urinary bladder which leads to urinary retention and then can cause overflow UI (Urinary incontinence (women): Current Care Guideline 2017). UI can be caused by neuronal injury as well as other reasons leading to chronic urinary retention. Mixed UI is combination of stress and urge UI. Overactive bladder is defined as urinary urgency, usually with urinary frequency and nocturia, with or without urge UI (Abrams et al. 2003).

UI is a common and disturbing symptom experienced by older persons (Suhr and Lahmann 2017). In Finland, the prevalence of stress, urge and mixed incontinence among persons ≥70 years was 2%, 17% and 6%, respectively in men, the corresponding values in women were 23%, 6% and 30% (Nuotio et al. 2003). Thus, urge UI is the most common form of UI among men, whereas women suffer mostly from stress or mixed type of UI. The current estimate of the prevalence of UI among home care clients in Germany is over 60 percent (Suhr and Lahmann 2017); previous estimates of the prevalence among persons with dementia have varied from 11% to 90% in several different countries (Hägglund 2010).

By its very nature, UI is by multicatorial in older persons and associated with chronic diseases, such as cerebrovascular disorders, chronic obstructive pulmonary disease (COPD) and neurodegenerative diseases such as AD and Parkinson disease, and physical disabilities (Maggi et al. 2001, Suhr and Lahmann 2017, Tuong et al. 2016). In men, UI is a common symptom of benign prostatic hyperplasia (BPH) (Benign prostatic hyperplasia: Current Care Guideline 2018). Among women, vaginal atrophy may underlie UI symptoms (Urinary incontinence (women): Current Care Guideline 2017).

The prevalence of UI among persons with AD is higher than in those without AD, especially in the severe stage of the disease, probably because of disability and inability to recognize the need of voiding properly and early enough (Hellström et al. 1994, Lee et al. 2017, Memory disorders: Current Care Guideline 2017). One reason for UI among persons with AD is that it may be an adverse effect of the AChEIs used for treatment of AD (Lampela et al. 2016). There is a lack of evidence that non-pharmacological options for treatment of UI, such as toilet assistance, timed voiding, and prompted voiding are feasible in persons with AD (Hägglund 2010). Thus, pharmacological options, such as urinary antispasmodics (oxybutynin, tolterodine, solifenacin, trospium, darifenacin and fesoterodine) or mirabegron, are often used. In addition, UI may be experienced as a stressful symptom also by caregivers, and it also increases the risk for nursing home placement (Bühr et al. 2006, Maxwell et al. 2013).
2.2 HIP FRACTURES

Falling is the most frequent cause of injury (such as hip fracture), disability and death and thus, it is a significant health issue among older persons (Kannus et al. 2018). In the USA, the 2-year prevalence of self-reported falls has increased from 28.2% in 1998 to 36.3% in 2010 among persons aged ≥65 years (Cigolle et al. 2015). According to a study based on Causes of Death Register, there were 579 fall-induced deaths among men aged ≥50 years, and 532 among women aged ≥50 years in 2015 in Finland (Kannus et al. 2018). The incidence of falls has been previously reported to be higher among persons with cognitive disorders compared to controls (Allan et al. 2009).

In several previous studies, the use of psychotropic drugs, including antidepressants, has been associated with an increased risk of falling among older persons (Hartikainen et al. 2007, Woolcott et al. 2009, Marcum et al. 2016, Du et al. 2017). According to a novel meta-analysis, ORs for falls were 1.54 [95% confidence interval (CI) 1.28–1.85] for antipsychotics, 1.57 (95% CI 1.43–1.74) for antidepressants and 1.42 (95% CI 1.22–1.65) for benzodiazepines (Seppälä et al. 2018). Due to the increased risk of falling, the use of psychotropic drugs is also associated with the consequent fractures resulting from falling.

Hip fractures are serious consequences of falling and a major health concern among older persons and persons with AD (Bentler et al. 2009, Suttanon et al. 2013, Tolppanen et al. 2013a). Almost all (approximately 90%) hip fractures are caused by a fall (Ranhoff et al. 2010). Hip fractures diminish the quality of life and are responsible for restrictions in mobility and self-care (Bentler et al. 2009, Dyer et al. 2016). They often lead to disability and increase the need for long-term care (Leibson et al. 2002). It is estimated that fewer than every second community-dwelling person who experienced a hip fracture can perform independently at home at the same level than before their hip fracture (Hip fractures: Current Care Guideline 2017). According to a Finnish study concerning the first hip fractures among persons ≥65 years, over 5% of previously community-dwelling persons with a hip fracture were living in long-term care one year after the hip fracture (Pajulammi et al. 2015). A study conducted in Minnesota reported that 51% of persons who experienced a hip fracture had increased disability compared to level before hip fracture, whereas the figure was 16% among controls without hip fracture (Leibson et al. 2002). They also required twice as many nursing home days compared to controls.

Age is the most significant risk factor for hip fracture (Benetos et al. 2007). In Finland, in 2015, the mean age at the first hip fracture (N=4,370) among home-dwelling persons was 79 years (National Institute of Health and Welfare 2017). Other risk factors are female sex, previous fracture, stroke, a family history of fracture, malnutrition, vitamin D insufficiency, smoking, alcohol consumption, visual disturbances and many chronic diseases such as osteoporosis, diabetes and cardiovascular diseases (Benetos et al. 2007, Stolée et al. 2009, Coleman et al. 2009, Luan et al. 2016). Furthermore, cognitive disorders are risks factors for hip fractures (Tolppanen et al. 2013a). In addition, mortality after a hip fracture is greater among persons with AD compared to the general older population (Baker et al. 2011, Tolppanen et al. 2016b). Living in an institutional setting has been associated with an increased risk of hip fracture compared to community-dwelling persons (Butler et al. 1996, Norton et al. 1999).

Several drugs which affect the central nervous system (CNS), are associated with an increased risk of hip fractures; examples are presented in Table 1. Antihypertensive drugs have been linked with an increased risk of hip fracture among older community-dwelling persons especially after the initiation of use, which is likely due to the risk of falling caused by orthostatic hypotension (Butt et al. 2012). Another study concerning antihypertensive drugs and the risk of hip fracture, found that the risk was increased only with loop diuretics and ACE inhibitors, whereas a reduced risk was associated with the use of most antihypertensive drugs (Ruths et al. 2015). The Swedish register-based study found no
association between use of cardiovascular drugs and the risk of hip fracture among older persons (Thorell et al. 2014).

Table 1. Examples of studies of CNS affecting drugs associated with an increased risk of hip fractures

<table>
<thead>
<tr>
<th>Drug</th>
<th>Population</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adult population</td>
<td>Bakken et al. 2013, Leavy et al. 2017</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>Older population (≥65 years)</td>
<td>Oderda et al. 2012</td>
</tr>
<tr>
<td></td>
<td>Persons with AD</td>
<td>Koponen et al. 2017a</td>
</tr>
<tr>
<td>BZDRs</td>
<td>Older population (≥75 years)</td>
<td>Thorell et al. 2014</td>
</tr>
<tr>
<td></td>
<td>Adult population</td>
<td>Donnelly et al. 2017</td>
</tr>
<tr>
<td></td>
<td>Persons with AD</td>
<td>Saarelainen et al. 2017</td>
</tr>
<tr>
<td>Antiepileptics</td>
<td>Total population</td>
<td>Tsiropoulos et al. 2008</td>
</tr>
<tr>
<td></td>
<td>Postmenopausal women</td>
<td>Carbone et al. 2010</td>
</tr>
<tr>
<td>Antiparkinson drugs</td>
<td>Older population (≥75 years)</td>
<td>Thorell et al. 2014</td>
</tr>
<tr>
<td></td>
<td>Adult population</td>
<td>Leavy et al. 2017</td>
</tr>
<tr>
<td>Opioids</td>
<td>Older population (≥75 years)</td>
<td>Thorell et al. 2014</td>
</tr>
<tr>
<td></td>
<td>Adult population</td>
<td>Ping et al. 2017</td>
</tr>
</tbody>
</table>

Abbreviations: CNS, Central Nervous System; BZDRs, benzodiazepines and related drugs; AD, Alzheimer's disease

Hip fractures and their treatment are a major economic burden (Braithwaite et al. 2003, Williamson et al. 2017). They are associated with an increased level of hospital days even 1–2 years after the incident fracture, and the number of hospital days in women was 6-fold greater; in men they were 9-fold when compared to controls among persons aged ≥70 years (Lönnroos et al. 2009). Based on a meta-analysis examining 112 studies from 27 different countries, the estimated costs during one year after hip fracture were near to 44,000 dollars (corresponding to approximately 38,800 euros) per patient (Williamson et al. 2017). In Finland, the adjusted health costs of hip fracture during the first year after fracture were over 30,000 euros per patient at 2011–2013 (National Institute of Health and Welfare 2017).

In addition to costs, hip fractures are associated with increased mortality (Leibson et al. 2002, Bentler et al. 2009, Pajulammi et al. 2015). In Finland, the mortality of persons aged 80 or older with hip fracture was over 30% during one year follow-up in 2014 (National Institute of Health and Welfare 2017). In previous studies, the overall, one-year mortality after a hip fracture has been reported to range from 17% to 33% (Leibson et al. 2002, Lönnroos et al. 2009, Bentler et al. 2009, Pajulammi et al. 2015, Hektoen et al. 2016). In a Finnish study, 25% of the 1017 study participants ≥65 years, had died within one year of their hip fracture (Pajulammi et al. 2015), whereas another Finnish study (N=498) reported one-year mortality of 32.7% in ≥70 years persons (Lönnroos et al. 2009). During the first 3 months after the hip fracture, older persons seem to experience somewhere between a 5- to 8-fold elevated risk for all-cause mortality (Haentjens et al. 2010). The increased mortality risk seems to decrease over time, but remains elevated as compared to age matched control persons even with as long as an 8–10 years of follow-up (Haentjens et al. 2010, Katsoulis et al. 2017).
2.3 URINARY ANTAGONICS

Urinary antispasmodics (UAs) are indicated for the treatment of urge UI. These drugs antagonize the muscarine receptors normally activated by acetylcholine in the urinary tract and thus inhibit the stimulation of the detrusor muscle (Abrams et al. 2006). The anticholinergic effects of UAs’ are not restricted to the detrusor muscle, since the five different subtypes of muscarinic receptors are found in a variety of locations (Kay et al. 2005). In fact, the most common adverse effects of UAs’ include dry mouth, constipation, tachycardia and blurred vision, i.e., these drugs exert many systemic unwanted effects (Erdem and Chu 2006). Furthermore, all of the receptor subtypes are located in the CNS (Table 2), which means that when UAs are administered, these drugs may exert to sedative effects and impairments of cognitive function.

Table 2. Locations of muscarinic receptor subtypes (Kay et al. 2005, Lampela 2013)

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Location in the CNS</th>
<th>Locations outside the CNS</th>
</tr>
</thead>
<tbody>
<tr>
<td>M₁</td>
<td>Cerebral cortex (high levels), hippocampus and neostratium</td>
<td>Salivary glands, sympathetic ganglia</td>
</tr>
<tr>
<td>M₂</td>
<td>Throughout brain</td>
<td>Smooth muscle, cardiac muscle, detrusor muscle</td>
</tr>
<tr>
<td>M₃</td>
<td>Throughout brain (low levels)</td>
<td>Smooth muscle, salivary glands, eyes, detrusor muscle</td>
</tr>
<tr>
<td>M₄</td>
<td>Neostratium (high levels), cortex and hippocampus</td>
<td>Salivary glands</td>
</tr>
<tr>
<td>M₅</td>
<td>Substantia nigra and hippocampus</td>
<td>Eyes (ciliary muscle)</td>
</tr>
</tbody>
</table>

Abbreviation: CNS, Central Nervous System

In Finland, the anticholinergic UAs on the market are oxybutynin, tolterodine, solifenacin, trosplum, darifenacin and fesoterodine (Finnish Medicines Agency 2018). Overall, these drug substances lack explicit receptor subtype selectivity (Kay et al. 2005). Oxybutynin is a relatively nonselective muscarinic receptor antagonist, and due to its high lipophilicity, neutral charge and low molecular weight it can readily penetrate the blood brain barrier (Lam and Hilas 2007, Chancellor and Boone 2012). Tolterodine is a competitive muscarinic receptor antagonist, and solifenacin is a competitive muscarine-1 and muscarine-3 receptor antagonist (Lam and Hilas 2007). Trosplum has good water solubility, low oral bioavailability and thus it is considered to have a poor ability to cross the blood brain barrier (Lam and Hilas 2007). Darifenacin is lipophilic and in theory, it potentially crosses the blood brain barrier. Fesoterodine has the same active metabolite (5-hydroxymethyl-tolterodin) as tolterodine (Chancellor and Boone 2012). The clinical significance of these differences remains unclear.

UAs are not recommended for older persons, especially for persons with cognitive disorders, due to their anticholinergic adverse effects, such as dizziness, tiredness and confusion (Chancellor and Boone 2012, Vouri et al. 2017). Due to pharmacokinetic and pharmacodynamic changes, older persons are more sensitive to anticholinergic adverse effects (Turnheim 2004). The blood brain barrier of older persons and persons with AD is more permeable and since anticholinergic drugs may cross the blood brain barrier, their adverse effects may accumulate (Sweeney et al. 2018). In addition, the anticholinergic UAs may antagonize the effect of AChEI and even lead to a failure of the AChEI treatment. This pharmacodynamic interaction will be described in more detail in chapter 2.3.1. Moreover, the efficacy of UAs for urge UI is rather limited (Shamliyan et al. 2012).

According to a meta-analysis of RCTs, the effectiveness of UAs in the treatment of urge UI seems to be similar for all drug substances (Shamliyan et al. 2012). However, older
persons and persons with cognitive disorders are usually excluded from RCTs and thus, real-world effectiveness and safety may differ among them.

Mirabegron is the only β-3 adrenoreceptor (AR) agonist available for the treatment of overactive bladder (Thiagamoorthy et al. 2016), and it represents a different pharmacological option for antimuscarinic treatment. The pharmacological mechanism of mirabegron is β-3 AR stimulation which results in detrusor muscle relaxation and thus, an increase in bladder capacity and a reduction in symptoms of overactive bladder (Igawa et al. 1998). A case series study reported that mirabegron relieved symptoms during one year of treatment among most of the users (Duckett and Balachandran 2016). However, in the same study, only 25% of all the persons who were prescribed mirabegron (N=354) continued with the therapy at one year, and 26% of the participants who used mirabegron for more than six weeks but less than one year (N=90) discontinued the treatment because of a lack of efficacy. Mirabegron can be combined with an anticholinergic drug for UI (Urinary incontinence (women); Current Care Guideline 2017). In the study of Duckett and Balachandran (2016), 37% of the cohort participants after one year of follow-up (N=184) were using an anticholinergic drug concomitantly with mirabegron.

2.3.1 Concomitant use of acetylcholine esterase inhibitors and urinary antispasmodics

The mechanism by which AChEIs relieve the symptoms of AD is the inhibition of acetylcholine breakdown by the enzyme, acetylcholine esterase. Acetylcholine is a neurotransmitter which is essential for cognition, and by preventing its metabolism, the actions of acetylcholine are prolonged at brain synapses, and this is thought to preserve cognitive function (Martorana et al. 2010). The pharmacological effect of UAs is opposite, they decrease the actions of acetylcholine, and their impact is not restricted to the detrusor muscle (Abrams et al. 2006) (Table 2). Thus, use of UAs antagonizes the desired effect of AChEI and may even lead to a treatment failure. It has been previously observed that UAs are more likely to be prescribed to persons receiving AChEI treatment than those without this kind of treatment (Roe et al. 2002, Johnell and Fastbom 2008). This may be due to UI as an adverse effect of AChEI treatment (Hashimoto et al. 2000, Lampela et al. 2016).

There are few previous studies investigating the concomitant use of AChEIs and UAs (Roe et al. 2002, Carnahan et al. 2004, Johnell and Fastbom 2008, Green et al. 2017). A summary of these studies is shown in Table 3. The newest study was conducted in the USA as a cross-sectional cohort among ≥65 years-old community-dwelling persons, reported that at the time of UA initiation, 27% (95% CI 24–29%) were taking AChEI, and persons with MCI or dementia were more likely to receive UA as compared with persons with normal cognition (Green et al. 2017). During a ten year study period, a UA was used by 6.0% (95% CI = 5.5–6.4%) of participants with dementia. Another study from the USA focused only on community-dwelling persons; it was found that 3.6% of donepezil users also were using oxybutynin (Roe et al. 2002). Information of drug use was collected during the year 1998 in the study of Roe et al. (2002) and during the years 2005–2015 in the study of Green et al. (2017), and prescribing patterns and collection of available drugs may have varied over time. Another difference between those two studies conducted among community-dwellers were in the number of study participants, i.e. Green et al. (2017) had a study population of 10,491 persons with dementia at the end of the follow-up period, compared to Roe’s et al. (2002) 418 donepezil users. Moreover, the concomitant use was reported differently, i.e. as the percentages of AChEI users (Roe et al. 2002) or UA initiators (Green et al. 2017). The Swedish register-based study of Johnell and Fastbom (2008) reported the concomitant use of AChEI and UAs as 3.6% among men and 2.9% among women living outside hospitals. The cross-sectional study of Carnahan et al. (2004) reported the prevalence of concomitant use of AChEI and oxybutynin as 3.9% and similarly, 3.4% were using AChEI and tolterodine. The study was restricted to Iowa Medicaid beneficiaries without reporting living conditions and with a relatively small sample size (n=557). Studies by Sink et al. (2008) and Modi et al. (2009) conducted in a nursing home setting and estimated a 6–11%
prevalence of concomitant use of AChEIs and UAs. A rather similar prevalence (10%) was reported in the cohort study of Boudreau et al. (2011) conducted also in the USA, which did not specify the living conditions of the study participants.

In conclusion, the concomitant use of AChEI and UA is evident despite the fact that these drugs have opposing pharmacologic mechanisms. The sample sizes of previous studies have tended to be rather small. However, there is no previous study which has focused on community-dwelling persons with a clinically verified diagnosis of AD. Furthermore, there are no previous studies of concomitant use among community-dwellers conducted in Finland.
Table 3. Summary of studies concerning concomitant use of acetylcholine esterase inhibitors (AChEIs) and urinary antispasmodics (UAs)

<table>
<thead>
<tr>
<th>Reference, country</th>
<th>Study design</th>
<th>Data, follow-up</th>
<th>Included UAs</th>
<th>N</th>
<th>Age, sex</th>
<th>Residential setting</th>
<th>Concomitant use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Green et al. 2017, USA</td>
<td>Cross-sectional, self-reported drug use annually</td>
<td>National Alzheimer's Coordinating Center 2005–2015 Drug use at the last visit during the 10-year study period</td>
<td>Oxybutynin, tolterodine, fesoterodine, flavoxate</td>
<td>Total 24,106; 10,491 persons with dementia</td>
<td>≥65 years, 43.7% women</td>
<td>Community-dwelling</td>
<td>27% at the UA initiation</td>
</tr>
<tr>
<td>Boudreau et al. 2011, USA</td>
<td>Retrospective cohort study</td>
<td>Group Health Cooperative and Kaiser Permanente Colorado, 2000–2008</td>
<td>Darifenacin, fesoterodine, flavoxate, oxybutynin, solifenasin, tolterodine, trospium</td>
<td>5,625 new use of a AChEI between 2000 and 2007</td>
<td>≥50 years, 60.3% women</td>
<td>Not reported</td>
<td>10%</td>
</tr>
<tr>
<td>Modi et al. 2009, USA</td>
<td>Cross-sectional survey of medical claims data</td>
<td>Indiana Medicaid claims for 2004</td>
<td>Tolterodine, oxybutynin</td>
<td>3,251 persons with AD or other dementia</td>
<td>≥65 years, 75.3% women</td>
<td>Nursing homes</td>
<td>6% tolterodin, 7.4% oxybutynin</td>
</tr>
<tr>
<td>Johnell and Fastbom 2008, Sweden</td>
<td>Cross-sectional</td>
<td>Prescribed Drug Register, 10–12/2005</td>
<td>National Board of Health and Welfare Classification</td>
<td>AChEI users: Men: 6,359 Women: 11,967</td>
<td>≥75 years, 61.6% women</td>
<td>Outside hospitals</td>
<td>Men: 3.6%, Women: 2.9%</td>
</tr>
<tr>
<td>Sink et al. 2008, USA</td>
<td>Prospective cohort study</td>
<td>2003–2004</td>
<td>Tolterodine, oxybutynin</td>
<td>3,536</td>
<td>≥65 years, 75.3% women</td>
<td>Nursing homes</td>
<td>10.6%</td>
</tr>
<tr>
<td>Carnahan et al. 2004, USA</td>
<td>Cross-sectional</td>
<td>Iowa Medicaid beneficiaries with a pharmacy claim, 1–2/2000</td>
<td>Tolterodine, oxybutynin</td>
<td>557</td>
<td>≥50 years, 73.6% women</td>
<td>Not reported</td>
<td>3.4% tolterodin, 3.9% oxybutynin</td>
</tr>
<tr>
<td>Roe et al. 2002, USA</td>
<td>Cohort</td>
<td>3–12 months from donepezil dispensing, 1998</td>
<td>Oxybutynin</td>
<td>418</td>
<td>≥65 years, 51% women</td>
<td>Home-dwelling</td>
<td>3.6% of donepezil users</td>
</tr>
</tbody>
</table>
2.4 ANTIDEPRESSANTS

Antidepressants are commonly used not only for the treatment of depression, but also for other indications such as anxiety disorders, panic disorder, social phobia and neuropathic pain (Takayanagi et al. 2015). They are also used for the treatment of BPSD, especially for depressive symptoms, agitation, aggression and anxiety (Memory disorders: Current Care Guideline 2017). In the treatment of BPSDs, the recommended first-line antidepressants are selective serotonin reuptake inhibitors (SSRIs). Tricyclic antidepressants (TCAs; amitriptyline, imipramine or clomipramine) and serotonin and noradrenaline reuptake inhibitors (SNRIs; venlafaxine or duloxetine) are recommended as first-line pharmacotherapy for neuropathic pain as an option for pregabalin or gabapentin (Finnerup et al. 2015). According to the database of pharmacotherapy of older persons (Meds75+) maintained by the Finnish Medicine Agency, TCAs are recommended to be avoided for the treatment of older persons (Finnish Medicines Agency 2018), in the USA, TCAs are not recommended at doses greater than 75 mg/day in adults aged ≥65 years due to their major anticholinergic and sedative side effects and the potential risk of falls (Finnerup et al. 2015).

SSRIs increase the extracellular serotonin (5-hydroxytryptamine; 5-HT) levels in the synaptic cleft by inhibiting the activity of the serotonin transporter (Tavoulari et al. 2009, Kroze et al. 2012). SNRIs inhibit both serotonin and noradrenaline reuptake (Rudolph and Derivan 1996). Mirtazapine increases noradrenergic release by blocking central α2-adrenoceptors, as well as some of the serotonergic receptor subtypes i.e. it is a potent 5-HT2 and 5-HT3 antagonist (Alam et al. 2013). A low dose of mirtazapine is frequently used for treatment of sleeping disorders and insomnia (Alam et al. 2013). The antihistaminergic effects (H1-receptor antagonism) of mirtazapine cause drowsiness and sedation, and have been thought to predominate at lower doses (Watanabe et al. 2011). For the treatment of depression, higher doses are needed and these dose levels increase noradrenergic neurotransmission.

Previous studies have investigated the prevalence of antidepressant use to be approximately three times higher in persons with cognitive disorders than among the general older population (Laitinen et al. 2014, Norgaard et al. 2015). The prevalence of antidepressant use is also reported to increase after the diagnosis of a cognitive disorder (Martinez et al. 2013). In that study from the UK, the prevalence increased from 7.2% at 10 years before and from 18.6% at one year before the dementia diagnosis, to 24.7% at the date of the diagnosis and finally up to 31.6% at 4 years after the dementia diagnosis.

There are rather few studies about the effectiveness of antidepressants in older persons suffering from cognitive disorders. According to a Cochrane review which summarized nine studies and 692 persons, sertraline and citalopram were associated with a reduction in symptoms of agitation when compared to placebo in two studies (Seitz et al. 2011). According to the meta-analysis conducted by Sepehry et al. (2012), SSRIs in the treatment of depression among persons with AD had no efficacy compared to placebo. This meta-analysis included six studies i.e. 298 SSRI users and 323 placebo treated controls with AD and depression (Sepehry et al. 2012). Another meta-analysis included seven placebo-controlled trials published in the period 1989–2010, which were conducted among persons with a cognitive disorder and depression (Nelson and Devanand 2011). Two of these trials were conducted with TCA, four with SSRIs and one with an SNRI (venlafaxine). This meta-analysis also did not detect any efficacy of antidepressant treatment compared to placebo for depression. These two meta-analyses (Nelson and Devanand 2011, Sepehry et al. 2012) included three of the same studies. Due to the small sample size of trials, there has been a demand for larger studies to clarify the efficacy of antidepressants among older persons. In the general population, all antidepressants were more efficacious compared to placebo in the treatment of a major depressive disorder (Cipriani et al. 2018). Differences between drug substances were found in tolerability and treatment discontinuation rates.
Antidepressant use is associated with many severe adverse effects/events, such as increased risk of falls and fractures, gastrointestinal bleedings, stroke and hyponatremia (Dalton et al. 2006, Coupland et al. 2011b, Oderda et al. 2012). The newer antidepressant classes, SSRIs and SNRIs, were thought to be safer than older TCAs, but according to several studies, these classes of drugs have risks as well. The increased incidence of severe adverse events among older persons may be due to age-related changes in pharmacodynamics and pharmacokinetics (Coupland et al. 2011a). The association between antidepressant use and mortality, mainly due to cardiovascular causes, has also been investigated and an increased mortality risk has been found among the general population (Hansen et al. 2016). Due to the increased risk of QT prolongation, the European Medicines Agency has reduced the maximum daily dose of citalopram to 40 mg for the general population and to 20 mg for older persons and persons with impaired liver function (European Medicines Agency 2011). Furthermore, as recommended by the World Health Organization, escitalopram 10 mg per day is the maximum dose for patients aged 65 years or older, those with liver problems or who are using omeprazole or cimetidine, on the basis of results from a clinical trial conducted in Canada (World Health Organization 2012). SSRIs are also associated with an increased risk of hyponatremia especially among older persons (Jacob and Spinler 2006). A recent meta-analysis detected an association between the risk of falling and use of tricyclic antidepressants as OR 1.41 (95% CI 1.07–1.86) and SSRIs even higher as 2.02 (95% CI 1.85–2.20) (Seppälä et al. 2018).

### 2.4.1 Risk of hip fracture associated with antidepressant use

The basis for studies investigating the association between antidepressant use and the risk of fractures is the hypothesis that psychotropic drugs increase the risk of falling and thus, would lead to fractures (Leipzig et al. 1999). The putative mechanisms include sedation, orthostatic hypotension, arrhythmias such as QT interval prolongation, hyponatremia and confusion associated with the use of these drugs (European Medicines Agency 2011, Kvelde et al. 2013, Sultana et al. 2015, Tachi et al. 2015). These effects may cause falling and then lead to injurious fractures. The serotonergic effect of antidepressants on bone physiology is another feasible mechanism (Bliziotes 2010). An association has been found between SSRI use and decreased bone mineral density among older women (Diem et al. 2007a, Diem et al. 2007b). However, the specific biochemical role of serotonergic pathways and their effects on bone metabolism are still unclear (Haney et al. 2010, Bliziotes 2010).

A summary of the previous studies concerning antidepressant use and the risk of hip fracture is presented in Table 4. Studies which included ≥200 hip fracture cases and were published in the year 1998 or later are included in Table 4. Some of the previous studies had concentrated on some other psychotropic drugs (Wang et al. 2001, Chang et al. 2008) or chronic diseases (Leavy et al. 2017) as the exposure, but also reported data on antidepressants. Some of the studies were focused only on antidepressants (Liu et al. 1998, Hubbard et al. 2003, Bakken et al. 2013).

The mean age of the study populations has varied from 72.1 to 82.3 years in previous studies (Wang et al. 2001, Hubbard et al. 2003, Ensrud et al. 2003, Chang et al. 2008, Bakken et al. 2013). Three studies did not report the mean age of the study population but included persons aged over 50 (Leavy et al. 2017), 66 (Liu et al. 1998) or 85 (Thorell et al. 2014) years. In the study of Leavy et al. (2017), every third hip fracture case was living in residential care. The study of Ensrud et al. (2003) from the USA included only community-dwelling persons, whereas other studies did not report the living conditions, or the living conditions were not an inclusion criterion. However, studies that comprised only persons living in institutional settings, were not included in this comparison.

In most of the previous studies, antidepressants were categorized into TCAs and SSRIs (Liu et al. 1998, Ensrud et al. 2003, Hubbard et al. 2003), whereas one study investigated also MAO-inhibitors and other antidepressants (Bakken et al. 2013). Some studies did not specify the antidepressants by classes or substances (Wang et al. 2001, Chang et al. 2008,

Three previous cohort studies described the association between antidepressant use and an increased risk of hip fracture (Ensrud et al. 2003, Bakken et al. 2013, Leavy et al. 2017). In comparison to nonuse of antidepressants, the adjusted risk estimates have varied from 1.65 to 1.90. The follow-up time in these studies has varied from one to six years. The largest cohort study was a register-based Norwegian study including 153,301 community-dwelling antidepressant users and 29,938 incident hip fractures between 2005 and 2010 (Bakken et al. 2013). In this study, incident users were identified with a 360 days’ washout period. The use of SSRIs was associated with an even higher risk (standardized incidence ratio) 1.8 (1.7–1.8) than TCAs 1.4 (1.3–1.5). Antidepressants were assumed to be used at 1 DDD per day when calculating person-time on drugs. The utilized prescription register does not provide information of drug use was extracted from. Any antidepressant drug dispensing during one year before the exclusion of persons with previous events (Hubbard et al. 2003, Thorell et al. 2014). One study excluded persons who

The dose response was examined by Liu et al. (1998) in Canada with three dose categories: low (<0.5 DDD), medium (0.5–1.5 DDD), and high (>1.5 DDD); there were no significant differences in risk estimates across dose categories within any of the three drug classes.

Some of the previous studies had considered the first hip fracture as the outcome (Wang et al. 2001, Ensrud et al. 2003), whereas some did not report the exclusion of persons with previous events (Hubbard et al. 2003, Thorell et al. 2014). One study excluded persons who
had had a previous hip fracture during the three years before the start of the follow-up (Chang et al. 2008), whereas some studies had applied more specific exclusion criteria, such as pathological fracture (Liu et al. 1998, Leavy et al. 2017) or periprosthetic fracture (Leavy et al. 2017). Previous fractures are known to be a risk factor for new fractures (Kanis et al. 2004, Benetos et al. 2007)

New antidepressant use has been assessed in two case-control studies. The case-control study conducted by Hubbard et al. investigated also the risk of hip fracture by the time since antidepressant exposure, reporting the risk as being highest when the first prescription of antidepressant was 0–14 days before the fracture (TCA aOR 4.76, 95% CI 3.06–7.41; SSRIs 6.30, (2.65–14.97) and remaining increased also with 15–42 and ≥43 days of exposure (Hubbard et al. 2003). Liu et al. (1998) classified antidepressant users as current, indeterminate and former users. Current users were further classified as new current users, if they had not received a prescription for 31–365 days before the index date. Indeterminate users were those in whom the most recent drug prescription was dispensed between 31 and 90 days before the index date. A former user was one in whom the most recent prescription was dispensed 91–365 days before the index date. The increased risk of hip fracture was found in current SSRI and TCA users and with indeterminate use of SSRIs but not with TCAs. The risk estimates were higher among new current users than other current users. No association was found between former antidepressant use and the risk of hip fracture after adjusting for confounders.

There is also one meta-analysis concerning the association between antidepressant use and the risk of hip fracture (Oderda et al. 2012). It examined 14 studies, and divided antidepressants as first generation (TCAs) and second generation (SSRI, SNRI, bupropion, mirtazapine, and trazodone) substances. Most of the studies included were case-controlled (N=11). The mean age of the participants in all of the included studies was over 65 years, whereas residential conditions were not reported. The OR for all antidepressants and hip fracture was 1.78 (95% CI 1.53–2.07), for second generation substances 1.94 (95% CI 1.37–2.76) and for TCAs it was estimated as 1.71 (95% CI 1.43–2.04). The studies included in the meta-analysis were published in 1991–2009 with most concentrating only on TCAs. Only four of the included studies were involved data from the second generation drugs.

In conclusion, antidepressant use has been associated with an increased risk of hip fracture among community-dwelling older persons in previous studies. There have been major differences between studies with respect to exposure definitions and the use of the new user design. There were also major variations in sample sizes as well as in the covariates used for adjusting the results. None of the previous studies have investigated the association between antidepressant use and the risk of incident hip fracture among persons with AD or cognitive disorders. Furthermore, no studies have assessed the risk associated with SNRIs and mirtazapine, as most of the previous studies have focused on TCAs.
Table 4. Summary of studies concerning association between antidepressant use and hip fractures (nonuse as a reference).

<table>
<thead>
<tr>
<th>Reference, country</th>
<th>Data, follow-up</th>
<th>Exposure definition</th>
<th>Hip fractures, N</th>
<th>Age, sex</th>
<th>Living setting</th>
<th>Risk measures (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cohort studies</strong></td>
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<tr>
<td>Leavy et al. 2017, Sweden (Uppsala)</td>
<td>Prescribed drug register, 8.7.2009–8.7.2010</td>
<td>ATC-class N06A</td>
<td>477</td>
<td>≥50, Women 69.8% of events</td>
<td>Mixed</td>
<td>Age- and sex-standardized RR 1.90 (1.55–2.32)</td>
</tr>
<tr>
<td>Bakken et al. 2013, Norway</td>
<td>Prescription Database 2004–2010, Hip Fracture Registry 2005–2010</td>
<td>TCAs, SSRIs and other antidepressants</td>
<td>39,938</td>
<td>Mean age 72.8, 56% women</td>
<td>CD</td>
<td>Any antidepressant SIR 1.7 (1.7–1.8), SSRI: 1.8 (1.7–1.8), TCA: 1.4 (1.3–1.5), other 1.6 (1.5–1.7)</td>
</tr>
<tr>
<td>Ensrud et al. 2003, USA</td>
<td>Study of Osteoporotic Fractures</td>
<td>TCAs, SSRIs</td>
<td>288</td>
<td>Mean age of antidepressant users 77.1, 100% women</td>
<td>CD</td>
<td>aHR, 1.65 (1.05–2.57), TCA: 1.83 (1.08–3.09); SSRI: 2.54 (0.62–3.82)</td>
</tr>
<tr>
<td><strong>Case-control studies</strong></td>
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</tr>
<tr>
<td>Thorell et al. 2014, Sweden</td>
<td>Prescribed drug register, 2006–2007, CDWÖ</td>
<td>ATC-class N06A</td>
<td>795</td>
<td>≥75, 74% women of cases</td>
<td>NA</td>
<td>aOR 1.66 (1.42–1.95)</td>
</tr>
<tr>
<td>Chang et al. 2008, Taiwan</td>
<td>National Health Insurance Program, 2001–2004</td>
<td>NA</td>
<td>217</td>
<td>≥65, Mean age 78.2</td>
<td>NA</td>
<td>Unadjusted OR 2.10 (1.3–3.3)</td>
</tr>
<tr>
<td>Hubbard et al. 2003, UK</td>
<td>General Practice Research Database, 1987–1999</td>
<td>TCAs, SSRIs</td>
<td>16,341</td>
<td>Mean age 79</td>
<td>Mixed</td>
<td>TCAs: aOR 1.22 (1.15–1.29); SSRIs: aOR 1.42 (1.28–1.58)</td>
</tr>
<tr>
<td>Wang et al. 2001, USA (New Jersey)</td>
<td>Medicare/ Medicaid 1994</td>
<td>NA</td>
<td>1,222</td>
<td>≥65; Mean age of cases 82.3, controls 82.4; Women 83.8% of cases, 83.6% of controls</td>
<td>Mixed</td>
<td>aOR 1.46 (1.22–1.75)</td>
</tr>
<tr>
<td>Liu et al. 1998, Canada</td>
<td>Registers for Ontario residents, 1.4.1994–31.3.1995</td>
<td>SSRIs; secondary-amine TCAs*; tertiary-amine TCAs*</td>
<td>8,239</td>
<td>≥66, 77.5% women</td>
<td>NA</td>
<td>Current SSR use aOR: 2.4 (2.0–2.7), secondary-amine TCA-use 2.2 (1.8–2.0), tertiary-amine TCA-use 1.5 (1.3–1.7)</td>
</tr>
</tbody>
</table>

Abbreviations: TCAs=tricyclic antidepressants, SSRIs=selective serotonin reuptake inhibitors, SIR=standardised incidence ratio, CD=Community dwelling, aOR=adjusted odds ratio, NA=Not reported, CDWÖ=Care Data Warehouse in Östergotland
*Secondary-amine TCAs included nortriptyline, protriptyline, desipramine; tertiary-amine TCAs included amitriptyline, clomipramine, doxepin, imipramine, trimipramine
2.5 PROTON PUMP INHIBITORS

Proton pump inhibitors (PPIs) are drugs used to treat gastric acid-related diseases, such as duodenal ulcers, gastric ulcers, erosive esophagitis, gastroesophageal reflux disorder, the eradication of helicobacter pylori with antibiotics, and pathological hypersecretory conditions such as Zollinger–Ellison syndrome (Shi and Klotz 2008). In addition, because of their gastro-protective properties, they are often co-prescribed with non-steroidal anti-inflammatory drugs (NSAIDs), low-dose aspirin and corticosteroids (Lanza et al. 2009, Munson et al. 2012, Masclee et al. 2014, Juntunen et al. 2017).

PPIs act by selectively and irreversibly inhibiting the parietal cell H+/K+ATP pump (proton pump), which leads to a reduced secretion of gastric acid (Sachs et al. 2006, Shi and Klotz 2008). In the Current Care Guideline, PPIs are recommended as the first choice pharmacotherapy for gastroesophageal reflux disorders and dyspepsia, mainly due to their superior effectiveness in inhibiting gastric acid secretion compared with other options such as H2-blockers and antacids. (Current Care Guideline: Recurrent upper gastrointestinal symptoms 2012).

Due to the pharmacological mechanism of PPI, their use is associated with several adverse effects, such as vitamin B12 deficiency, hypomagnesemia and decreased calcium absorption (O’Connell et al. 2005, Hess et al. 2012, Lam et al. 2013). These adverse effects have been suggested to lead to bone fractures. However, the claims that there is an association between PPI use and changes in bone mineral density have also been rejected (Targownik et al. 2017). Other severe adverse events associated with PPI use, especially among older persons, are an increased risk of pneumonia and clostridium difficile infection (Leonard et al. 2007, Eom et al. 2011). The in vivo mechanisms behind the associations between these infections and PPI use remain uncertain, although results from in vitro studies have suggested two different mechanisms (Yang and Metz 2010). First, PPIs may interfere with neutrophil function which would further increase the risk of bacterial infection. Second, PPI-induced hypochlorhydria could lead to respiratory infections by allowing transmission of ingested viable pathogens through reflux or enteric infections.

According to a Danish study, the prevalence of PPI use strongly increases with age, as the prevalence among persons >80 years surpasses over 20% compared to 7% among general adult population (Pottegård et al. 2016). In Ireland, the prevalence of PPI use among persons ≥65 years was as high as 48% and the prevalence of long-term use was (>8 weeks) 36% in 2012 (Moriarty et al. 2016). Nonetheless, the long-term use of PPIs among older persons is discouraged, mainly due to adverse effects, and decreased secretion of hydrochloric acid as the individual grows older (Mangoni and Jackson 2004, Masclee et al. 2014, Moriarty et al. 2016).

In the MEDALZ-cohort, the prevalence of PPI use was 35.8% among persons with AD i.e. almost double that of the 20.3% value among comparison persons without AD (Juntunen et al. 2017). Long-term (continuous use ≥180 days) use was also somewhat more common among persons with AD (20.3%) than in comparison persons (17.9%).
2.5.1 Risk of hip fracture associated with proton pump inhibitor use

The putative mechanism behind the association between PPI use and risk of hip fractures is that PPI use would reduce calcium absorption and thus, lead to bone loss and increased risk of fractures (Gray et al. 2010). However, there are studies which have reported that PPI use exerts no effects on bone structure (O’Connell et al. 2005, Targownik et al. 2010, Targownik et al. 2017). Other suggested mechanisms for the association are vitamin B12-deficiency, myopathy and hypomagnesemia (Clark and Strandell 2006, Hess et al. 2012, Lam et al. 2013). However, the evidence supporting these mechanisms remains unclear, and the results of the observational studies have been contradictory.

The risk of hip fracture associated with PPI use has been investigated previously in five cohort studies (Yu et al. 2008, De Vries et al. 2009, Gray et al. 2010, Khalili et al. 2012, Ding et al. 2014) and ten case-control or nested case-control studies (Yang et al. 2006, Vestergaard et al. 2006, Kaye and Jick 2008, Targownik et al. 2008, Corley et al. 2010, Chiu et al. 2010, Pouwels et al. 2011, Reyes et al. 2013, Adams et al. 2014, Cea Soriano et al. 2014), and the results are mixed (Table 5). Only studies published in or after 2006 were included. There are also several previous reports which have investigated the association between PPI use and any fractures, which did not report hip fracture separately and thus, are excluded from this comparison.

In most of the previous studies, the majority of the participants were women, in fact two studies investigated only women (Gray et al. 2010, Khalili et al. 2012) with one study concentrating only on men (Adams et al. 2014). Some of the previous studies focused on the first hip fractures by excluding persons with previous events (Yang et al. 2006, Yu et al. 2008, Kaye and Jick 2008, Gray et al. 2010, Corley et al. 2010, Chiu et al. 2010, Adams et al. 2014), whereas one study included as cases those persons with a previous fracture (Cea Soriano et al. 2014). More specific exclusion criteria, such as previous hip fractures with high energy trauma (such as a skiing accident) (Khalili et al. 2012, Reyes et al. 2013), cancer (Reyes et al. 2013, Cea Soriano et al. 2014) and osteoprotective medications in the year before the fracture (Targownik et al. 2008) were stated.

Risk estimates in cohort studies have varied from 0.62 to 1.36, with the follow-up times ranging from six months to over seven years. Two of the cohort studies (Khalili et al. 2012, Ding et al. 2014) detected an increased risk, but this was not confirmed in two other studies (Yu et al. 2008, Gray et al. 2010). The study of De Vries et al. (2009) reported an increased risk with <2 years of use compared to past use, but not with longer use. One cohort study was mainly focused on adherence to PPI use and found a slightly increased risk of hip fracture (aOR 1.32, 95% CI 1.01–1.71) when incident users were compared to nonusers (Ding et al. 2014). Three cohort studies assessed drug exposure by interviewing participants (Yu et al. 2010, Gray et al. 2010, Khalili et al. 2012), whereas two used register-based data from pharmacy dispensings (Ding et al. 2014) or prescriptions (De Vries et al. 2009).

The adjusted risk estimates varied from 0.96 to 2.51 in case-control studies (Vestergaard et al. 2006, Targownik et al. 2008, Chiu et al. 2010, Pouwels et al. 2011, Reyes et al. 2013, Adams et al. 2014) and from 0.9 to 1.44 in nested case-control studies (Yang et al. 2006, Kaye and Jick 2008, Corley et al. 2010, Cea Soriano et al. 2014). Seven studies (Yang et al. 2006, Vestergaard et al. 2006, Corley et al. 2010, Chiu et al. 2010, Pouwels et al. 2011, Cea Soriano et al. 2014, Adams et al. 2014) did report an increased risk, but these results could not be confirmed in three studies (Targownik et al. 2008, Kaye and Jick 2008, Reyes et al. 2013). Of these studies, the majority used register-based pharmacy dispensing data for exposure assessment (Vestergaard et al. 2006, Targownik et al. 2008, Chiu et al. 2010, Corley et al. 2010, Pouwels et al. 2011, Adams et al. 2014), two used prescription data (Kaye and Jick 2008, Cea Soriano et al. 2014) and one inquired about PPI use by questionnaire for hip fracture cases (Reyes et al. 2012). If any assumptions for modelling continuous drug use were reported in register-based studies, PPIs were assumed to be used at 1 DDD per day (Vestergaard et al. 2006).
The duration of PPI use associated with the risk of hip fracture was evaluated in four studies (Targownik et al. 2008, De Vries et al. 2009, Pouwels et al. 2011, Adams et al. 2014). The study of Targownik et al. (2008) found an increased risk for ≥5 years of continuous use, but no association with <5 years of continuous use. Pouwels et al. (2011) found no association for any duration (≤3 months, 4–12 months, 13–36 months or >36 months) of PPI use, whereas Adams et al. (2014) reported that an increased risk was associated with the longest durations of use of omeprazole (330–3272 days) and pantoprazole (417–1931 days). In addition, the study of Cea Soriano et al. (2014) reported results for different durations of current single use (when only one drug substance was used during 90 days before the index date), and found no significant association with the risk of hip fracture, or differences between durations. The study of Pouwels et al. (2011) was the only one that used a washout period for continuous PPI use to estimate incident use was In their report, the results of current users and first time users were reported separately, as the aOR for first time users was 1.29 (95% CI 0.79–2.09) and aOR for current users as 1.20 (95% CI 1.04–1.40).

The association between cumulative exposure to PPIs and the risk of hip fracture was investigated in two publications (Corley et al. 2010, Chiu et al. 2010). Corley et al. (2010) reported increased risks with all cumulative classifications up to ≥10 year, and Chiu et al. (2010) detected increased risks associated with both classifications of 29–70 DDDs and >70 DDDs during an 11 year follow-up. However, the category of >70 DDDs during such a long follow-up period can be considered as a very low cumulative value.

In addition, four previous studies examined the association according to the recentness of PPI use, i.e. when the last PPI use ended, compared to the time of hip fracture (Vestergaard et al. 2006, Pouwels et al. 2011, Adams et al. 2014, Cea Soriano et al. 2014). The results emerging from these publications are mixed. Cea Soriano et al. (2014) reported a slightly increased risk with recent (the most recent prescription ended 31–90 days before the index date; aOR 1.29, 95% CI 1.07–1.56) but not with past use (91–365 days before; aOR 0.95, 95% CI 0.83–1.09). Adams et al. (2014) categorized the recentness of PPI use according to tertiles in days, and found slightly increased risks in the most recent use tertiles for omeprazole (1–7 days) and pantoprazole (1–33 days), but not with other categories of use. In the study of Pouwels et al. (2011), the risk was evident only if the last dispensing time was >1 year before the index date (aOR 1.24, 95% CI 1.08–1.43) in addition to current use (aOR 1.20, 95% CI 1.04–1.40). On the contrary, no association was found if the last PPI was >1 year previously in the study of Vestergaard et al. (2006), aOR 1.08 (95% CI 0.94–1.23).

The dose-response was evaluated in the study of De Vries et al. (2009); the aRR for hip fracture in current use with <1 DDD per day was 1.13 (95% CI 0.98–1.31), 1.27 (95% CI 1.12–1.45) for 1–1.75 DDDs and 1.45 (95% CI 1.06–1.99) for >1.75 DDDs when compared to the past use of PPI. The study of Pouwels et al. (2011) examined the dose response; they reported aORs for incident users as 1.21 (95% CI 0.93–1.57) when the average dose used was <1 DDDs per day, 1.12 (95% CI 0.88–1.42) for 1.00–1.75 DDDs, and 1.35 (CI 95% 1.02–1.77) for >1.75 DDDs per day.

Three previous studies reported the risk estimates for hip fracture in terms of which specific PPI drug substance was being administered (Kaye and Jick 2008, Cea Soriano et al. 2014, Adams et al. 2014). Both Cea Soriano et al. (2014) and Adams et al. (2014) reported slightly increased risks for omeprazole (aOR 1.14, 95% CI 1.03–1.27; aOR 1.13, 95% CI 1.01–1.27, respectively) but not for other PPI substances. The study of Kaye and Jick (2008) did not detect any differences between PPI drug substances in terms of hip fracture risk, as none of them were associated with an increased risk of hip fracture.

The meta-analysis of the association between PPI use and the risk of any fractures summarized the risk estimate for hip fracture as being 1.26 (95% CI 1.16–1.36) based on 15 studies (Zhou et al. 2016). Statistically significant positive results were detected in 8 studies, neutral findings in 6 studies and negative in 1 study included in the meta-analysis. According to this meta-analysis, both short-term (<1 year) and long-term (>1 year) PPI use are associated with an increased risk of hip fracture.
In conclusion, there are several publications investigating the association between PPI use and the risk of hip fracture among persons in mixed living conditions. The results of previous studies have been contradictory, as some studies indicated an increased risk of hip fracture whereas some others did not found any association. The results are mixed also with respect to the risk of long-term or short-term use, which may be at least partly due to differences in the definitions of exposure. Variation was also evident in which covariates were applied for adjusting the results, which may be one reason accounting for the different risk estimates. The size of study populations has varied from a few hundred to several thousands of participants and the mean age of study participants ranged from persons in their forties to those over eighty, reflecting the extensive heterogeneity in study populations. None of the previous studies, however, has focused on community-dwelling persons with AD or other cognitive disorders.
<table>
<thead>
<tr>
<th>Reference, country</th>
<th>Data, follow-up</th>
<th>Exposure definition</th>
<th>Hip fractures, N</th>
<th>Age, sex</th>
<th>Living setting</th>
<th>Risk measures (95% CI)</th>
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<tbody>
<tr>
<td><strong>Cohort studies</strong></td>
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<tr>
<td>Ding et al. 2014, USA</td>
<td>PACE and Medicare, 1999–2003</td>
<td>PPI users with ≥2 refills and one refill during the last 6 months of the observation period</td>
<td>819</td>
<td>Mean age 78.6 y, PPI users: 82.9% women; non-users: 81.3% women</td>
<td>CD</td>
<td>aHR 1.32 (1.01–1.71),</td>
</tr>
<tr>
<td>Khalili et al. 2012, USA</td>
<td>The Nurses’ Health Study, 2000–2008</td>
<td>PPI</td>
<td>893</td>
<td>Mean age of PPI users 67 y, non-users 66.6 y; 100% women</td>
<td>NA</td>
<td>Regular use ≥ 2 y: aHR 1.36 (1.13–1.63)</td>
</tr>
<tr>
<td>Gray et al. 2010, USA</td>
<td>Women’s Health Initiative (WHI), drug use from interview, 1993–2005</td>
<td>Omeprazole (84.7%), lansoprazole (15.3%) were the only PPIs used</td>
<td>1,500</td>
<td>50–79 y, women Mean age of PPI users 63.1 y; non-users 68.8 y</td>
<td>NA</td>
<td>aHR 1.00 (0.71–1.40)</td>
</tr>
<tr>
<td>De Vries et al. 2009, UK</td>
<td>General Practice Research Database (GPRD), 1988–2007</td>
<td>Omeprazole, pantoprazole, lansoprazole, rabeprazole, esomeprazole</td>
<td>848</td>
<td>Mean age of PPI users 62 y</td>
<td>NA</td>
<td>Current vs. past use aRR 1.22 (1.10–1.37) Duration of use (current vs. past): &lt;1 year: aRR 1.31 (1.09–1.58) 1-2 years: 1.34 (1.10–1.63) 2-3 years: 1.06 (0.83–1.34) &gt;3 years: 1.17 (0.98–1.41)</td>
</tr>
<tr>
<td>Yu et al. 2008, USA</td>
<td>SOF (Women) and MrOS (Men) cohorts, 2000–2007</td>
<td>PPI</td>
<td>SOF 451 MrOS 89</td>
<td>&gt;65 y Mean age: SOF:79 y MrOS: 74 y</td>
<td>SOF:CDM MrOS:NA</td>
<td>Adjusted RHs: Men: 0.62 (0.26–1.44) Women: 1.16 (0.80–1.67)</td>
</tr>
<tr>
<td><strong>Nested case-control studies</strong></td>
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<tr>
<td>Cea Soriano et al. 2014, UK</td>
<td>The Health Improvement Network (THIN), 2000–2008</td>
<td>Esomeprazole, omeprazole, lansoprazole, pantoprazole, rabeprazole</td>
<td>10,958</td>
<td>40–89 y, women 75.2% of cases and 74.4% of controls</td>
<td>NA</td>
<td>aOR, current use: 1.07 (1.00–1.16); recent use: 1.29 (1.07–1.56)</td>
</tr>
</tbody>
</table>

(Continued)
Table 5. (Continued)

| Study                        | Setting                                      | Comparator | Methods                                                                 | Results                              |
|------------------------------|----------------------------------------------|------------|-------------------------------------------------------------------------|                                     |
| **Case-control studies**     |                                              |            |                                                                         |                                     |
|                              |                                              |            |                                                                         | Cumulative duration of use:         |
|                              |                                              |            |                                                                         | <1 year 1.25 (1.19–1.31),           |
|                              |                                              |            |                                                                         | 1–1.9 years 1.31 (1.20–1.42),       |
|                              |                                              |            |                                                                         | 2–3.9 years 1.34 (1.24–1.44),       |
|                              |                                              |            |                                                                         | 4–5.9 years 1.21 (1.10–1.33),       |
|                              |                                              |            |                                                                         | 6–7.9 years 1.33 (1.19–1.49),       |
|                              |                                              |            |                                                                         | 8–9.9 years 1.33 (1.12–1.57),       |
|                              |                                              |            |                                                                         | ≥10 years 1.85 (1.41–2.43)          |
| Kaye and Jick 2008, UK       | General Practice Research Database (GPRD), 2005 | Omeprazole, lansoprazole, pantoprazole, rabeprazole, esomeprazole—at any time before their index date | 1,098                                  | RR 0.9 (0.7–1.1)                     |
| Yang et al. 2006, UK         | General Practice Research Database (GPRD), 1987–2003 | PPI        | 13,556                                                                 | >1 year use aOR 1.44 (1.30–1.59)    |
| Case-control studies         |                                              |            |                                                                         |                                     |
| Adams et al. 2014, USA       | Kaiser Permanente Southern California (KPSC), 1997–2006 | Omeprazole, pantoprazole ever used vs. never used; recentness of use; duration of use | 6,774                                  | Omeprazole (aORs): ever use, 1.13 (1.01–1.27); most recent (1–7 d) use 1.22 (1.02–1.47); longest duration (330–3272 d) 1.23 (1.02–1.48) of use |
|                              |                                              |            |                                                                         | Pantoprazole (aORs): ever use, 1.10 (0.97–1.24); most recent (1–33 d) use 1.38 (1.12–1.71); longest duration (417–1931 d) of use 1.25 (1.02–1.53) |

(Continued)
Table 5. (Continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Data source</th>
<th>PPI</th>
<th>Cases: mean age ( hip/femur fracture)</th>
<th>Controls: mean age</th>
<th>CD</th>
<th>aORs: Current use (1–30 d before)</th>
<th>31–91 d before</th>
<th>&gt;1 year before</th>
<th>Duration of current use:</th>
<th>4–12 m</th>
<th>13–36 m</th>
<th>&gt;36 m</th>
<th>Never use as a reference.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pouwels et al. 2011, Netherlands</td>
<td>PHARMO record linkage system, 1991–2002</td>
<td>6,763</td>
<td>75.7 y controls: mean age 75.3 y;</td>
<td>73% women</td>
<td>CD</td>
<td>1.20 (1.04–1.40), 0.97 (0.74–1.26), 1.24 (1.08–1.43).</td>
<td>0.96 (0.83–1.12), 1.07 (0.97–1.14), 0.94 (0.96–1.03).</td>
<td>0.74 (0.62–0.90), 1.01 (0.91–1.13), 0.73 (0.61–0.89).</td>
<td>0.81 (0.69–0.95), 0.92 (0.80–1.05), 0.84 (0.71–0.98).</td>
<td>0.81 (0.69–0.95), 0.92 (0.80–1.05), 0.84 (0.71–0.98).</td>
<td>0.80 (0.67–0.95), 0.91 (0.78–1.06), 0.82 (0.68–0.97).</td>
<td>0.80 (0.67–0.95), 0.91 (0.78–1.06), 0.82 (0.68–0.97).</td>
<td></td>
</tr>
<tr>
<td>Reyes et al. 2012, Spain</td>
<td>Six primary health care centers in Catalonia, 2007–2010</td>
<td>358</td>
<td>Mean age 82 y, 77% women</td>
<td>NA</td>
<td>aOR 1.24 (95% CI, 0.93–1.65)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Chiu et al. 2010, Taiwan</td>
<td>Taiwan National health insurance Research Database, 2005–2006</td>
<td>1,241</td>
<td>≥50 y, 58% women</td>
<td>NA</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Targownik et al. 2008, Canada (Manitoba)</td>
<td>Population Health Research Data Repository, 4/1996–3/2004</td>
<td>4,145</td>
<td>≥50 y, Cases: 70.3% women</td>
<td>Controls: 70.2% women</td>
<td>CD</td>
<td>1.09 (0.88–1.34), 1.01 (0.77–1.32), 1.43 (0.97–2.11), 1.62 (1.02–2.59), 2.49 (1.33–4.67), 4.55 (1.68–12.29)</td>
<td>0.97 (0.70–1.34), 1.43 (0.97–2.11), 1.62 (1.02–2.59), 2.49 (1.33–4.67), 4.55 (1.68–12.29)</td>
<td>0.97 (0.70–1.34), 1.43 (0.97–2.11), 1.62 (1.02–2.59), 2.49 (1.33–4.67), 4.55 (1.68–12.29)</td>
<td>0.97 (0.70–1.34), 1.43 (0.97–2.11), 1.62 (1.02–2.59), 2.49 (1.33–4.67), 4.55 (1.68–12.29)</td>
<td>0.97 (0.70–1.34), 1.43 (0.97–2.11), 1.62 (1.02–2.59), 2.49 (1.33–4.67), 4.55 (1.68–12.29)</td>
<td>0.97 (0.70–1.34), 1.43 (0.97–2.11), 1.62 (1.02–2.59), 2.49 (1.33–4.67), 4.55 (1.68–12.29)</td>
<td>0.97 (0.70–1.34), 1.43 (0.97–2.11), 1.62 (1.02–2.59), 2.49 (1.33–4.67), 4.55 (1.68–12.29)</td>
<td>0.97 (0.70–1.34), 1.43 (0.97–2.11), 1.62 (1.02–2.59), 2.49 (1.33–4.67), 4.55 (1.68–12.29)</td>
</tr>
<tr>
<td>Vestergaard et al. 2006, Denmark</td>
<td>Hospital Discharge Register, Prescription Register, 2000</td>
<td>124,655</td>
<td>Mean age 43.44 y (±27.39), 51.8% women</td>
<td>Mixed</td>
<td>aORs for hip fracture: 1.67 (1.11–2.51), 2.51 (1.77–3.55)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: PPI=proton pump inhibitor, PACE=Pennsylvania’s Pharmaceutical Assistance Contract for the Elderly program, aOR=Adjusted Odds Ratio, aHR=Adjusted Hazard Ratio, aRR=Adjusted relative rates, Rh=relative hazard, CD=Community dwelling, NA=Not reported, d=days, m=months, DDD=Defined daily dose
3 Aims of the Study

The overall objective of this study was to investigate possible risks associated with the selected pharmacotherapies used to treat symptoms related to AD among community-dwelling older persons.

The specific aims were to investigate:

1. the prevalence and duration of concomitant use of AChEIs and UAs among persons with AD (Study I)

2. the risk of hip fracture associated with antidepressant use among persons with and without AD according to durations of use as well as examining whether there are differences associated with the various antidepressant drug classes (Study II)

3. the association between long-term and cumulative, and current and past, PPI use and the risk of hip fracture among persons with AD according to the duration of PPI use and also the individual PPI drugs (Study III)

4. the prevalence of UA, antidepressant and PPI use from 3 years before and until 3 years after AD diagnosis (unpublished material)
4 Materials and Methods

4.1 STUDY COHORTS AND DATA SOURCES

This thesis is based on register-based data from two nationwide datasets, MEDALZ-2005 and MEDALZ (Medication use and Alzheimer’s disease). Cohort participants are persons with clinically verified diagnosis of AD in Finland, identified from the Special Reimbursement Register, maintained by the Social Insurance Institution of Finland (SII).

Both of MEDALZ datasets include information from several nationwide registers. The contents of the registers used in datasets are summarized in Table 6. All registers are linked by Personal Identification Numbers (PINs), which are replaced with research IDs before submission to the research team.

4.1.1 Diagnostic criteria of Alzheimer’s disease

To be eligible for a limited basic reimbursement for antidementia drugs, person had to meet specific, predefined diagnostic criteria for AD set by the SII (Social Insurance Institution 2017). These criteria are based on the NINCDS-ADRDA (McKhann et al., 1984) and DSM-IV criteria (American psychiatric association 1994). At the time of the diagnosis, the disease has to be in the mild or moderate state. These criteria include progressive impairment of cognition and decline in social skills and activities of daily living during at least previous three months assessed by interviewing the patient and caregivers and by neuropsychological tests. The decline is determined to be caused by a progressive worsening of memory and at least one other part of cognitive functioning from the earlier stage. Possible alternative diagnoses are excluded with laboratory test results and computed tomography or magnetic resonance scan. If a person displays features of other dementing diseases, such as vascular dementia or Lewy body dementia, reimbursement will be granted if the symptoms are mainly caused by AD. About half of the cases have pathologically solely AD while the remainder display also pathologic changes of other cognitive disorders, and their disease is called mixed form of dementia. The diagnosis has to be confirmed by a geriatrician or neurologist. The diagnostic statement describing clinical findings is sent to the SII for evaluation and reimbursement is granted if the criteria are fulfilled.

4.1.2 MEDALZ-2005 (Study I)

The MEDALZ-2005 cohort data includes all persons with clinically verified diagnosis of AD on December 31, 2005 in Finland (N=28,093) (Tolppanen et al. 2013b). Persons with AD who were alive and community-dwelling at the cohort entry, on December 31,2005, were included in the cohort. The diagnostic criteria are described in more detail in section 4.1.1.

The earliest diagnoses were from 1999, and persons with severe AD have been entitled to reimbursement since 2003 (Tolppanen et al. 2013b). Thus, the cohort consists of persons with all severity stages of AD. The mean age of the cohort participants at the baseline was 79.7 years (SD 6.8, range 42–101) and 67.8% were women. Cardiovascular diseases were the most common comorbidities of the study population (n=14,194; 50.8%), and the majority of persons (n=23,979; 85.8%) were being administered antidementia drugs at the baseline.

4.1.3 MEDALZ (Studies II and III)

The MEDALZ cohort data includes all residents who received a clinically verified diagnosis of AD between 2005 and 2011 and were not living in institutional settings at the time of diagnosis (N=70,718) (Tolppanen et al. 2016a). Persons with Parkinson dementia have been
entitled to a limited basic reimbursement for rivastigmine since 2007, but they were excluded from the MEDALZ-cohort.

The mean age of the participants at the baseline (the date of AD diagnosis) was 79.6 years (SD 7.1, range 34–104) and 65.2% of them were women (Tolppanen et al. 2016a). Cardiovascular diseases were the most common comorbidities among participants (n=35,921, 50.8%) at the baseline, with the majority taking drugs prescribed for cardiovascular diseases (n=60,856, 86.1%).

Four comparison persons without AD diagnosis were matched for each person with AD by age, sex and region of residence at the date of AD diagnoses. The comparison persons were identified by the SII from a nationwide database including all residents. Comparison persons were chosen as follows, not having diagnoses of AD or antidementia drug purchases at the index date (date of AD diagnosis for the case) or 12 months after that. Furthermore, the comparison person needed to be alive and not in long-term care facility during the month of AD diagnosis for the case. During the follow-up, 14,343 comparison persons developed AD and they were defined as AD cases (censored from being comparison persons without AD) and four comparison persons were identified as described.
<table>
<thead>
<tr>
<th>Maintainer</th>
<th>Prescription Register</th>
<th>Special Reimbursement Register</th>
<th>Hospital Discharge Register</th>
<th>Long-term institutional care</th>
<th>Causes of death</th>
<th>Occupational socioeconomic data</th>
</tr>
</thead>
<tbody>
<tr>
<td>SII</td>
<td>SII</td>
<td>THL</td>
<td>SII</td>
<td>Statistics Finland</td>
<td>Statistics Finland</td>
<td></td>
</tr>
<tr>
<td>Data content</td>
<td>Reimbursed prescription drug purchases</td>
<td>Special reimbursements due to chronic diseases</td>
<td>Hospital stays</td>
<td>Decisions of long-term institutional care</td>
<td>Causes of death</td>
<td>Socioeconomic position</td>
</tr>
<tr>
<td>Essential variables</td>
<td>Purchase dates, strength and dosage form of the drug, ATC code, Vnr number of the package, package size, number of packages, purchased amount in DDDs, costs</td>
<td>Special reimbursement code of the disease, diagnosis, the beginning and end of dates of entitlement</td>
<td>Hospital admission days, reasons for hospital stays based on ICD-codes, speciality of the caring unit, and to where the patient was discharged. Date of procedure and up to five operational codes (NOMESCO classification)</td>
<td>Date of death, and direct, underlying, intervening and up to four contributing causes of death (ICD-10)</td>
<td></td>
<td>Education, occupational status</td>
</tr>
</tbody>
</table>

4.2 DRUG EXPOSURE

Drug exposure was defined from the Prescription Register data. The register contains all reimbursed drug purchases from community pharmacies in Finland. Prescription Register data includes purchase date, drug substance, DDD of the dispensed amount of drug, Nordic Article number (Vnr number) of the package, size of the package, strength, number of dispensed packages, costs and PIN of the patient. Drugs were classified according to the Anatomical Therapeutic Chemical classification system (ATC) as defined by the World Health Organization (WHO). According to SII’s regulations, reimbursed drugs were dispensed for a maximum of three months’ treatment per purchase. Drugs used during hospital stays were not included.

4.2.1 Modelling of drug use; PRE2DUP

In both MEDALZ datasets, drug use periods were estimated by the PRE2DUP method (Prescriptions to Drug Use Periods) from drug purchases (Tanskanen et al. 2015). The results of the PRE2DUP modelling relate to drug use periods which describe when continuous drug use started and ended, for each participant and for each ATC code (Figure 2). Drug use periods were calculated individually for each cohort participant and drugs with temporal sliding averages of daily dose in DDDs. The PRE2DUP method does not include predefined assumptions of drug use such as that the drug will be used with a dose of 1 DDD per day, or other dose assumptions. Some general restrictions for joining of drug purchases are included in the method, e.g. that refill lengths of over 300 days will split drug use periods and the maximum duration for a single purchase is 150 days. Drug use periods are controlled with package-level parameters. The package-level information is coded according to package-specific Nordic Article number (vnr number) which identifies the strength of the drug, number of doses, dosage form and manufacturer. Vnr-based information is even more accurate than ATC-based, including information on administration route, whether drug is dividable or not, and distinguishes between different package sizes.

The PRE2DUP method takes into account stockpiling of drugs, and hospital care periods when drugs are not recorded in the Prescription Register. Duration of hospital care was calculated from Hospital Discharge Register, which includes admission and discharge dates. The maximum duration of hospital stay, included in the last purchase of a drug use period, was set to 30 days. This prevents extending the drug use period over long hospital stays.

One drug use period may contain one or more purchases and switching from one product to another within the same ATC code. If the participant has only one purchase of an ATC code, PRE2DUP uses the most common refill length for the package in the study population for defining the duration of drug use period.

The PRE2DUP method has been validated against information from self-reported drug use by interviewing patients, and by expert opinion (Tanskanen et al. 2015, Taipale et al. 2016b, Tanskanen et al. 2017). For example, mirtazapine use periods modelled with PRE2DUP achieved 94% correctness in an expert opinion evaluation (Tanskanen et al. 2017). When comparing register-based data modelled with PRE2DUP with drug use reported in a detailed interview, the agreement between these sources was 88% (Cohen’s Kappa 0.81, 95% CI 0.66–0.95) for urinary antispasmodics, 93% (Cohen’s Kappa 0.81, 95% CI 0.74–0.89) for antidepressants and 80% (Cohen’s Kappa 0.78, 95% CI 0.69–0.87) for proton pump inhibitors. The good or very good agreements highlight the validity of PRE2DUP method for estimating the use of these drugs (Taipale et al. 2016b).
Figure 2. An example of the PRE2DUP method operation from drug purchases and hospital days to a drug use period of citalopram. Abbreviations: DDD=defined daily dose, PIN=Personal Identification Number

4.2.2 Definition of the exposure in studies I-III

In the main analysis of study I, drug use periods of acetylcholine esterase inhibitors (AChEI) were defined as use of any AChEI with the possibility to switch from one drug substance to another in the same class. Similarly, drug use periods of urinary antispasmodics (UA) were combined to estimate the use of any UA and switching between substances within the class was allowed. Thus, drug use periods for AChEI and UA may contain concomitant use of drugs within these classes. In the drug substance analysis, only those persons who did not change their AChEI drug substance during the follow-up were included. Four examples of use and concomitant use periods are demonstrated in Figure 3.

Figure 3. Use periods of AChEI, UA, and their concomitant use. Abbreviations: AChEI=acetylcholine esterase inhibitor, UA=urinary antispasmodic.
In the main analysis of study II, antidepressant use was defined as use of any antidepressant. Switching to another drug substance and concomitant use within the antidepressant class was allowed during the follow-up period. In drug class analysis, SSRIs, mirtazapine, SNRIs and other antidepressants were modelled in a similar way and the follow-up ended when the drug class was changed to a drug in another class.

In study III, PPI exposure was defined as “current” if the PPI use period was ongoing during 0–30 days before, “past” if the PPI use period had been ongoing 31–90 days before (but not 0–30 days before) and “ever” if PPIs had been used during the 10 observation time years before the date of hip fracture or the corresponding date for controls (Figure 4). For duration of use, “any PPI use” was obtained by combining overlapping PPI use periods.

![Diagram of PPI use and user classification into current, past and ever users of PPIs in study III.](image)

*Figure 4. Five examples of PPI use and user classification into current, past and ever users of PPIs in study III.*

Specific definitions and ATC-codes for drug exposure in studies I-III are shown in Table 7. Exposures were restricted to those drugs which were on the market during the study period.
Table 7. Drug exposure definition in studies I-III.

<table>
<thead>
<tr>
<th>Drug class (Study number)</th>
<th>Drug substances</th>
<th>ATC-code</th>
<th>Study specific exposure definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>AChEIs (I)</td>
<td>donepezil</td>
<td>N06DA02</td>
<td>Use of any AChEIs was defined as use of ATC class N06DA</td>
</tr>
<tr>
<td></td>
<td>rivastigmine</td>
<td>N06DA03</td>
<td></td>
</tr>
<tr>
<td></td>
<td>galantamine</td>
<td>N06DA04</td>
<td></td>
</tr>
<tr>
<td>UAs (I)</td>
<td>oxybutynin</td>
<td>G04BD04</td>
<td>Use of any UAs was defined as use of G04BD</td>
</tr>
<tr>
<td></td>
<td>tolterodine</td>
<td>G04BD07</td>
<td></td>
</tr>
<tr>
<td></td>
<td>solifenasine</td>
<td>G04BD08</td>
<td></td>
</tr>
<tr>
<td></td>
<td>trospium</td>
<td>G04BD09</td>
<td></td>
</tr>
<tr>
<td></td>
<td>darifenacin</td>
<td>G04BD10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>fesoterodine</td>
<td>G04BD11</td>
<td></td>
</tr>
<tr>
<td>Antidepressants (II)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SSRIs</td>
<td>fluoxetine</td>
<td>N06AB04</td>
<td>Use of SSRIs was defined as use of ATC class N06AB</td>
</tr>
<tr>
<td></td>
<td>citalopram</td>
<td>N06AB05</td>
<td></td>
</tr>
<tr>
<td></td>
<td>escitalopram</td>
<td>N06AB10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>paroxetine</td>
<td>N06AB05</td>
<td></td>
</tr>
<tr>
<td></td>
<td>sertraline</td>
<td>N06AB06</td>
<td></td>
</tr>
<tr>
<td></td>
<td>fluvoxamine</td>
<td>N06AB08</td>
<td></td>
</tr>
<tr>
<td>Mirtazapine</td>
<td></td>
<td>N06AX11</td>
<td></td>
</tr>
<tr>
<td>SNRIs</td>
<td>venlafaxine</td>
<td>N06AX16</td>
<td></td>
</tr>
<tr>
<td></td>
<td>milnacipran</td>
<td>N06AX17</td>
<td></td>
</tr>
<tr>
<td></td>
<td>duloxetine</td>
<td>N06AX21</td>
<td></td>
</tr>
<tr>
<td>Other antidepressants</td>
<td>clomipramine</td>
<td>N06AA04</td>
<td></td>
</tr>
<tr>
<td></td>
<td>trimipramine</td>
<td>N06AA06</td>
<td></td>
</tr>
<tr>
<td></td>
<td>amitriptyline</td>
<td>N06AA09</td>
<td></td>
</tr>
<tr>
<td></td>
<td>nortriptyline</td>
<td>N06AA10</td>
<td></td>
</tr>
<tr>
<td></td>
<td>doxepin</td>
<td>N06AA12</td>
<td></td>
</tr>
<tr>
<td></td>
<td>moclobemide</td>
<td>N06AG02</td>
<td></td>
</tr>
<tr>
<td></td>
<td>mianserin</td>
<td>N06AX03</td>
<td></td>
</tr>
<tr>
<td></td>
<td>trazodone</td>
<td>N06AX05</td>
<td></td>
</tr>
<tr>
<td></td>
<td>bupropion</td>
<td>N06AX12</td>
<td></td>
</tr>
<tr>
<td></td>
<td>reboxetine</td>
<td>N06AX18</td>
<td></td>
</tr>
<tr>
<td>PPIs (III)</td>
<td>omeprazole</td>
<td>A02BC01</td>
<td>Use of PPI was defined as use of ATC class A02BC</td>
</tr>
<tr>
<td></td>
<td>pantoprazole</td>
<td>A02BC02</td>
<td></td>
</tr>
<tr>
<td></td>
<td>lansoprazole</td>
<td>A02BC03</td>
<td></td>
</tr>
<tr>
<td></td>
<td>rabeprazole</td>
<td>A02BC04</td>
<td></td>
</tr>
<tr>
<td></td>
<td>esomeprazole</td>
<td>A02BC05</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AChEIs=Acetylcholine esterase inhibitors, UAs=Urinary antispasmodics, SSRIs=Selective serotonin reuptake inhibitors, SNRIs=Serotonin and noradrenaline reuptake inhibitors, PPIs=proton pump inhibitors
4.3 OUTCOME MEASURES

4.3.1 Pharmacodynamic drug interaction (Study I)
Concomitant use of AChEIs and UAs were assessed as overlapping use periods of these drugs i.e. overlap of any length was considered as concomitant use. The outcome was chosen due to the potential that there is a detrimental pharmacodynamic interaction between these two classes of drugs. A description of the drug use periods and concomitant use is shown in Figure 3.

4.3.2 Hip fracture (Studies II and III)
Hip fractures were identified from Hospital Discharge Register based on ICD-10 codes (since 1996) S72.0 (fracture of neck of femur), S72.1 (pertrochanteric fracture) and S72.2 (subtrochanteric fracture). With respect to previous hip fractures, the corresponding ICD-8 (1972-1986) codes were 82000, 82010, 82090, 82001, 82011, 82091; and ICD-9-code (1987-1995) was 820. Only the first hip fracture for each person after the start of follow-up was taken into the analysis. Persons with previous hip fracture were excluded as it is difficult to separate new hip fracture events from the treatment of a previous fracture based on Hospital Discharge Register data. In a systematic review of validation studies, the accuracy of the hip fracture diagnosis in Finnish Hospital Discharge Register has been reported to be very good, and coverage of true positive diagnosis as high as 98% (Sund 2012).

4.4 STUDY DESIGNS

4.4.1 Descriptive cohort (Study I)
MEDALZ-2005 dataset was utilized. The study population included persons who used AChEIs during the four years of follow-up, between January 1, 2006 and December 31, 2009. Formation of the study sample and exclusions are shown in Figure 5. The reasons for end of follow-up were death, >90 days hospitalization or institutionalization or the end of the study follow-up, which ever occurred first.

![Figure 5. Formation of the study sample of the study I.](image-url)
4.4.2 Cohort study (Study II)
The population examined in Study II consisted of persons with and without AD from the MEDALZ dataset. Persons with antidepressant use during the one year washout period (WO) before diagnosis of AD were excluded to avoid prevalent user bias (Ray 2003). Other exclusion criteria were hospitalization/institutionalization >50% of the WO, ongoing >90 days hospitalization period on the last day of WO or hospitalization throughout the follow-up, as register-based data does not include information of drug use during hospital stays.

After these exclusions, two comparison persons without AD (N=100,982) were matched for age and sex, at the date of AD diagnosis for each person with AD (N=50,491), with similar exclusion criteria applied to the comparison persons. The index date was the matching date and started the follow-up. The ending points for follow-up were incident hip fracture, ≥90 days’ hospital stay, discontinuation of antidepressant use, after 1,500 days or at the end of the study period (December 31, 2012), whichever came first.

4.4.3 Nested case-control study (Study III)
In study III, we investigated the association between PPI use and the risk of hip fracture among persons with AD. The study was restricted to new hip fractures. From the MEDALZ study population (N=70,718), persons with a hip fracture before the diagnosis of AD (N=3,714) were excluded whereas persons with an incident hip fracture after the diagnosis of AD were defined as cases. After these exclusions, the study sample consisted of 4,818 cases with an incident hip fracture. For each hip fracture case, up to four controls without a hip fracture (N=19,235) were matched at the date of hip fracture with incidence density sampling. Controls were matched by age (± 2 years), sex and time since AD diagnosis (±90 days). The index date was defined as the date of hip fracture for cases and the corresponding matching date for controls.

The formation of the final study samples in studies I-III is summarized in Table 8.
Table 8. Summary of the formation of final study sample in each study

<table>
<thead>
<tr>
<th>Study I</th>
<th>Study II</th>
<th>Study III</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Data</strong></td>
<td>MEDALZ-2005</td>
<td>MEDALZ</td>
</tr>
<tr>
<td><strong>Initial study sample</strong></td>
<td>Persons with AD on December 31, 2005, N=28,093</td>
<td>Persons with AD, N=70,718</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Comparison persons without AD for matching, N=282,858</td>
</tr>
<tr>
<td><strong>Design</strong></td>
<td>Cohort</td>
<td>Nested case-control</td>
</tr>
<tr>
<td><strong>Exclusion criteria:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long-term hospitalization/ institutionalization</td>
<td>Whole follow-up or at the beginning of follow-up, N=2,680</td>
<td>&gt;50% of WO, or ongoing &gt;90 days at the last day of WO, or whole follow-up, AD N=854</td>
</tr>
<tr>
<td>Study specific exclusion criteria</td>
<td>Non-users of AChEIs, N=4,971</td>
<td>Antidepressant use during the 1 year WO, AD N=16,920 Previous hip fracture, AD N=2,453</td>
</tr>
<tr>
<td>Matching</td>
<td>NA</td>
<td>1:2 persons without AD for each person with AD, based on age and sex at the date of AD diagnosis</td>
</tr>
<tr>
<td>Final study sample</td>
<td>AChEI-users, N=20,442</td>
<td>Persons with AD, N=50,491 Matched persons without AD, N=100,982</td>
</tr>
</tbody>
</table>

Abbreviations: AD=Alzheimer’s disease, WO=Washout period, AChEIs=Acetylcholine esterase inhibitors

4.5 COVARIATES

Covariates of studies I–III were extracted from the Special Reimbursement Register, Hospital Discharge Register and Prescription Register, and are defined in Tables 9–11. Age and sex were obtained from the SII. Occupational socioeconomic position was obtained from Statistics Finland and the highest socioeconomic position at the age of 45-55 was used. The lowest class included unemployed persons and students, medium class included manual employees and lower clerical workers, the highest class included entrepreneurs and higher clerical workers; there was a fourth class for persons with unknown occupational positions. Hospital days (Study III) were based on Hospital Discharge Register and investigated 10 years before the index date and divided to <90 days and ≥90 days at hospital during the follow-up. Covariates, drugs and comorbidities associated with exposure and outcome, were chosen based on the literature (Thorell et al. 2014, Bakken et al. 2014, Tolppanen et al. 2013a, Juntunen et al. 2017).
Table 9. Definitions of covariates extracted from the Special Reimbursement Register

<table>
<thead>
<tr>
<th>Covariates (Study number)</th>
<th>Measurement point (Study number)</th>
<th>Comorbidity and special reimbursement code(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular diseases (I,II,II)</td>
<td>At the beginning of the follow-up (January 1, 2006) (I) Since 1972 until - the start of follow-up (II) - the date of hip fracture (III)</td>
<td>Chronic heart failure, arterial hypertension, coronary artery disease or chronic arrhythmia (one or more of them) 201, 205, 206</td>
</tr>
<tr>
<td>Diabetes (I,II,III)</td>
<td>At the beginning of the follow-up (January 1, 2006) (I) Since 1972 until - the start of follow-up (II) - the date of hip fracture (III)</td>
<td>Diabetes 103</td>
</tr>
<tr>
<td>Asthma/COPD (I,II,III)</td>
<td>At the beginning of the follow-up (January 1, 2006) (I) Since 1972 until - the start of follow-up (II) - the date of hip fracture (III)</td>
<td>Asthma/COPD 203</td>
</tr>
<tr>
<td>Hypothyreosis (I)</td>
<td>At the beginning of the follow-up (January 1, 2006) (I)</td>
<td>Hypothyreosis 104</td>
</tr>
<tr>
<td>Rheumatoid arthritis and disseminated connective tissue diseases (I,II,III)</td>
<td>At the beginning of the follow-up (January 1, 2006) (I) Since 1972 until - the start of follow-up (II) - the date of hip fracture (III)</td>
<td>Rheumatoid arthritis and disseminated connective tissue diseases 202</td>
</tr>
<tr>
<td>Epilepsy (I,II,III)</td>
<td>At the beginning of the follow-up (January 1, 2006) (I) Since 1972 until - the start of follow-up (II) - the date of hip fracture (III)</td>
<td>Epilepsy 111</td>
</tr>
<tr>
<td>Parkinson disease (I)</td>
<td>At the beginning of the follow-up (January 1, 2006) (I)</td>
<td>Parkinson disease 110</td>
</tr>
<tr>
<td>Prostate cancer (I)</td>
<td>At the beginning of the follow-up (January 1, 2006) (I)</td>
<td>Prostate cancer 116</td>
</tr>
<tr>
<td>Cancer (II,III)</td>
<td>Since 1972 until - the start of follow-up (II) - the date of hip fracture (III)</td>
<td>Breast cancer, prostate cancer, gynecologic cancer, leukemia, and other malignant tumor 115, 116, 128, 117 and 130</td>
</tr>
<tr>
<td>Time from AD diagnosis (I)</td>
<td>At the beginning of the follow-up (January 1, 2006) (I)</td>
<td>Time from entitlement to special reimbursement (307) for antidementia drugs</td>
</tr>
</tbody>
</table>

Abbreviation: COPD=Chronic obstructive pulmonary disease
### Table 10. Definitions of covariates extracted from the Hospital Discharge Register

<table>
<thead>
<tr>
<th>Covariates</th>
<th>Measurement point</th>
<th>ICD-10 codes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>History of Stroke (II,III)</strong></td>
<td>Since 1972 until the diagnosis of AD and corresponding matching date for comparisons (II)</td>
<td>I60-I64</td>
</tr>
<tr>
<td></td>
<td>- the date of hip fracture or corresponding date for comparisons (III)</td>
<td>(ICD-9 codes 430, 431, 432, 4339A, 4340A, 4340A, 4341A, 4349A, 4360 and ICD-8 codes 430, 431, 432, 433, 434)</td>
</tr>
<tr>
<td><strong>Substance abuse (II,III)</strong></td>
<td>Since 1972 until the diagnosis of AD and corresponding matching date for comparisons (II)</td>
<td>Diagnoses of alcohol-induced chronic pancreatitis (K860), mental and behavioral disorders due to psychoactive substance use (F10-19) or substance abuse as reason for hospital admission before the date of AD diagnoses (Corresponding ICD8-codes: drugs: 291*, 303*, 304* and * ICD9-codes: drugs: 291*, 292*, 303*, 304*, 305* ICD-10 drugs: F1*)</td>
</tr>
<tr>
<td></td>
<td>- the date of hip fracture or corresponding date for comparisons (III)</td>
<td></td>
</tr>
<tr>
<td><strong>Depression or bipolar disorder (II,III)</strong></td>
<td>Since 1972, at least 5 years before the diagnosis of AD (II,III)</td>
<td>Manic episode: F30; bipolar disorder: F31; depression: F32-34, F38-39</td>
</tr>
<tr>
<td><strong>Schizophrenia (II,III)</strong></td>
<td>Since 1972, at least 5 years before the diagnosis of AD (II,III)</td>
<td>Schizophrenia, schizotypal or delusional disorders F20-29</td>
</tr>
<tr>
<td><strong>Anxiety disorders (II)</strong></td>
<td>Since 1972, at least 5 years before the diagnosis of AD (II)</td>
<td>Neurotic, stress-related, and somatoform disorders: F4</td>
</tr>
<tr>
<td><strong>Previous fracture (III)</strong></td>
<td>Since 1972, limited to 10 years before index date (III)</td>
<td>S*2 or T02 (any fracture)</td>
</tr>
</tbody>
</table>

Abbreviations: AD=Alzheimer’s disease, ICD=International Classification of Diseases
Table 11. Definitions of covariates extracted from the Prescription Register

<table>
<thead>
<tr>
<th>Covariates (study number)</th>
<th>Measurement point (study number)</th>
<th>ATC codes (study number)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteoporosis (II)</td>
<td>Since year 1995 until the diagnosis of AD (II)</td>
<td>M05BA, M05BB (bisphosphonates) (II)</td>
</tr>
<tr>
<td>Use of BZDRs (II,III)</td>
<td>At the time of AD diagnosis and corresponding matching date for persons without AD in main analysis (II)</td>
<td>Classes N05BA, N05CF or N05CD (II, III)</td>
</tr>
<tr>
<td></td>
<td>Time dependently in sensitivity analysis (II)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>30 days before hip fracture or corresponding date for comparisons (III)</td>
<td></td>
</tr>
<tr>
<td>Use of antipsychotics (II,III)</td>
<td>At the time of AD diagnosis and corresponding matching date for persons without AD in main analysis (II)</td>
<td>N05A (excluding prochlorperazine N05AB00 and lithium N05AN01) (II, III)</td>
</tr>
<tr>
<td></td>
<td>Time dependently in sensitivity analysis (II)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>30 days before hip fracture and corresponding date for comparisons (III)</td>
<td></td>
</tr>
<tr>
<td>Use of other psychotropic drug (II)</td>
<td>At the time of AD diagnosis and corresponding matching date for persons without AD in main analysis (II)</td>
<td>N06C (combinations)</td>
</tr>
<tr>
<td></td>
<td>Time dependently in sensitivity analysis (II)</td>
<td></td>
</tr>
<tr>
<td>Use of opioids (II,III)</td>
<td>At the time of AD diagnosis and corresponding matching date for persons without AD in main analysis (II)</td>
<td>N02A</td>
</tr>
<tr>
<td></td>
<td>Time dependently in sensitivity analysis (II)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>30 days before hip fracture and corresponding date for comparisons (III)</td>
<td></td>
</tr>
<tr>
<td>Use of AChEIs (III)</td>
<td>30 days before hip fracture and corresponding date for comparisons (III)</td>
<td>N06DA</td>
</tr>
<tr>
<td>Use of memantine (III)</td>
<td>30 days before hip fracture and corresponding date for comparisons (III)</td>
<td>N06DX01</td>
</tr>
<tr>
<td>Use of antithrombotics (III)</td>
<td>Since 1995 until the hip fracture and corresponding date for comparisons (III)</td>
<td>B01A</td>
</tr>
<tr>
<td>Use of H2-blockers (III)</td>
<td>Since 1995 until the hip fracture and corresponding date for comparisons (III)</td>
<td>A02BA</td>
</tr>
</tbody>
</table>

Abbreviations: AD=Alzheimer’s disease, ATC=Anatomic Therapeutic Chemical, BZDR=benzodiazepines and related drugs, AChEIs=Acetylcholine esterase inhibitors
4.6 STATISTICAL ANALYSES

All analyses in studies I and II were performed using SAS statistical software, version 9.3 (SAS Institute, Inc., Cary, NC), and all analysis in study III with SAS, version 9.4 (SAS Institute, Inc., Cary, NC).

In study I, descriptive analyses were used for defining means, medians with interquartile ranges (IQRs) and Chi Square test of the characteristics of the study population (age <80 vs ≥80 years, sex, cardiovascular disease, diabetes, asthma/COPD, rheumatoid arthritis and disseminated connective tissue diseases, epilepsy, Parkinson disease, prostate cancer and time from AD diagnosis) and differences between AChEI only users and concomitant users of AChEIs and UAs (January 1, 2006). Factors associated with concomitant use of AChEIs and UAs were examined by using conditional logistic regression analysis and adjusted for confounders. The use of AChEI (but not UA) was used as a reference. The confounders for adjustments were age, sex, Parkinson disease, diabetes and prostate cancer, measured until the beginning of the follow-up. Results were reported as crude and adjusted odds ratios (ORs) with 95% Confidence Intervals (CIs). The total AChEI use duration during the follow-up was calculated from combined separate drug use periods of any AChEI drug. The duration of UA use was constructed similarly. Concomitant use with UA was also reported by choice of AChEI drug substance. The choice of AChEI drug substance was evaluated only among those study persons who started the AChEI treatment and used the same substance during the whole follow-up.

In study II, the duration of antidepressant use was reported in days, subdivided into 1–30, 31–180, 181–365, 366–729 and 730–1500 days. The duration of use was limited to 1500 days because of sparsity of data. Age-adjusted rates of hip fractures were calculated for every classified duration of antidepressant use, and every antidepressant drug class studied. Cox proportional hazard models were used and adjusted for confounders. Antidepressant use was modelled as time dependent exposure, with censoring to discontinuation of use. Nonuse of antidepressants was used as a reference. Baseline confounders for adjustments were sex, age, cardiovascular diseases, diabetes, asthma/COPD, epilepsy, rheumatoid arthritis, glaucoma, socioeconomic status, history of substance abuse, history of cancer, osteoporosis, use of BZDRs, use of antipsychotics, use of opioids, history of stroke, history of depression or bipolar syndrome, history of schizophrenia and history of anxiety disorders. All analyses were conducted separately among persons with AD and persons without AD. Results were reported as crude and adjusted hazard ratios (HRs) with 95% CI. Sensitivity analysis was performed by adjusting the main analysis time dependently (instead of baseline covariates) for the use of antipsychotics, other psychotropic drugs (drug combinations), BZDRs and opioids.

In study III, a conditional logistic regression model was used to investigate whether current (0–30 days before hip fracture), past (31–90 days before hip fracture), or cumulative (during 10 years before hip fracture) drug use, as well as the duration of drug use, were associated with risk of hip fracture. Different PPI drug substances (lansoprazole, omeprazole, pantoprazole, esomeprazole and rabeprazole) were compared according to their risk of hip fracture. All analyses considered the nonuse of PPI as the reference. The results were adjusted for confounders and reported as crude and adjusted ORs with 95% CI and p-values.

In the sensitivity analysis, investigation of number of hospital stays and admissions during one year from the index date was conducted. These were reported separately for cases and controls as well as for PPI users and non-users.

Prevalence of urinary antispasmodic (G04BD), antidepressant (N06A), and PPI (A02BC) uses was investigated for persons with AD during 3 years before and until 3 years after diagnosis. Three months' prevalence was chosen to capture also “as needed” use of these drugs. Persons were defined as prevalent users if a drug use period was ongoing
within the time window. Persons were censored, if they were in hospital/institutional care for two months (67%) or more of the three months’ time window, and excluded after death.

4.7 ETHICAL CONSIDERATIONS AND DATA PROTECTION

According to Finnish legislation, approval of Ethical Committee was not needed because only pseudonymized data was used and study persons were not contacted or identified from register-based data. The register maintainers, National Institute for Health and Welfare and SII, provided permission to use the MEDALZ data.

Data is protected by a pseudonymized protocol, in which the study participants have only research identification codes instead of personal identification numbers (PINs). The data key between research identification codes and PINs has been constructed and stored by SII and is not available for researchers. Only persons who have been granted permission from the register maintainers have access to the MEDALZ datasets. The computer which stores the data used in this thesis, is protected by password and not available for general use.
5 Results

5.1 CONCOMITANT USE OF ACETYLCHOLINE ESTERASE INHIBITORS AND URINARY ANTISPASMODICS (STUDY I)

During the four-year follow-up, 7.3% (n=1,491) of all AChEI users (n=20,442) were using UA concomitantly. The median duration of all AChEI periods summed together was 932 (IQR 392–1460) days; for all the concomitant AChEI and UA use periods it was 236 (IQR 74–586) days. A significant proportion (39%) of concomitant users, were taking AChEI and UA concomitantly for at least one year.

There were some differences between AChEI only users (n=18,951) and concomitant users of AChEI and UA i.e. concomitant users had a higher prevalence of diabetes, Parkinson disease and prostate cancer. Concomitant users were younger (mean age 78.8 years; SD 6.3 years) than AChEI only users (mean age 79.3 years; SD 6.9 years). In all, 38% of concomitant users were men; similarly 33% of AChEI only users were male.

Factors significantly associated with concomitant use were age <80 years, male sex, diabetes, Parkinson disease and prostate cancer (Figure 6). In the drug substance analysis, there were no differences in concomitant use of AChEI and UA between donepezil, rivastigmine or galantamine users.

Figure 6. Factors associated with concomitant use of AChEis and UAs compared to AChEI use only. Age in comparison with ≥80 years. ORs adjusted for age, sex, Parkinson disease and prostate cancer.
Abbreviations: AChEI=Acetylcholine esterase inhibitors, UAs=Urinary antispasmodics, OR=odds ratio, CI=confidence interval
5.2. ASSOCIATION BETWEEN ANTIDEPRESSANT USE AND RISK OF HIP FRACTURE AMONG PERSONS WITH AND WITHOUT ALZHEIMER’S DISEASE (STUDY II)

Antidepressant use was more common among persons with AD as compared to persons without AD: 22.4% of persons with AD (n=11,329) initiated antidepressant use during the follow-up compared to 9.9% (n=10,001) of persons without AD.

The age-adjusted rate of hip fractures per 100 person-years was 3.01 (95% CI 2.75–3.34) among persons with AD and 2.28 (95% CI 1.94–2.61) among persons without AD during antidepressant use (Figure 7). The rate was highest at the beginning of antidepressant use in persons with and without AD.

![Figure 7. Age-adjusted event rates per 100 person-years for the risk of hip fracture by antidepressant use among persons with and without Alzheimer’s disease (AD). Abbreviations: AD=Alzheimer’s disease, CI=confidence interval](image)

Antidepressant use was associated with an increased risk of hip fracture among persons with AD (aHR [adjusted HR] 1.61, 95% CI 1.45–1.80) and among persons without AD (aHR 2.71, 95% CI 2.35–3.14) compared with nonuse (Figure 8). The risk was highest at the beginning of antidepressant use in both persons with and without AD, but remained elevated for the whole follow-up.
Figure 8. Adjusted hazard ratios for risk of hip fracture by antidepressant use among persons with and without Alzheimer’s disease (AD).
Abbreviations: AD=Alzheimer’s disease, CI=confidence interval

In the drug class analysis, all investigated antidepressant classes (SSRIs, SNRIs and mirtazapine) were associated with an increased risk of hip fracture among both persons with and without AD.
5.3 ASSOCIATION BETWEEN PROTON PUMP INHIBITOR USE AND RISK OF HIP FRACTURE AMONG PERSONS WITH ALZHEIMER’S DISEASE (STUDY III)

Current PPI use was associated with an increased risk of hip fracture (aOR 1.12, 95% CI 1.03–1.22) (Figure 9). With respect to the duration of current use, the risk was increased only with short-term use (<1 year) (aOR 1.23, 95% CI 1.10–1.37), but not with use longer than one year (aOR 1.00, 95% CI 0.89–1.13) after adjusting for confounders.

![Figure 9. Duration of current proton pump inhibitor (PPI) use and association with risk of hip fracture. Odds ratios adjusted for age, sex, socioeconomic position; ≥90 hospital days during the follow-up; cardiovascular diseases, diabetes, asthma/COPD, glaucoma, rheumatoid arthritis, epilepsy; previous fracture, stroke, cancer, depression or bipolar syndrome, schizophrenia, substance abuse; use of AChEIs, memantine, oral corticosteroids, bisphosphonates, antipsychotics, antidepressants, BZDRs, opioids, antithrombotics, H2-blockers. Abbreviations: COPD=chronic obstructive pulmonary disease, AChEIs = Acetylcholinesterase inhibitors, BZDRs=Benzodiazepines and related drugs, CI=confidence interval](image)

Cumulative use was not associated with an increased risk for hip fracture compared to non-users in the adjusted model. In the drug substance analysis, there were no significant differences between PPI drug substances and associated risk of hip fracture after adjusting for confounders.
5.4 PREVALENCE OF URINARY ANTISPASMODICS, ANTIDEPRESSANTS AND PROTON PUMP INHIBITORS USE BEFORE AND AFTER ALZHEIMER’S DISEASE DIAGNOSIS

The prevalence of urinary antispasmodic use was 3.0% three years before AD diagnosis, 4.1% at the time of AD diagnosis and 3.1% at three years after the diagnosis (Figure 10). The prevalence of antidepressant use was 10.4% three years before the diagnosis, 20.1% at the time of the diagnosis and 28.7% at three years after the diagnosis. The prevalence of PPI use was 9.5% at three years before the diagnosis, 14.0% at the time of the diagnosis and 20.3% three years after the diagnosis.

Figure 10. Prevalence of urinary antispasmodics, antidepressants and proton pump inhibitors (PPIs) use before and after Alzheimer’s disease (AD) diagnosis (0-point at y-axis).
6 Discussion

To summarize, a comparatively high prevalence of concomitant use of AChEI and UA was found during 4 years’ follow-up among persons with AD. In fact, a significant number (39%) of the concomitant users had been consuming both an AChEI and an UA concurrently for at least one year. Furthermore, antidepressant use was associated with an increased risk of hip fracture among persons with and without AD. The risk was highest at the initiation of antidepressant use, but remained elevated for up to four years. The increased risk was found for all antidepressant drug classes and remained elevated even after adjusting for consumption of other drugs and the presence of diseases increasing the risk of fall. No association was detected between long-term or cumulative PPI use and the risk of hip fracture. The assessment of symptomatic drug use in relation to AD diagnoses revealed that the prevalence of antidepressant and PPI, but not UA, use increased strongly after the AD diagnosis.

6.1 DISCUSSION OF RESULTS

6.1.1 Concomitant use of acetylcholine esterase inhibitors and urinary antispasmodics (Study I)
The prevalence of concomitant use of AChEI and UA was 8.6% among men and 6.7% among women during the 4 years’ follow-up; these values are approximately at the same level as in previous studies although the variability in study designs make comparisons difficult. It is more likely that one can capture concomitant use with longer follow-up times than is possible in cross-sectional studies based on one time point; in fact, the longer follow-up times may be one reason for the higher prevalences observed in cohort studies such as ours. In addition to variability in study designs and populations, differences in prevalence may result from UA availability at the time of study, as the number of UA drug substances to which a subject has been exposed has varied from one to six in previous studies.

The median duration of all concomitant drug use periods was about eight months. Thus, the duration of concomitant use in our study was the longest reported, as a previous study reported the median duration of concomitant use as 5.6 months during 9 years of follow-up (Boudreau et al. 2011). The long duration of concomitant use in our study may indicate, that this pharmacodynamic drug interaction may have been unrecognized or the medication regimen of persons with AD is not being assessed as frequently as recommended in Finland. However, none of the previous studies were focused on community-dwelling persons with AD.

The relatively high prevalence of concomitant use of AChEIs and UAs might be due to the lack of other pharmacological alternatives for the treatment of urinary incontinence. During the study period, anticholinergic drugs were the only pharmacological option for the treatment of incontinence, as the β-3 adrenoreceptor agonist, mirabegron, only entered the market after the study period. Mirabegron does not have anticholinergic properties and thus in theory it should be a better option for the treatment of UI among older persons and persons with AD (Igawa et al. 1998). However, the real-world evidence of its effectiveness is still mainly lacking (Duckett and Balachandran 2016).

UI may also be an adverse effect of AChEI drug use, and consequently lead to initiation of UA therapy (Hashimoto et al. 2000, Lampela et al. 2016). As the AChEI treatment is recommended for all patients with mild or moderate stage of AD if there is no
contraindication for treatment (Memory disorders: Current Care Guideline 2017), the majority of persons with AD are receiving these agents. Thus, after initiating UA, they became also concomitant users of AChEI and UA. Since 2009 when the study period ended, new functions have been supplemented into drug interaction software; at least some of them now alert about the pharmacodynamic drug interactions in addition to their pharmacokinetic counterparts. Thus, it is possible that this software will now have reduced the frequency of concomitant use.

Another reason why individuals prefer UA drugs may be the inconvenience associated with incontinence pads or other equipment for incontinence, or difficulties in frequently changing the pads so that the subject feels comfortable. Further, AD may cause difficulties in basic activities of daily living including an increased need of assistance with toileting and hygiene (Dove et al. 2017). If an AD patient lives at home alone or with an old partner, there may be a lack of help in toilet visits and hygiene. Further, non-pharmacological aids and making timed visits to the toilet may be too demanding for many AD patients (Gove et al. 2017).

Parkinson disease, diabetes and prostate cancer were associated with concomitant use of AChEI and UA. Urinary incontinence can be one of the symptoms encountered in Parkinson disease (Khoo et al. 2013) and diabetes (Izci et al. 2009) and it is likely due to the neuropathy associated with these diseases. The prevalence of urinary incontinence has been previously shown to be higher among men with a history of prostate cancer (Kopp et al. 2013), which may be one reason for the more frequent UA use. In addition, the treatment of prostate cancer, such as surgery, radiation therapy and androgen-deprivation therapy, has been associated with acute and even long-term incontinence (Boettcher et al. 2012, Kopp et al. 2013).

Male sex was associated with the concomitant use of AChEI and UA. Similarly, this association with male sex was found in a previous study (Johnell and Fastbom 2008). However, the majority of our study participants were women, and the prevalence of urinary incontinence among women has been previously shown to be higher compared to that in men (Maggi et al. 2001, Suhr and Lahmann 2017). One reason for the difference in UA use between men and women may be that UI among women is treated with local vaginal estrogens instead of UAs. In fact, local vaginal estrogens are recommended in the Finnish Current Care Guideline for the treatment of urge and mixed UI and may be used also for treatment of stress UI (Urinary incontinence (women): Current Care Guideline 2017). Another explanation for the difference between UA use in men and women may be that women might consider UI as a normal part of aging and because of this, they might also be more willing than men to wear incontinence pads and thus, UA use was relatively more common among men. In addition, fear of prostate cancer may lead men with urinary symptoms to visit a physician, and furthermore, the symptoms of BPH may require the initiation of UA therapy.

The concomitant use of AChEI and UA is inappropriate, and in theory may lead to a failure of AChEI treatment and consequently, worsening of AD symptoms. However, the clinical relevance of concomitant use could not be evaluated in study I and this will needed to be investigated further. Due to the adverse effects of blockade of cholinergic receptors, especially their impact on cognition, and the putative drug interaction between AChEIs and UAs, it is evident that initiation of UA therapy should be avoided among older persons with cognitive disorders. Therefore, non-pharmacologic options or pharmacotherapy without anticholinergic properties should be the preferred treatment of UI.

6.1.2 Antidepressant use and risk of hip fracture (Study II)
Compared to the non-use of antidepressants, we found that antidepressant use was associated with a three times higher age-adjusted event rate for hip fractures among persons with AD as well as being over two times higher among persons without AD.
However, the event rate was higher also among nonusers with AD (1.63; 95% CI 1.56–1.70) as compared with nonusers without AD (0.69; 95% CI 0.66–0.71). Previous studies have reported that persons with AD are at a higher risk of suffering a hip fracture compared to the general older population (Tolppanen et al. 2013b, Zhao et al. 2012), which is likely due to the effect of AD on balance, mobility and attention. The difference in event rates during antidepressant use compared with nonuse indicated that antidepressant users with AD are at a high risk for hip fracture. The higher baseline rate of hip fracture among persons with AD likely reflects the impact of AD on the risk of falling.

In our study, antidepressant use was associated with an increased relative risk of hip fracture among persons with and without AD. None of the previous studies have investigated this association among persons with AD, but previous cohort studies examining older populations reported increased risk ratios i.e. 1.4–2.5 (95% CI 0.6–3.8) (Ensrud et al. 2003, Bakken et al. 2013, Leavy et al. 2017). Thus, our risk estimates were approximately at the same level as observed in previous studies.

The elevated hazard ratio among persons without AD compared to persons with AD may be partly related to the fact that among persons without AD, the antidepressant nonusers may include healthier older persons than those who had been prescribed antidepressant medication. Furthermore, it was found that comorbid conditions were more frequent among users than nonusers, such as cardiovascular diseases (55% of users vs. 49% of nonusers) and osteoporosis (13% of users vs. 9% of nonusers) and they used BZDRs more frequently (34% of antidepressant users vs. 15% of antidepressant nonusers). The analyses were adjusted for these conditions but some unmeasured residual confounding may still exist. These differences in comorbidities were observed also between users and nonusers among persons with AD, but they may have a smaller role because of the shared, major risk factor, AD.

The risk of hip fracture was highest at the beginning of antidepressant use, a similar finding was obtained from the UK (Hubbard et al. 2003). The authors of that study considered the remarkably high risk estimates might have been overestimated due to problems with selection and indication bias. Similarly to our study, the risk increase at the beginning of the use may be confounded by the fact that antidepressant therapy is initiated when either the underlying illness or symptoms may have worsened and this may explain, at least to some extent, the increased risk of falling and consequent fractures. However, the risk of hip fracture in our study remained elevated with a longer duration of use. We did not have data on the indication or severity of symptoms for which the antidepressant was prescribed, or data on the severity or frequency of BPSDs among persons with AD. Thus, in our study, as in all observational studies, results may be confounded by the indication for antidepressant use. We applied a new user design in an attempt to avoid survival bias (Ray 2003), which will be further discussed in section 6.2.2.

In our study, all classes of antidepressant drugs (SSRIs, SNRIs and mirtazapine) were associated with an increased risk of hip fracture. The oldest previous studies published investigating the risk of hip fracture associated with antidepressant use evaluated only TCAs, but with time, studies have expanded to examine also newer drug classes such as SSRIs. At the time of our study, TCAs were mainly used to treat neuropathic pain, not for depression, nor in treatment of BPSD. Thus, since the antidepressant use consisted of different antidepressant classes as well as the lack of information about SNRI and mirtazapine in previous studies, the results in these older reports may not be comparable to our study which included these newer drugs. It is important to investigate mirtazapine separately due to its unique pharmacological mechanism of action, and because mirtazapine can be used for treating sleeping disturbances (Alam et al. 2013). One could speculate that mirtazapine is being prescribed to treat insomnia in older persons more often than in the general adult population even though its use is not recommended for primary insomnia without depressive symptoms (Insomnia: Current Care Guideline 2015). One
reason for prescribing mirtazapine may be that there have been extensive discussions among health care professionals about the adverse effects of BZDRs such as the risk of falling (Seppälä et al. 2018), especially in older persons.

Our results of the AD group are generalizable to community-dwelling persons with AD. The results of persons without AD are not directly generalizable, i.e. those individuals were matched to persons with AD. Therefore, their mean age is higher than in the general older population and furthermore, majority of persons with dementia are missing from this population. Thus, the comparison persons without AD do not represent the whole general older population.

According to our results, antidepressant use is associated with an increased risk of hip fracture. Therefore replacing antipsychotic drugs or BZDRs with antidepressants in the treatment of BPSD may not be a safer option, at least in terms of hip fracture risk.

6.1.3 Proton pump inhibitor use and risk of hip fracture (Study III)

We used two definitions, current and cumulative, for PPI use. Current use refers to use ongoing at the time of hip fracture whereas cumulative use sums up all PPI use during the observation period. Current and cumulative PPI use were further categorized according to the duration of use in order to assess the impact of increasing treatment duration on the risk and whether it supported the putative mechanisms behind the association between PPI use and hip fractures.

No association was found between long-term (current use of ≥1 year) use or cumulative (up to 10 years) PPI use and the risk of hip fracture. This is contrary to many previous studies, which have reported an increased risk associated with long-term (Yang et al. 2006, Targownik et al. 2008, Khalili et al. 2012, Adams et al. 2014) or cumulative use (Corley et al. 2010, Chiu et al. 2010) of PPIs. However, also some previous studies have reported that there is no risk linked with long-term use (De Vries et al. 2009, Pouwels et al. 2011). None of the previous studies have investigated the association between long-term or cumulative PPI use and the risk of hip fracture among persons with AD.

The putative mechanisms for the association between PPI use and risk of hip fracture are reduction of calcium absorption and B12-vitamin deficiency (Gray et al. 2010, Lam et al. 2013). The bioavailability of dietary calcium depends on several issues, such as vitamin D intake, but calcium salts also need gastric acid before they become dissociated (Sipponen and Härkönen 2010), and PPIs decrease the secretion of gastric acid. Therefore one could speculate that a reduction of calcium absorption could lead to a decrease in bone mineral density and consequently, to an increased risk of bone fractures (Gray et al. 2010). However, changes in bone structure happen very slowly and thus, the possible impact of PPIs would be more likely to be observed after long-term PPI use. Gastric acid is also required to cleave vitamin B12 from ingested dietary proteins before the vitamin can be absorbed (Lam et al. 2013). Vitamin B12 deficiency may cause peripheral neuropathy leading to deficiencies in sensory functions which may increase the risk of falling and consequently of suffering fractures (Lam et al. 2013, Shipton and Thachil 2015). This would also require a long time period before it would develop, and thus we conclude that these mechanisms seem unlikely i.e. we had up to 10 years of follow-up, but still found no association between long-term or cumulative PPI use and any increased risk of hip fracture.

We found a slightly increased risk of hip fracture associated with current PPI use. The risk was highest when the duration of current use was <1 year. These results are in line with previous studies conducted among the general population (Vestergaard et al. 2006, De Vries et al. 2009).

The mechanism behind the association between short-term use and an increased risk of hip fracture is far from clear. The association may be confounded by underlying factors also increasing the risk of falling, such as previous falls, dizziness or gait problems which cannot be captured from registers (Deandrea et al. 2010). PPIs may also be prescribed for
persons with more serious health conditions, or together with gastro-irritating drugs, such as NSAIDs. However, we adjusted our results for the use of oral corticosteroids, AChEIs, BZDRs and opioids, but have no information on symptoms behind the use of these drugs. It might be that the indication for these drugs could have influenced the increased risk of hip fracture among current users of PPIs.

Two previous studies which investigated dose-response found evidence that a high dose of the PPI had a stronger association with hip fracture than lower doses (De Vries et al. 2009, Pouwels et al. 2011). However, these differences between lower and higher doses were small and had overlapping confidence intervals. Therefore, it is unlikely that there is a dose-response between PPI use and risk of hip fracture.

We found no increased risk of hip fracture associated with the individual drugs in the PPI class when they were investigated separately. There are three previous studies which have studied individual PPI drugs and the risk of hip fracture (Kaye and Jick 2008, Cea Soriano et al. 2014, Adams et al. 2014). One of them found no association (Kaye and Jick 2008), whereas the two others found an increased risk with omeprazole use compared to nonuse of omeprazole (Adams et al. 2014, Cea Soriano et al. 2014).

Based on our results and previous studies, the association between PPI use and hip fracture is not likely to be causal. However, when prescribing a PPI, other associated risks of these drugs, such as the risk of enteric infections or pneumonia (Leonard et al. 2007, Eom et al. 2011) should be taken into account. If the PPI has been prescribed for gastroprotection to combat some other medication, then obviously the PPI treatment should be discontinued as soon as the treatment with the other drug is terminated. In addition, possible drug interactions, such as a reduction of antiplatelet efficacy of clopidogrel with the concomitant use of PPIs other than pantoprazole (Juurink et al. 2009, Bundhun et al. 2017), should be taken into account when assessing the need for PPI treatment.

6.1.4 Prevalence of urinary antispasmodics, antidepressants and proton pump inhibitors use before and after Alzheimer’s disease diagnosis

The prevalence of UA use increased slightly at the time of AD diagnosis (4%) compared to three years before AD diagnosis (3%), but stabilized to a level of 3% by three years after AD diagnosis. The slight peak in prevalence may reflect a higher level of health service use and contacts with physicians near the time of diagnosis. Another possible reason is the initiation and adverse effect of the AChEI treatment, emerging soon after AChEI initiation and influencing the start of UA treatment (Lampela et al. 2016).

In our study, the prevalence of antidepressant use doubled from three years before diagnosis (10%) compared with the time of diagnosis (20%) and then was further elevated at three years after the diagnosis (29%). The prevalence peaked at the time of diagnosis or immediately thereafter. A previous Finnish study which was based on interviews of patients and caregivers, reported that the prevalence of antidepressant use increased from 11% (n=326) to 18% (n=131) in the three years after the AD diagnosis (Törmälehto et al. 2017). The results of these two studies point to a similar increasing trend but in our study more users were captured from register-based data than were identified by interview. Our findings suggest that antidepressants are being used for the treatment of BPSDs, including sleep disturbances. Furthermore, the further elevated prevalence at three years after the diagnosis may reflect the increased frequency of BPSDs throughout the course of AD. The increased prevalence observed in our study was consistent with a study from the UK, which reported that the prevalence of antidepressant use increased over four-fold from 10 years (7%) before to 4 years (32%) after the dementia diagnosis (Martinez et al. 2013).

The prevalence of PPI use doubled from three years before the AD diagnosis (10%) to three years after the diagnosis (20%). There was a strong increase in prevalence from 9 months before the diagnosis to approximately 9 months after the diagnosis. The prevalence of PPI use surrounding the AD diagnosis has not been previously studied. Even long-term
use of PPIs seems to be rather common among persons with AD (Juntunen et al. 2017). Another possible reason for the increased prevalence around the time of AD diagnosis is the initiation of new drugs, which possibly have gastro-irritating properties. One reason for the increased prevalence might be treatment of nausea or vomiting which may occur as adverse effects of the newly initiated AChEI treatment (Winblad et al. 2007). In addition, increased use of health care services around the AD diagnosis (Taipale et al. 2016a), may lead to initiation of symptomatic pharmacotherapy such as the treatment of BPSDs.

Symptomatic pharmacotherapies such as antidepressants and PPIs are more frequently used after AD diagnosis as compared to the time before the diagnosis. However, the prevalence of UAs did not increase after the AD diagnosis, which may indicate that physicians are aware of the anticholinergic adverse effects of these drugs.

6.2 METHODOLOGICAL CONSIDERATIONS

6.2.1 Finnish registers

Registers offer a great opportunity for conducting pharmacoepidemiologic effectiveness studies with large population-based samples, which are impossible to collect or manage by questionnaires or interviews. In MEDALZ-2005 and MEDALZ, several health-related registers, i.e. Prescription Register, Hospital Discharge Register and socioeconomic information from Statistic of Finland were linked together. A great strength of Finnish registers is their coverage of the entire population (Furu et al. 2010).

The validity of hip fracture diagnoses, which represent the outcome measure of Studies II and III, has been proven to be very good for incident hip fractures (Sund et al. 2007, Sund 2012). Due to nationwide coverage of registers, we were able to access data on socioeconomic positions from Statistics Finland and on chronic diseases from the Special Reimbursement Register which allowed us to adjust for many covariates. The diagnoses in the Special Reimbursement Register includes data also about chronic diseases diagnosed in the outpatient setting and thus is important data beside the Hospital Discharge data. Special reimbursement diagnoses are assumed to be valid because they are based on a statement from a physician and granted by the SI only if prespecified diagnostic criteria are fulfilled. However, the mildest forms of the diseases are not granted special reimbursement status and thus will be missing from our data.

Compared to studies in which the results were adjusted for only basic variables such as age and sex, our results provide stronger evidence due to the possibility to take into account several confounding factors which are known to be associated with the risk of falling and the risk of hip fracture.

However, register-based real-world data lacks information about whether the drugs were actually taken. This limitation applies to all register-based studies, as it is not possible to monitor the drug use with laboratory testing of drug blood concentrations or laborious pill counting.

MEDALZ-2005 and MEDALZ

The main strengths of this thesis are that studies of it are based on the nationwide MEDALZ-2005 and MEDALZ-datasets. These cover all residents in Finland with diagnosed AD. For example, our study population is not restricted according to living area or socioeconomic position unlike studies from insurance-based (Carnahan et al. 2004) or region-based data (Reyes et al. 2013).

The validity of AD diagnoses recorded in the Special Reimbursement Register has been studied during 1999–2008 (Solomon et al. 2014). This validation study reported the Special Reimbursement Register as having very good accuracy for AD diagnoses (97.1%) and fairly good sensitivity for AD (63.5%). The lower sensitivity is likely related to the fact that the
study of Solomon et al. did not evaluate whether persons diagnosed with AD would have fulfilled the criteria for special reimbursement of AD i.e. it may have included persons in the early stages of AD.

Comparison persons without AD were matched for persons with AD according to age, sex and living region. However, comparison persons may have other forms of cognitive disorders without the features of AD. Therefore these persons may not be representable of older population in all respects other than they do not have AD. Thus, the results are not generalizable to whole older population.

The lack of information of the stage of AD is a limitation of our studies. The time since AD diagnosis was used as a proxy for disease stage in study III when matching with control persons without hip fracture to hip fracture cases. Special reimbursement is granted in mild to moderate stages of AD but there may be differences in the actual timing of diagnoses and also in the progression of the disease and these could not be controlled for in our analyses. Persons with a more advanced stage of AD may be at higher risk for hip fracture, for example due to balance problems in comparison with persons with milder stage of AD.

For MEDALZ-2005 and MEDALZ cohorts, drug use has been identified from the Prescription Register, which covers all reimbursed drug purchases from all community pharmacies in Finland. Compared to self-reported information, the Prescription Register provides valid information of drug use without recall bias or bias due to a subject’s unwillingness to report drug use (Rikala et al. 2010). The Prescription Register lacks information on drug use during hospital/institution stays. Therefore, the results of these studies cannot be generalized for older persons living in institutional environments.

Drug purchases were modelled to drug use periods with the PRE2DUP method, which results in more accurate exposure times than other previously used methods (Tanskanen et al 2017). The use of the PRE2DUP method and time-dependent assessment of exposure minimized misclassification of users and nonusers during the follow-up. In the definitions applied in cross-sectional exposure methods which have been utilized in some previous studies, baseline users may become nonusers or baseline nonusers may initiate the use during the follow-up. Furthermore, PRE2DUP enables a definition of duration of use. The method takes into account personal purchasing styles, stockpiling and possible hospitalizations. However, indications for drug use are not recorded.

The PRE2DUP method has been validated by comparing the PRE2DUP modelled drug use periods with information from a comprehensive interview of older persons (Taipale et al. 2016); it was found that agreement between these two approaches is good (considered as Cohen’s kappa 0.61–0.80) or very good (Cohen’s kappa 0.81–1.00) for frequently used drugs (including AChEIs, UAs, antidepressants and PPIs).

MEDALZ-datasets lack details about OTC and non-reimbursed drugs, because they are not recorded in the Prescription Register. Both AChEIs and UAs are reimbursed and not available OTC. Only some starting packages of AChEI given by physicians might have been missed; these are provided as there is a short waiting time before the decision is received about special reimbursement for antidementia drugs. A limitation in study I is that it was not possible to adjust for the use by women of some non-reimbursed, local vaginal estrogen preparations. Antidepressants are available only with prescription, with their costs mainly reimbursed. Some packages of TCAs do not have reimbursement status and thus, would not be included in our study. Therefore, in our study, some TCA users may have been categorized as nonusers of antidepressants. However, according to drug use statistics, the use of TCAs is relatively uncommon (Finnish Medicines Agency 2018). Since 2010, PPIs have been available OTC in packages containing up to 14 tablets (Finnish Medicines Agency 2015) and these could not be included into PPI use in our analyses; this may have led to a possible underestimation of PPI exposure. However, in case of persons with chronic diseases, such as AD, PPIs, especially in long-term use, are likely to have been
prescribed since the individuals have regular contacts with health care personnel and it is cheaper to pay for the prescribed drugs in comparison with their OTC counterparts e.g. the price per PPI unit (tablet of capsule) is usually much cheaper in larger packages and these are available only with prescription. In addition, prescribed packages are reimbursed by the SII, which reduces even further the expenses for the patient. The impact of the failure to include OTC and non-reimbursed packages is assumed to be small, and unlikely have to affected the results.

Milder forms of diseases are treated in primary care and thus are not recorded in the Hospital Discharge Register, which details only conditions requiring hospital care and operations conducted during hospital care. Therefore, BPH or vaginal atrophy as the cause of the UI and consequently UA use are not recorded in hospital discharge data, which are register-based limitations of study I.

MEDALZ-datasets lack information on lifestyle factors of the study population such as diet, smoking and alcohol intake, as well as muscle strength, balance, nutritional status or frailty. In addition, in studies II and III, there was a lack of data on some other risk factors for hip fracture, such as stressfull health situations or the severity of comorbidities. Furthermore, we had no information on well-known predictors of falls, such as previous falls, dizziness or gait problems (Deandrea et al. 2010). The failure to take these variables into account may have led to some overestimation of the association between drug use and the risk of hip fracture. However, we adjusted the analyses for a large number of diseases and drugs associated with falling and fracture risk and at least partly, these covariates probably captured the impact of the unmeasured comorbidities.

6.2.2 Study designs
In study I, we investigated the prevalence and duration of concomitant use of AChEI and UA among persons with AD during the four year study period. The advantage of our study was that the duration of concomitant use could be evaluated in the cohort design, and the continuity of drug use was modelled with the validated PRE2DUP method. Thus, concomitant users of AChEIs and UAs were effectively captured and the duration of concomitant use could be measured. One limitation in the definition of concomitant use was that some switches between drugs may have been defined as short concomitant use periods in our modelling. However, the durations of concomitant use were relatively long which reduced the possible impact.

In study II, only incident antidepressant users were included to avoid survival bias, or as it has been described, the prevalent-user bias. According to Ray (2003), prevalent users may represent survivors, which in this study would have been those who tolerated the possible adverse effects of antidepressants. Thus, if we had included also prevalent users into the analysis, then the risk estimates would have been underestimated. Only one previous cohort study was conducted with a new user design (Bakken et al. 2013), whereas two other studies considered all antidepressant users as being exposed (Ensrud et al. 2003, Leavy et al. 2017).

It is important to estimate the risk of a hip fracture in terms of duration of antidepressant use because it may help to clarify the mechanisms behind the association. We assessed the risk according to duration of use with the PRE2DUP modelled drug use approach which is an advantage in comparison to previous studies (Ensrud et al. 2003, Thorell et al. 2014); in these, the drug exposure was defined at one time point, which may lead to a serious misclassification to exposed persons.

Analyses were conducted separately in persons with AD and in those without AD to determine whether there were any possible differences between these groups. For example, AD itself is a risk factor for hip fractures (Tolppanen et al. 2013a), and this was taken into account in these analyses.
Study III was conducted with a nested case-control design. Cumulative use was studied during the 10 years before the index date, which is the longest observation time so far investigated. The case-control design was chosen since this would be able to track a long history of PPI use and to assess the impacts of cumulative use. The PPI users had several comorbidities, many of them requiring drug treatment and thus, residual confounding cannot be ruled out and may explain the association between short-term PPI use and hip fracture.
7 Conclusions

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

1. Acetylcholine esterase inhibitors (AChEIs) and urinary antispasmodics (UAs) are used concomitantly by community-dwelling persons with AD, despite their opposite pharmacological actions. Due to possible weakened response of AChEIs and the anticholinergic adverse effects of UA, other treatment options should be preferred for the treatment of UI among persons with AD.

2. The risks and benefits should be assessed carefully before prescribing antidepressant drugs for older persons, because antidepressant use was associated with an increased risk of hip fracture. The risk was highest at the beginning of use and remained elevated for up to four years among community-dwelling older persons with and without AD.

3. Long-term or cumulative PPI use was not associated with a risk of hip fracture among community-dwelling persons with AD. However, the need for long-term PPI use should be assessed carefully as there may be other risks associated with this therapy.

4. The prevalence of antidepressant and PPI use was high after the AD diagnosis; this finding raises concerns because the use of these drugs may elevate the risks for adverse effects and unwanted events.
8 Implications

8.1 CLINICAL IMPLICATIONS

1. Pharmacotherapy of older persons and especially older persons with cognitive disorders should be regularly assessed in order to avoid drug-related adverse effects and events.

2. Pharmacodynamic drug interactions should be taken into account.

3. Urinary antispasmodic drugs with anticholinergic properties should be avoided in persons with cognitive disorders. The use of these drugs should be discontinued in persons with a cognitive disorder and before the initiation of AChEI treatment.

4. Non-pharmacological options should be recommended for the treatment of UI in clinical practice.

5. The causes of BPSDs should be evaluated and treated before initiating any psychotropic drug. Non-pharmacological options for the treatment of BPSD should be preferred.

6. When the physician is considering prescribing an antidepressant drug, its benefits and risks, such as the risk of falling, should be assessed.

8.2 SUGGESTIONS FOR FUTURE RESEARCH

1. The benefits of non-anticholinergic drugs and non-pharmacological methods for the treatment of UI should be examined. In addition, the efficacy and effectiveness of drugs for UI should be investigated among older persons and persons with cognitive disorders.

2. Further studies are needed to identify those persons with AD who will benefit from symptomatic pharmacotherapy for BPSDs, as well as those who are at the highest risk for experiencing severe adverse events from this therapy. In addition, non-pharmacological treatment of BPSD should be investigated.

3. The real-world effectiveness of symptomatic pharmacotherapy should be studied against the possibility of adverse events in older populations.
9 References


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This register-based thesis was based on nationwide MEDALZ-cohorts including persons with Alzheimer’s disease and their comparison persons. Thesis determined the prevalence and duration of concomitant use of acetylcholinesterase inhibitors and urinary antispasmodics. Furthermore, the risk of hip fracture associated with antidepressant, or proton pump inhibitor, use was investigated. The prevalence of use of these drugs before and after Alzheimer’s diagnosis was also examined.