Pain is a common symptom among persons with Alzheimer’s disease that is frequently treated with analgesics. This thesis examined the prevalence of analgesic use and long-term opioid use in a nationwide sample of persons with Alzheimer’s disease and compared them to matched persons without the disease. The impact of opioid initiation on psychotropic drug use and the association between incident opioid use and hospital-treated pneumonia were also investigated.
ANALGESIC USE AND OUTCOMES ASSOCIATED WITH INCIDENT OPIOID USE

THE MEDICATION USE AND ALZHEIMER’S DISEASE STUDY
Aleksi Hamina

ANALGESIC USE AND OUTCOMES ASSOCIATED WITH INCIDENT OPIOID USE
THE MEDICATION USE AND ALZHEIMER’S DISEASE STUDY

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ABSTRACT

Alzheimer’s disease (AD) is the most common cognitive disorder. Among persons with AD as well as in older persons in general, pain is an important factor impairing health and limiting the quality of life. Analgesics are the most frequently used treatment for pain, but little is known about their use among persons with AD.

This thesis aimed to study in persons with and without AD I) the prevalence of analgesic use and II) the prevalence of long-term opioid use. Another aim was to investigate among persons with AD, III) the impact of opioid initiation on psychotropic drug use and IV) to examine whether the risk of hospital-treated pneumonia was associated with incident opioid use.

This thesis is based on the register-based MEDALZ cohort, consisting of all community-dwellers newly diagnosed with AD in Finland from 2005 to 2011 (N = 70,718). These persons were identified from a nationwide Special Reimbursement Register, which includes data on reimbursements for chronic diseases. Comparison persons without AD were also identified, matched for age, sex, and region of residence. Data on drug use were collected from a Prescription Register. Data on hospital days and diagnoses were extracted from a Hospital Discharge Register.

Analgesics were used by 34.9% of persons with AD and by 33.5% without AD over a six-month period. With respect to the opioid users, 34.2% of persons with and 32.3% without AD were long-term users of opioids. In persons with AD, opioid initiation was associated with a downward trend of antipsychotic and benzodiazepine and related drug use, but not of antidepressant use. Incident opioid use was associated with a 34% increased risk of pneumonia compared to non-use.

Analgesic use and long-term opioid use were common among persons with and without AD. New opioid use was associated with a decreasing trend for some psychotropic drug use but also with an increased risk for pneumonia. These results underline the importance of pain and medication assessment among older persons with and without AD.

National Library of Medicine Classification: QV 77.2, QV 89, QV 95, WL 704.6, WT 155
Medical Subject Headings: Alzheimer Disease; Dementia; Pain/drug therapy; Analgesics; Analgesics, Opioid; Psychotropic Drugs; Pneumonia; Aged; Pharmacoepidemiology; Cohort Studies; Registries; Finland
Hamina, Aleksi

Kipulääkkeiden käyttö ja opioidien käyttöön liittyvät päätetapahtumat, Lääkkeiden käyttö ja Alzheimerin tauti -tutkimus

Kuopio: Itä-Suomen yliopisto

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TIIVISTELMÄ

Alzheimerin tauti (AT) on yleisin muistisairaus. AT:a sairastavilla kipu on yleinen oire, joka rajoittaa terveyttä ja heikentää elämänlaatua. Kipulääkkeet ovat yleisin kivun hoidon muoto, mutta niiden käyttöä AT:a sairastavilla tiedetään vain vähän.

Tämän tutkimuksen tavoitteina oli tarkastella I) kipulääkkeiden käytön ja II) opioidien pitkäaikaiskäytön prevalenssia AT:a sairastavilla ja tautia sairastamattomilla verrokeilla. Lisäksi tavoitteina oli tutkia opioidin aloituksen vaikutusta III) psykykenlääkkeiden käyttöön ja IV) keuhkokuumeen riskiin AT:a sairastavilla.


Puolen vuoden ajanjaksolla kipulääkkeitä käytti 34,9 % AT:a sairastavista ja 33,5 % tautia sairastamattomista. Opioidin aloittaneista 34,2 % AT:a sairastavista ja 32,3 % verrokeista käytti lääketta pitkääikaisesti, eli vähintään puoli vuotta. AT:a sairastavilla opioidin aloitus oli yhteydessä laskevaan psykoosilääkkeiden ja bentsodiasepiinien ja niiden kaltaisten lääkkeiden käyttötrendin, mutta samaa ei havaittu masennuslääkkeillä. Lisäksi opioidin aloitus lisäsi keuhkokuumeen riskiä 34 % verrattuna opioidia käyttämättömiin henkilöihin.

Kipulääkkeiden käyttö ja opioidien pitkäaikaiskäyttö olivat yleisiä sekä AT:a sairastavilla että sairastamattomilla. AT:ia sairastavilla opioidin aloitukseen liittyi joidenkin psykykenlääkkeiden laskeva käyttötrendi, mutta myös suurentunut keuhkokuumeen riski. Tulokset korostavat kivun ja lääketyksen arvioinnin tärkeyttä kaikilla iäkkäillä henkilöillä.

Luokitus: QV 77.2, QV 89, QV 95, WL 704.6, WT 155
Yleinen suomalainen ontologia: Alzheimerin tauti; dementia; kivunhoito; kipulääkkeet; opioidit; psyykenlääkkeet; keuhkokuume; ikääntyneet; epidemiologia; kohorttitutkimus; rekisterit; Suomi
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Many thanks go to my friends and family. Olli Kärkkäinen provided me with technical help but also invaluable discussions on the essence of research almost every day. My deepest gratitude belongs to my significant other Heli Järvinen, without whom this would not have been possible and this thesis would not have been written.

Kuopio 13th of December, 2019

Aleksi Hamina
LIST OF ORIGINAL PUBLICATIONS

This dissertation is based on the following original publications:


The publications were adapted with the permission of the copyright owners. In addition, this thesis contains previously unpublished data, presented in chapter 5.3.
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<thead>
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<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>AD</td>
<td>Alzheimer’s disease</td>
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<tr>
<td>ADE</td>
<td>Adverse drug effect</td>
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<td>ADL</td>
<td>Activities in daily living</td>
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<td>AGS</td>
<td>American Geriatrics Society</td>
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<tr>
<td>aHR</td>
<td>Adjusted hazard ratio</td>
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<tr>
<td>aOR</td>
<td>Adjusted odds ratio</td>
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<tr>
<td>ASA</td>
<td>Acetylsalicylic acid</td>
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<tr>
<td>ATC</td>
<td>Anatomical therapeutic chemical</td>
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<tr>
<td>BGS</td>
<td>British Geriatrics Society</td>
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<td>BPSD</td>
<td>Behavioural and psychological symptoms of dementia</td>
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<tr>
<td>CAIDE</td>
<td>Cardiovascular risk factors, aging and dementia study</td>
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<tr>
<td>CDR</td>
<td>Clinical Dementia Rating</td>
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<tr>
<td>ChEI</td>
<td>Cholinesterase inhibitors</td>
</tr>
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<td>COPD</td>
<td>Chronic obstructive pulmonary disease</td>
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<tr>
<td>CMAI</td>
<td>Cohen-Mansfield agitation inventory</td>
</tr>
<tr>
<td>CNS</td>
<td>Central nervous system</td>
</tr>
<tr>
<td>COX</td>
<td>Cyclo-oxygenase</td>
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<tr>
<td>CYP</td>
<td>Cytochrome P450</td>
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<tr>
<td>DCM</td>
<td>Dementia care mapping</td>
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<tr>
<td>DS-DAT</td>
<td>Discomfort scale - dementia of the Alzheimer type</td>
</tr>
<tr>
<td>DSM</td>
<td>Diagnostic and statistical manual of mental disorders</td>
</tr>
<tr>
<td>HIV</td>
<td>Human immunodeficiency virus</td>
</tr>
<tr>
<td>IADL</td>
<td>Instrumental activities of daily living</td>
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<tr>
<td>IASP</td>
<td>International Society for Pain research</td>
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<tr>
<td>ICD</td>
<td>International Classification of Diseases</td>
</tr>
<tr>
<td>ITT</td>
<td>Intention-to-treat</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>MME</td>
<td>Morphine milligram equivalent</td>
</tr>
<tr>
<td>MMSE</td>
<td>Mini-mental state exam</td>
</tr>
<tr>
<td>NINCDS-ADRDA</td>
<td>National Institute of Neurological and Communicative Diseases and Stroke/Alzheimer’s Disease and Related Disorders Association</td>
</tr>
<tr>
<td>Acronym</td>
<td>Description</td>
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<tr>
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<tr>
<td>NOMESCO</td>
<td>Nordic Medico-Statistical Committee Classification</td>
</tr>
<tr>
<td>NPI</td>
<td>Neuropsychiatric inventory</td>
</tr>
<tr>
<td>NSAID</td>
<td>Non-steroidal anti-inflammatory drugs</td>
</tr>
<tr>
<td>OTC</td>
<td>Over-the-counter</td>
</tr>
<tr>
<td>PACSLAC</td>
<td>Pain Assessment Checklist for Seniors with Limited Ability to Communicate</td>
</tr>
<tr>
<td>PAINAD</td>
<td>Pain Assessment in Advanced Dementia</td>
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<tr>
<td>PIN</td>
<td>Personal identification number</td>
</tr>
<tr>
<td>PPI</td>
<td>Proton-pump inhibitor</td>
</tr>
<tr>
<td>PRE2DUP</td>
<td>From prescription drug purchases to drug use periods method</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised controlled trial</td>
</tr>
<tr>
<td>SII</td>
<td>Social Insurance Institution</td>
</tr>
<tr>
<td>SSRI</td>
<td>Selective serotonin reuptake inhibitor</td>
</tr>
<tr>
<td>TD</td>
<td>Transdermal</td>
</tr>
<tr>
<td>THL</td>
<td>National Institute for Health and Welfare (Terveyden ja hyvinvoinnin laitos)</td>
</tr>
<tr>
<td>USA</td>
<td>United States of America</td>
</tr>
<tr>
<td>VNR</td>
<td>Nordic article number</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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1 INTRODUCTION

All around the world, the population is ageing at a fast rate (United Nations, 2017). It is estimated that the number of persons aged over 80 will triple from 137 million in 2017 to 425 million in 2050. This means societies, health care systems, and health care professionals will need to find ways to ensure that the needs of the growing numbers of older adults are met and their care well managed. The term ‘older adults’ has previously referred to persons over 65, but as life expectancies have risen and older persons’ functionality has improved, the term more commonly refers to persons over 75, as is the case in this thesis.

One of the most dramatic illnesses facing older adults and thus societies at large are cognitive disorders and especially Alzheimer’s disease (AD) (Prince et al., 2013). Despite decades of research, no cure for AD has emerged. For this aged population, one important aspect of good care is pain management, as pain is one of the most common problems limiting the quality of life among older adults, including those with AD (Abdulla et al., 2013).

Analgesics are some of the most common forms of pain management (Abdulla et al., 2013). However, there is a scarcity of research into how well analgesics alleviate pain among persons with AD or what kinds of safety issues are associated with analgesic use in this population (Corbett et al., 2012; Erdal et al., 2019). Older adults are frequently excluded from randomised controlled trials (RCTs) due to age, co-medication, or comorbidities such as cognitive impairment (Liberopoulos et al., 2009; Lockett et al., 2019). The real-life users of the drugs are subsequently not well represented in these trials. Observational study designs, utilising representative populations through register-based data have the benefit of analysing the consequences of drug use among the actual individuals using a particular drug (Furu et al., 2010). Moreover, the risk for rare events, which cannot be evaluated in the relatively small trials, can be assessed in register-based studies. Pharmacoepidemiological register-based research thus offers excellent opportunities for studying drug use and associated outcomes among older adults with or without AD (Hilmer et al., 2012).

The Medication use and Alzheimer’s disease (MEDALZ) cohort utilised in this thesis is based on inclusive, nationwide registers from multiple years, including all clinically diagnosed persons with AD living in Finland in the years 2005–2011. The cohort provides extensive information on drug use, hospital days, diagnoses, and other aspects of health, thus providing a unique opportunity to investigate analgesic use among persons with AD.
2 REVIEW OF THE LITERATURE

2.1 PAIN IN OLD AGE

2.1.1 Definition and biology of pain

Pain has been described by the International Association for the Study of Pain (IASP) as an ‘unpleasant sensory or emotional experience associated with actual or potential tissue damage or described in terms of such damage’ (Loeser and Treede, 2008). Pain is a complex, subjective phenomenon modified by an individual’s memories, expectations, and emotions (Ickowicz et al., 2009).

The sensory physiology of the perception of acute pain is based on nociception, which refers to the neural processes of encoding and processing noxious stimuli (Julius and Basbaum, 2001; Loeser and Treede, 2008; Kuner, 2010; Baliki and Apkarian, 2015). Nociception refers to the stimulation of specialised sensory neurons, nociceptors, by noxious heat, intense pressure or irritant chemicals (Julius and Basbaum, 2001; Kuner, 2010). In acute pain, the main nociceptors are the slowly conducting, unmyelinated C fibres and the thinly myelinated, more rapidly conducting Aδ fibres. The input from peripheral nociceptors is transferred to second-order neurons in the spinal dorsal horn, from where the output is transmitted to the brain (Kuner, 2010). Importantly, the lateral spinothalamic tract projects to the lateral thalamus which is an important cerebral region in the processing of sensory and discriminative aspects of pain. The medial spinothalamic tract and the spinoparabrachial tract project to the medial thalamus and limbic structures, e.g. to the hippocampus and the amygdala; these structures are important in appreciating the emotional and aversive components of pain. The descending inhibitory system is another important part of pain perception; this system blocks the spinal transmission of nociceptive signals from the periphery, leading to a reduced sensation of pain.

In contrast to acute pain, chronic pain may persist after the initial injury has healed and it can even emerge without any obvious pathological trigger (Kuner, 2010). The IASP defines chronic pain as pain that persists or recurs for more than 3 months (Treede et al., 2019). Recently, the IASP has suggested that a distinction should be drawn between chronic primary pain and chronic secondary pain syndromes. Chronic primary pain cannot be better accounted for by any other chronic pain condition whereas chronic secondary pain syndromes are linked to other diseases as its underlying cause; in this case, pain may primarily be regarded as a symptom. The causes of chronic secondary pain include cancers, traumas and musculoskeletal diseases, such as osteoarthritis. The pathology of chronic pain syndromes is commonly characterised by a dysfunction of the physiological pathways conveying and inhibiting pain (Kuner, 2010). Presentations of hyperalgesia and allodynia are common; in hyperalgesia, patients may have increased sensitivity to pain; in allodynia, they may experience a painful response to innocuous stimuli.
In older adults, the physiological perception of pain may be somewhat altered. Older adults may possess lower pain thresholds than their younger counterparts if the applied noxious stimuli are mechanical, although significant heterogeneity of results exists in the literature (El Tumi et al., 2017). However, pain thresholds may even be higher as compared to young people if the stimuli are electrical current or heat (Lautenbacher, 2012). Some research has indicated that older adults perceive pain later, but once perceived, the pain becomes rapidly intolerable (Gagliese, 2009; Varrassi et al., 2015). This proposition is supported by evidence of decreased pain inhibition and increased perception of pain after repetitive painful stimuli (temporal summation) in experimental pain studies (Lautenbacher, 2012; Defrin et al., 2015). Experimental research suggests these changes are at least partly due to a decline in the function of the myelinated Aδ-fibres and a reduction in the efficiency of endogenous pain inhibition processes, although studies on age-related changes in pain perception systems are still somewhat scarce (Chakour et al., 1996; Edwards et al., 2003; Lautenbacher et al., 2005; Farrell and Gibson, 2007; Lautenbacher, 2012; Kemp et al., 2014).

2.1.2 Prevalence of pain and types of pain among community-dwelling older adults

The complexity and subjectivity of pain perception and the methodological challenges in their evaluation have complicated the study of pain prevalence among community-dwelling older adults (Abdulla et al., 2013). The prevalence of current pain in this population has been estimated to range from 20 to 46%, whereas estimations of the prevalence of chronic pain have even greater variations i.e. from every fourth to three out of every four. Chronic pain in this population can also be very persistent; in a Finnish study, more than 70% of those older adults who reported chronic pain, still continued to experience it after 2 years of follow-up (Karttunen et al., 2015). There are disagreements in the literature as to whether pain prevalence increases with age (Abdulla et al., 2013; Schofield, 2018). Some studies report a continual increase in pain prevalence with age, whereas some note a decrease after the ages 75–85, and yet others detected an overall decrease, or no change according to age (Abdulla et al., 2013).

Nonetheless, both stoic attitudes toward pain and verbal communication problems are more common among older adults and may lead to an under-reporting of pain (Abdulla et al., 2013; Schofield and Abdulla, 2018). Moreover, the type and site of pain differ between young and old adults. Older adults also frequently describe their chronic pain with affective, sensory, and neuropathic pain descriptions, which are indications that they are experiencing more severe pain (Thakral et al., 2016).

There are significant gender-related differences among older adults: women report higher prevalences of pain than men (Abdulla et al. 2013). Women may also have a lower threshold for seeking help for pain (Cornally and McCarthy, 2011) but also pain-inducing illnesses, such as osteoarthritis, may be more frequent among
women than men (Prieto-Alhambra et al., 2014). Moreover, women report a higher pain intensity than men (Miller et al., 2017).

Pain-inducing illnesses are common among older adults (Ickowicz et al., 2009). Musculoskeletal conditions, e.g. osteoarthritis, low back pain, osteoporosis, and rheumatoid arthritis, are major contributors to the pain experienced by older adults (Ingram and Symmons, 2018). For example, more than a third of the over 65 population have osteoarthritis, and this prevalence increases further with age (Palazzo et al., 2014). Chronic pain among older adults is frequently musculoskeletal and reported in knees, hips, and back (Abdulla et al., 2013). Furthermore, among older adults, musculoskeletal pain is especially commonly experienced simultaneously at multiple sites (Dragioti et al. 2017). Multisite pain is often of a higher intensity as compared to pain at a single site (Carnes et al., 2007; Denkinger et al., 2014; Dragioti et al., 2017). It is also a significant predictor of disability among older adults (Eggermont et al., 2014).

Other causes of pain among older adults include injuries. More than a third of those over 65 and almost half of those over 85 reported falling in the past two years (Cigolle et al., 2015), which is a significant risk factor for subsequent fractures and the related pain (Morrison et al., 2013). Pain and injuries likely exhibit a bi-directional relationship, as chronic pain increases the risk of falling among older adults (Leveille et al., 2009).

Cancer is a major source of severe pain among older adults (Guerard and Cleary, 2017). In Finland, most incident cancers are diagnosed in people over 65, and as the population ages, the numbers of cancer patients are likely to increase (Finnish Cancer Registry, 2019). The vast majority, approximately 80%, of older adults with advanced cancer experience pain (Rao and Cohen, 2004). In addition, cancer treatment may result in pain, even in the development of chronic pain syndromes (Guerard and Cleary, 2017).

Furthermore, chronic neuropathic pain, or pain associated with the somatosensory system, is more frequent among older adults as compared to younger people (Torrance et al., 2006; Bouhassira et al., 2008). This is due to disease states such as diabetic neuropathy and post-herpetic neuralgia, which become more common with age (Smith and Torrance, 2012). Other causes of neuropathic pain include trigeminal neuralgia, peripheral nerve injury, and central neuropathic pain, for example due to a brain injury or stroke (Colloca et al., 2017). Neuropathic pain is frequently communicated with sensory descriptors (e.g. tingling, burning, or electrical-like pain) and commonly causes allodynia. In addition to neuropathic pain in isolation, musculoskeletal pain among older adults may have a neuropathic component (Jones et al., 2014). This is the case in spinal stenosis, which may present with back pain in addition to radiculopathy.

2.1.3 The consequences of pain

Pain has an enormous effect not only on the individual’s health and emotional well-being but it is also a major, social and economic burden. Among the general
global population, low back pain is the leading cause of disability and osteoarthritis is the main contributor to activity limitations (Hoy et al., 2014; Ingram and Symmons, 2018). In older adults, musculoskeletal disorders, especially osteoarthritis, continue to be the most important cause of disability (Palazzo et al., 2014; James et al., 2018). Pain is also frequently the main reason for primary health care visits and among older adults, also for emergency department attendance (Mäntyselkä et al., 2001; Frießem et al., 2009; Covino et al., 2019).

In addition to physical disability, chronic pain can be devastating at the psychological level and it has been associated with multiple adverse outcomes among older adults e.g. depression and anxiety (Arola et al., 2010; Zis et al., 2017), cognitive impairment (Van Der Leeuw et al., 2016; Whitlock et al., 2017), frailty (Coelho et al., 2016), falls (Stubbs et al., 2014), sleep difficulties (Chen et al., 2011), and decreased overall quality of life (Jakobsson et al., 2003; Lacey et al., 2014; Dragioti et al., 2017).

### 2.2 ALZHEIMER’S DISEASE

Cognitive disorders are neurodegenerative diseases causing a decline in memory or in other cognitive skills and in a person’s ability to perform everyday activities (Alzheimer’s Association, 2016). AD is the most common cognitive disorder, comprising 60–80% of all cases. Other common types of dementia include dementia with Lewy bodies and vascular, and frontotemporal dementia. In addition, mixed types of dementias, i.e. diseases displaying features of AD with other types of cognitive disorders are not uncommon. In addition to the progressive decline in cognition, individuals with AD frequently have worsening neuropsychiatric symptoms or the so-called behavioural and psychological symptoms of dementia (BPSDs). For example, these include depression, apathy, agitation, anxiety, and sleep disturbances. Other symptoms of AD include impaired communication, disorientation, confusion, poor judgment, and eventually, impairment of primary reflexes, difficulties in walking, and problems in swallowing; ultimately AD is fatal. Ageing is the greatest risk factor for AD (Alzheimer’s Association, 2016). Most people diagnosed with AD are over 65 years old. Approximately 11% of persons aged 65 years and above and 32% of those aged 85 years and above have AD. In Finland, the average age at AD diagnosis is 80 years (Tolppanen et al., 2016), which is similar to other European countries (Anthony et al., 2014; Religa et al., 2015). Due to the ageing of the global population, the number of persons with a cognitive disorder is expected to multiply in the coming decades. According to estimates from the World Health Organization (WHO), there were approximately 46.8 million people living with a cognitive disorder in 2015, and this number will increase to 131.5 million in 2050 (Figure 1) (World Health Organization and Alzheimer’s Disease International, 2012). Most of this increase will be in the currently low- and middle-income countries. In 2016, cognitive disorders were the fifth-largest cause of death globally, causing 2.4 million deaths (Nichols et al., 2018). Among persons aged more than 70
years, cognitive disorders were the second most common cause of death after ischaemic heart disease. The Alzheimer’s Disease International has estimated that in 2015, the global cost of cognitive disorders was US $818 billion (Alzheimer’s Disease International 2015). However, in these calculations, China’s role may have been underestimated. More recent evaluations have estimated the global costs for cognitive disorders to have been as high as US $957.56 billion in 2015 (Jia et al., 2018). Projections of global costs would then rise to US $2.54 trillion in 2030, and US $9.12 trillion in 2050.


The population of Finland is also rapidly ageing. The percentage of the population over 75 years old is projected to increase from 10% in 2019 to 17% in 2050 (Official Statistics of Finland, 2018). In 2019, there were more than 500 thousand in the age group of over 75 years; this number is expected to more than double to over 1.1 million in 2070. In 2013, there were an estimated 200,000 persons with impaired cognition, 100,000 persons with a mild cognitive disorder, and an additional 93,000 persons with at least a moderately severe cognitive disorder (Finnish Medical Society Duodecim, 2017a). There are approximately 14,500 new cases of a cognitive disorder diagnosed every year in Finland.

The neuropathological hallmarks of AD are the accumulation of proteins as beta-amyloid plaques and tau fibrils in the brain, which precede brain atrophy (Alzheimer’s Association, 2016). The presence of neurofibrils in the brain of a person with AD were described already in 1907 by Alois Alzheimer (Alzheimer, 1907; Toodayan, 2016). Protein accumulation and neuronal changes have been detected decades before the first cognitive symptoms appear, as there are compensatory systems that ensure normal functioning (Alzheimer’s Association, 2016). Atrophy of hippocampal areas and the entorhinal cortex are common early findings in AD (Duyckaerts et al., 2009). The exact mechanisms underlying the AD pathology are still
to be resolved. Multiple age-related alterations contributing to neurodegeneration have been identified, including inflammation, impaired autophagy, mitochondrial dysfunction, vascular changes, epigenetic changes, and loss of synapses (Figure 2) (Hara et al., 2018). So far, after several decades of research, all drugs aimed at slowing or preventing the progression of AD pathology have failed, giving rise to alternative theories other than simply amyloid accumulation as being the triggering point of the disease (Panza et al., 2019).

Figure 2. Age-related alterations in biological processes which contribute to neurodegeneration in Alzheimer’s disease (modified from Hara et al. 2018).

The symptomatic phase of AD frequently begins with mild cognitive impairment (MCI), in which there is no disturbance with activities of daily living (ADL) (Roberts and Knopman, 2013; Alzheimer’s Association, 2016). MCI is common among older adults, with an estimated prevalence of 16-20% among persons aged 65 or older. However, not all MCI is due to progressive cognitive disorders; the conversion of MCI to AD has been estimated to range from 11–38% over 5 years (Ward et al., 2013).

Clinically, AD can be classified according to its symptoms into early, mild, moderate and severe disease by applying clinical scales, such as the Mini-Mental
State Examination (MMSE) or the Clinical Dementia Rating (CDR) (Folstein et al., 1975; Hughes et al., 1982; Finnish Medical Society Duodecim, 2017a). These stages reflect the progressive deterioration of cognitive functions and skills to maintain ADL and instrumental ADL (IADL) (Table 1).

Table 1. Examples of cognitive and functional symptoms in mild, moderate, and severe Alzheimer’s disease (AD) (modified from Finnish Medical Society Duodecim, 2017).

<table>
<thead>
<tr>
<th>Cognitive symptoms</th>
<th>Mild AD</th>
<th>Moderate AD</th>
<th>Severe AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Impaired episodic memory</td>
<td>Impaired memory</td>
<td>Severely impaired memory</td>
<td></td>
</tr>
<tr>
<td>Impaired learning, counting, and executive functioning</td>
<td>Apraxia</td>
<td>Severe apraxia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Visuospatial difficulties</td>
<td>Severe aphasia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Aphasia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Changes to ADL</th>
<th>Difficulties in IADL, e.g. not managing household finances, medication.</th>
<th>Inabilities in IADL, e.g. cooking</th>
<th>Inabilities in ADL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Problems driving, following complex conversations</td>
<td>Need to be reminded of ADL</td>
<td>Misplacing belongings, getting lost</td>
<td>Incontinence</td>
</tr>
</tbody>
</table>

ADL = Activities of daily living; IADL = Instrumental activities of daily living.

In Finland, four drugs are approved for the treatment of symptoms of AD (Finnish Medical Society Duodecim, 2017a). There are three cholinesterase inhibitors (ChEIs) donepezil, galantamine, and rivastigmine with the fourth drug being a N-methyl D-aspartate (NMDA) receptor antagonist, memantine. Acetylcholine is a neurotransmitter present in the peripheral and central nervous systems and metabolised in the synapse by the enzyme cholinesterase (Douchamps and Mathis, 2017). Depletion of acetylcholine in the basal forebrain was associated with memory impairment, which led to the introduction of ChEIs in AD therapy in the 1990s. Similarly, dysfunctional glutaminergic activity, mediated by the NMDA receptors, was found in AD, paving the way for the development of memantine (Wang and Reddy, 2017). Finnish Current Care Guidelines for memory disorders recommend prescribing ChEIs as the first line of pharmacological treatment for early and mild AD. Memantine can be prescribed alongside ChEIs in moderate to severe AD, or as monotherapy if ChEIs are not tolerated or are contraindicated. All ChEIs provide small or marginal benefits in cognitive function, ADLs and clinician-rated global clinical state, but are well tolerated with gastrointestinal adverse drug effects (ADEs) being the most frequently reported (Birks, 2006; Raina et al., 2008; Birks and Grimley Evans, 2015; Birks and Harvey, 2018; Dou et al., 2018). Similarly, memantine slightly improves cognition, functional activity, and global assessment and may be better tolerated than the ChEIs (Raina et al., 2008; Dou et al., 2018; McShane et al., 2019). At
the time of writing, there is no curative treatment to AD and the current treatments do not slow the progress of the disease.

2.2.1 Behavioural and psychological symptoms of dementia (BPSDs)

BPSDs among persons with AD are common (Alzheimer’s Association, 2016). These are signs and symptoms of disturbed perception, thought content, mood, or behaviour (Finkel et al., 1996; Kales et al., 2015). They are estimated to affect almost all individuals with AD at some point in the course of their disease but they may be present even in the early stages of AD (Cerejeira et al., 2012; Kales et al., 2015). The most common BPSDs are apathy, depression, and anxiety (Kales et al., 2015). Others symptoms include agitation, aggression, disinhibition, motor disturbances, psychotic symptoms, sleeping problems and disturbed night-time behaviours, and eating problems. Many symptoms, such as depression and anxiety, are prone to co-occur (Matthews et al., 2009; Kales et al., 2015). However, in contrast to cognitive impairment, BPSDs do not worsen progressively over time, but rather seem to fluctuate, although sometimes persisting for months. Multiple ways of subgrouping BPSDs exist, one example being that devised by Aalten et al. (2003) (Table 2).

Table 2. Subgrouping of behavioural and psychological symptoms of dementia in the Neuropsychiatric Inventory (NPI) (Aalten et al., 2003).

<table>
<thead>
<tr>
<th>Mood/apathy symptoms</th>
<th>Depression, loss of sleep and appetite, apathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychotic symptoms</td>
<td>Delusions, hallucinations</td>
</tr>
<tr>
<td>Hyperactivity symptoms</td>
<td>Agitation/aggression, aberrant motor behaviour, disinhibition, euphoria</td>
</tr>
<tr>
<td>Anxiety</td>
<td></td>
</tr>
</tbody>
</table>

BPSDs often represent the heaviest burden for people with the disease, their caregivers, and providers (Cerejeira et al., 2012; Kales et al., 2015). In particular, psychotic and aggressive behaviour is perceived as burdensome by the caregivers. Moreover, BPSDs are associated with earlier institutionalisation (Yaffe et al., 2002; Kales et al., 2005; Belger et al., 2018), declining cognition (Poulin et al., 2017), decreased functioning (Palmer et al., 2011; Poulin et al., 2017), worse quality of life (Hurt et al., 2008), and psychotic symptoms with higher mortality (Russ et al., 2012) in comparison to those AD patients without BPSDs.

The pathophysiology of BPSDs in AD includes multiple deficits in brain function, which are caused by disruption of neural networks, neurotransmitter dysfunction, and atrophy (Cerejeira et al., 2012; Kales et al., 2015). In addition to the changes in neurobiology, acute, untreated medical conditions and/or unmet needs may act as
triggers for BPSDs. These underlying medical illnesses and symptoms may include pain, infections, constipation, dehydration and drug-related problems (Kales et al., 2015). Similarly, caregiver-related factors, such as caregiver stress, depression or anxiety and environmental factors, such as physical and social changes are known to trigger or exacerbate BPSDs.

**Treatment of behavioural and psychological symptoms of dementia**

According to multiple treatment guidelines, the first-line treatment of BPSDs should be non-pharmacological (APA Work Group on Alzheimer’s Disease and other Dementias, 2007; Gauthier et al., 2012; Finnish Medical Society Duodecim, 2017a; National Institute for Health and Care Excellence, 2018; Kales et al., 2019). First, the underlying medical, social and environmental causes of BPSDs should be assessed and managed. Secondly, non-pharmacological treatment options such as educational and supportive interventions for caregivers may be highly beneficial, i.e. there is convincing evidence of their benefits (Kales et al., 2015). Interventions targeting the individual with dementia include personally tailored activities, for example, music therapies, which have been reported to be beneficial in reducing BPSDs (Möhler et al., 2018; van der Steen et al., 2018).

According to Finnish care guidelines, if non-pharmacological treatment is insufficient, the first-line of pharmacotherapy should be antidementia drugs, (Finnish Medical Society Duodecim, 2017a). However, meta-analyses of ChEIs have found either no benefit in neuropsychiatric symptom scores (Birks and Harvey, 2018; Dou et al., 2018) or only a modest benefit (Wang et al., 2015; Tricco et al., 2018; Jin and Liu, 2019). Memantine, alone or in combination with ChEIs, has also been somewhat effective in reducing neuropsychiatric symptom scores in RCTs (Matsunaga et al., 2015; Kishi et al., 2017; Jin and Liu, 2019). One advantage of antidementia drugs over other pharmacotherapy is the simultaneous enhancement of cognition.

**Role of psychotropic drugs in the treatment of behavioural and psychological symptoms of dementia and associated adverse effects**

In the third and fourth line of therapy, psychotropic drugs can be considered for BPSDs (Kales et al., 2015). Antipsychotics are only recommended for severe agitation or psychotic symptoms or if the risk of self-harm or harm to others persists (Finnish Medical Society Duodecim, 2017a; National Institute for Health and Care Excellence, 2018). The use of antipsychotics is limited by the increased risk of severe adverse events; antipsychotics increase the risk of stroke and mortality (Ballard et al., 2006; Zhai, Yin and Zhang, 2016). ADEs include extrapyramidal effects and somnolence, increasing the risk for falls and fractures as well as elevating the risk of pneumonia (Ballard et al., 2006; Tolppanen et al., 2016a; Koponen et al., 2017).
Similarly, benzodiazepines and related drugs (BZDRs) are frequently administered to treat BPSDs in AD (Saarelainen et al., 2015). BZDRs are indicated for the treatment of anxiety and insomnia in the general population, but their efficacy is low to non-existent among persons with cognitive disorders (McCleery et al., 2014; Tampi and Tampi, 2014; Kales et al., 2015). BZDRs are associated with an increased risks e.g. for stroke, mortality, falls and fractures, and pneumonia (Obiora et al., 2013; Bakken et al., 2014; Saarelainen et al., 2016; Koponen et al., 2017; Taipale et al., 2017a, Saarelainen et al. 2018).

The third major group of psychotropic drugs used in the treatment of BPSDs is the antidepressants, most frequently selective serotonin reuptake inhibitors (SSRIs), serotonin and noradrenaline reuptake inhibitors (SNRIs), and mirtazapine (Nash and Nutt, 2007). There is only limited evidence supporting the use of antidepressants in depression in dementia (Gauthier et al., 2012; Finnish Medical Society Duodecim, 2017a; National Institute for Health and Care Excellence, 2018). Citalopram has shown some benefit in the treatment of agitation in dementia. The most common ADEs of SSRIs include gastrointestinal problems, hyponatremia, and prolongation of the QT interval (Drye et al., 2014; Porsteinsson et al., 2014; Kales et al., 2015). Other adverse events include falls, fractures, and head traumas (Kales et al., 2015; Taipale et al., 2017b; Torvinen-Kiiskinen et al., 2017) Mirtazapine has a unique side-effect profile, as it also is an antagonist of histamine receptors, in addition to increasing noradrenaline and serotonin release (Nash and Nutt, 2007). Thus, mirtazapine has sedative properties at low doses, and it can be used to treat people with sleep difficulties, although without an official indication and with little evidence of efficacy among persons with cognitive disorders (Banerjee et al., 2013; Scoralick et al., 2017).

At odds with the clinical guidelines, BPSDs are frequently treated with psychotropic drugs (Juhola et al., 2019). In Finland, 60% of community dwellers with AD used some kind of psychotropic compound during the first two years after their AD diagnosis, most commonly BZDRs. Moreover, although as stated, the nature of BPSDs frequently fluctuates, the use of psychotropic drugs does not: long-term use of antipsychotics, BZDRs and antidepressants is common (Koponen et al., 2015; Taipale et al., 2015; Kettunen et al., 2019). Psychotropic polypharmacy, i.e. using two or more drugs simultaneously, is also prevalent (Orsel et al., 2018), and some individuals with AD are using multiple antipsychotics concomitantly (Taipale et al., 2014a).

### 2.2.2 Pain in Alzheimer’s disease

Similar to the situation in the wider older population, pain is a common symptom among community dwellers with AD (Corbett et al., 2012; Achterberg et al., 2013). Importantly, pain is associated with BPSDs among individuals with AD (van Dalen-Kok et al., 2015). Pain combined with cognitive impairment also reduces the ability to perform IADL more than either pain or cognitive impairment alone and is
associated with a higher rate of emergency department visits in the last month of life (Shega et al., 2010; Hunt et al., 2018).

Pain prevalence studies have only evaluated persons with unspecified cognitive disorders. In small studies, the self-reported prevalence of concurrent pain has been in a range from 32% to 57% (Shega et al., 2004; Barry et al., 2015). In a Finnish clinical study, 43% of persons with a cognitive disorder reported having experienced pain in the last month (Mäntyselkä et al., 2004). A larger US-based study found a prevalence of 64% for bothersome pain in the last month; this was a higher percentage than among persons without cognitive disorders (Hunt et al., 2015). Caregivers appear to report patients’ pain even more frequently (Shega et al., 2004; Jensen-Dahm et al., 2012; Barry et al., 2015). Moreover, a significant proportion, 49% to 72%, received a diagnosis for a pain-related state within a year of the diagnosis of the cognitive disorder (Hoffmann et al., 2014; Lin et al., 2018). Most frequent diagnoses were osteoarthritis, neuropathic pain, headache, pain due to fractures, and osteoporosis. Pain is also a frequent symptom experienced near the end of life in individuals with advanced cognitive disorders (Mitchell et al., 2009).

There are, however, problems in pain assessment of persons with AD (Corbett et al., 2012; Hadjistavropoulos et al., 2014; Lichtner et al., 2014). There may be challenges in the assessment of the presence and severity of pain, but also on the type of pain (e.g. musculoskeletal, visceral, and/or neuropathic). Self-report is considered to be the gold standard for assessing pain, but in cognitive disorders the ability for verbal expression diminishes. In addition, persons with cognitive disorders may have difficulties recognising pain as the cause of their discomfort. These problems become more apparent as the disease progresses. Self-reporting is still considered to be the most important measure of pain in mild-to-moderate cognitive disorders, with instruments such as the Numeric Rating Scale and the Verbal Descriptor Scale being recommended (Corbett et al., 2012; Hadjistavropoulos et al., 2014). In evaluations of patients with severe cognitive disorders, observational pain scales have a greater importance; a plethora of these scales have been developed. Observations are made on multiple behaviours linked with pain, such as facial expressions, vocalisations, body movements, changes in interpersonal interactions and personal activity patterns, and changes in mental status. All pain scales have their own deficiencies but many have been validated and are moderately precise (Corbett et al., 2012; Hadjistavropoulos et al., 2014; Schofield and Abdulla, 2018). These include the Pain Assessment in Advanced Dementia (PAINAD) (Warden et al., 2003), Abbey (Abbey et al., 2004), Doloplus-2 (Monacelli et al., 2013), and the Pain Assessment Checklist for Seniors with Limited Ability to Communicate (PACSLAC) scales (Fuchs-Lacelle and Hadjistavropoulos, 2004).

In addition to problems with self-reporting, pain among persons with AD may go undetected because of its unconventional presentation (Corbett et al., 2012). Due to the changed perception of pain and the loss of communication skills, pain is often not communicated as such, but as BPSDs. In their systematic review, van Dalen-Kok et al. (2015) found the most convincing evidence for an association between pain and
depression, but also for pain and agitation/aggression in individuals with a cognitive disorder. In addition, pain in persons with cognitive disorders has been associated with socially inappropriate behaviour (Tosato et al., 2012), irritability (Malara et al., 2016), delusions (Tosato et al., 2012), disinhibition (Habiger et al., 2016), psychotic symptoms (Habiger et al., 2019) and, inversely, with wandering (Ahn and Horgas, 2013). In these individuals, pain also appears to correlate with increased use of antipsychotics, at least in nursing home residents (Rajkumar et al., 2017).

In addition to BPSDs, pain in individuals with AD may cause delirium, or the so-called acute confusional state (Feast et al., 2018). Delirium is common among hospitalised older adults and associated with severe adverse outcomes, such as increased mortality (Inouye et al., 2014). It is likely that delirium and AD share some of their pathophysiology and episodes of delirium also precede accelerated cognitive decline and institutionalisation in this population (Fong et al., 2009, Fong et al., 2012, Fong et al., 2019). Pain management is thus considered an important intervention for the prevention of delirium in individuals with AD (Inouye et al., 2014).

It has been claimed that pain processing is altered in individuals with AD (Scherder et al., 2003). There is some overlap between the brain regions affected by AD and those involved in pain processing. These include most of the areas of the medial pain system, i.e. the region that conveys the affective component of pain (Binnekade et al., 2017). In contrast, the lateral pain system, which conveys the sensory-discriminative aspects of the pain experience, remains largely unaffected at least by mild-to-moderate AD, which means that these patients have an intact sense of pain location and intensity (Monroe et al., 2012; Binnekade et al., 2017). However, not all of these findings have been supported by experimental studies on pain perception. In their systematic review, Binnekade et al. (2017) found significant inconsistencies in the literature on whether persons with mild-to-moderate dementia have a decreased pain threshold and/or decreased pain tolerance values. Moreover, in a functional brain neuroimaging study, persons with early AD did not show reduced activity in the specific brain areas involved in the medial pain systems (Cole et al., 2006). In fact, when compared to their cognitively intact peers, pain-related activity was greater in those with AD. Unfortunately, experimental studies on individuals with severe AD are scarce, which limits the generalisability of these results (Binnekade et al., 2017).

### 2.3 ANALGESICS

In the pharmacological treatment of pain, the most commonly used drugs are opioid and non-opioid analgesics, i.e. non-steroidal anti-inflammatory drugs (NSAIDs) and paracetamol. The review of this thesis does not include adjuvant drug therapy of pain, i.e. drugs originally used for other indications, such as antiepileptics or antidepressants, or drugs for specific pain-inducing diseases, e.g. those used to treat migraine.
Ageing affects the pharmacology of analgesics in multiple ways (Ickowicz et al., 2009; Abdulla et al., 2013). Renal insufficiency reduces the clearance of drugs excreted through the kidneys, commonly increasing drug and/or metabolite plasma levels. Similarly, hepatic metabolism may decrease as the individual grows older, possibly resulting in longer drug half-lives and the reduced activity of metabolism-dependent pro-drugs. Changes in body composition are also common in old age; the increased fat-to-lean body weight ratio may increase the volume of distribution of lipid-soluble drugs and thus result in longer half-lives. Similarly, transdermal absorption may be reduced, especially in severely cachectic patients (Heiskanen et al., 2009). On the pharmacodynamic side, central nervous system (CNS) ADEs, such as sedation and anticholinergic effects, seem to be more common among older adults, especially in the frailest individuals (Hilmer et al., 2007).

### 2.3.1 Non-steroidal anti-inflammatory drugs

Salicylates are found in many plants which have been used for medicinal purposes for several millennia (Vane and Botting, 1998). Acetylsalicylic acid (ASA, or aspirin) was first derived from salicylic acid in 1899, and its antipyretic, anti-inflammatory, and analgesic effects were soon recognised. In order to distinguish them from glucocorticoids, the group of ASA-like drugs was subsequently named “non-steroidal anti-inflammatory drugs”. Later, the antithrombotic effect of NSAIDs was recognised.

NSAIDs exert their pharmacological effects through inhibition of prostanoid biosynthesis, i.e. the synthesis of prostaglandins, prostacyclins, and thromboxanes (Vane and Botting, 1998; Day and Graham, 2013). NSAIDs inhibit cyclo-oxygenase isoenzymes COX-1 and COX-2, of which COX-1 is responsible for physiological reactions, such as gastro-protection, platelet aggregation, and vasodilation whereas COX-2 mediates mainly pain- and inflammation-related reactions. The effects of the individual NSAIDs depend largely on their selectivity for these two enzymes. The non-selective NSAIDs inhibit both COX-1 and COX-2 whereas the so-called coxibs are selective COX-2 inhibitors. In contrast to the reversible effects of other NSAIDs, ASA inhibits the COX-1-mediated synthesis of thromboxane A2 irreversibly, which explains why ASA is also used for inhibition of platelet aggregation (Day and Graham, 2013).

NSAIDs seem to be especially effective for alleviating pain with an inflammatory component, but their use is limited by their ADEs (Ickowicz et al., 2009; Day and Graham, 2013). Taken orally, NSAIDs dose-dependently increase the risk of gastrointestinal ADEs and severe adverse events, such as gastrointestinal ulcers (Gabriel et al., 1991; Boers et al., 2007); renal insufficiency (Weir, 2002; Ungprasert et al., 2015), and cardio- and cerebro-vascular events, such as stroke (Solomon et al., 2006; Chuang et al., 2015), myocardial infarction (Schlienger et al., 2002; Fischer et al., 2005), heart failure (Arfè et al., 2016), and venous thrombosis (Schmidt et al., 2011). Coxibs appear to have better gastrointestinal tolerability (Mallen et al., 2011), but carry a higher risk of cardiovascular events (McGettigan and Henry, 2011; Trelle et
Among older adults, these risks are frequently higher and NSAIDs can worsen pre-existing renal insufficiency and cardiac failure (Barkin et al., 2010). Moreover, NSAIDs frequently interact with some drugs commonly used by older adults, such as warfarin, antihypertensives, and SSRIs. In contrast, topical NSAIDs are safe and can be effective in relieving pain due to osteoarthritis (Derry et al., 2016; Zeng et al., 2018).

### 2.3.2 Paracetamol

Paracetamol, also known as acetaminophen, was first synthesized in 1878 and is still widely used as an analgesic and antipyretic; it is the analgesic most commonly used by older people (Morse, 1878; Mian et al., 2018). Despite the length of time since paracetamol’s discovery and its widespread use, its pharmacological effects have remained something of a mystery. It is now believed to centrally inhibit COX enzymes, preferring COX-2, possibly via its active metabolites (Anderson, 2008; Graham et al., 2013). Other suggested mechanisms of action include inhibition of nitric oxide, reinforcement of descending inhibitory serotonergic pain pathways, and effects on cannabinoid receptors.

Paracetamol’s clinical pharmacological effects do differ extensively from the NSAIDs. It does not exhibit antiplatelet or anti-inflammatory actions. At therapeutic doses, paracetamol is considered safe, although a small increased risk of gastrointestinal bleeding and a small increase in systolic blood pressure have been linked with long-term use (McCrae et al., 2018). However, acute liver damage can follow overdose (Mian et al., 2018).

Some 5–10% of paracetamol is metabolised into a toxic metabolite, N-acetyl-p-benzoquinone-imine (Mian et al., 2018). At regular doses, subsequent metabolism neutralises this substance by conjugation with glutathione, but depletion of this route follows in cases of overdose and possibly malnourishment. Old age and especially frailty reduce the volume of distribution and the clearance of paracetamol, but the clinical significance of these findings is unclear, and current evidence does not support dose reductions lower than 3 grams per day due to age alone.

### 2.3.3 Opioids

The opium poppy, Papaver somniferum, has been used for therapeutical purposes for more than 3000 years, but the main active ingredient, morphine, was first extracted in the early 19th century (Sertürner, 1817; Pathan and Williams, 2012). The poppy produces other opiate alkaloids (e.g. codeine), but semisynthetic (e.g. diamorphine, buprenorphine, and oxycodone) and synthetic opioids (e.g. pethidine and fentanyl) have been subsequently developed (Pathan and Williams, 2012; Pasternak and Pan, 2013).

Opioids primarily act on different subtypes of opioid receptors: the mu, kappa, and delta (Pathan and Williams, 2012). Agonism at the mu receptor evokes analgesia, but also sedation, respiratory depression, euphoria, dependence, and a reduction in
gastric motility, partly depending on the location of the receptor in the human body (Figure 3) (Trescot et al., 2008; Pathan and Williams, 2012; Volkow and McLellan, 2016). Similarly, kappa agonism causes analgesia, sedation and respiratory depression, but also dysphoria. The functions of the delta receptors are less well known (Trescot et al., 2008). Opioid receptor agonism in nociceptive neurons decreases the release of pain neurotransmitters and thus reduces pain signalling in the periphery. Centrally and in the spinal dorsal horn, the analgesic effects of opioid agonism are conveyed through activating the descending inhibitory pain pathways (Trescot et al., 2008; Pathan and Williams, 2012).

Figure 3. Locations of opioid mu opioid receptors. Reproduced with permission from Volkow & McLellan 2016, Copyright Massachusetts Medical Society.
Opioid analgesics differ in their effects on opioid receptors, and many of them do not bind to all receptor subtypes (Trescot et al., 2008; Pathan and Williams, 2012). Furthermore, opioids may act as receptor agonists, antagonist or partial agonists (buprenorphine), with different binding affinities (i.e. “strength”). However, only opioid agonists and buprenorphine are used in analgesia. In addition, tramadol uniquely also acts as a serotonin and noradrenaline reuptake inhibitor.

Opioids with weak affinity for opioid receptors, e.g. codeine and tramadol, typically are not tolerable at higher doses, whereas strong opioids, e.g. morphine and oxycodone, may in theory, be gradually increased in dose without a predefined limit (Trescot et al., 2008; Pathan and Williams, 2012). However, ADEs are more frequent at higher doses. Importantly, respiratory depression, following high doses of opioids, potentially leads to death. Common ADEs of opioids at therapeutic doses include constipation, sedation, dizziness, and confusion; these ADEs are more frequent in older adults (Guerriero, 2017). Repeated opioid agonism may lead to tolerance in analgesia, but also to tolerance to the sedation, respiratory depression and nausea, thus potentially allowing high doses of opioids to be administered in palliative care (Chang et al., 2007). However, the effect of tolerance on constipation is minimal.

Age-related changes in physiology, the presence of comorbidities, and the use of other drugs affect treatments with opioids (Ickowicz et al., 2009; Abdulla et al., 2013). Most opioids used in Finland require a dose reduction if glomerular filtration is reduced (Table 3). Similarly, most of the commonly used opioids are metabolised through the cytochrome P450 systems, thus increasing the risk of drug-drug interactions and genetic variation in their efficacy. Some of the common drug-drug interactions of opioids are displayed with other CNS depressive drugs, such as BZDRs. Concomitant use of opioids and BZDRs is not recommended due to increased risk for ADEs (American Geriatrics Society, 2019). In addition, due to their lipophilic profile, opioids may have a longer half-life among older adults.
Table 3. Pharmacology of opioids commonly used in Finland.

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Pharmacodynamics</th>
<th>Metabolism</th>
<th>Dose reduction in renal insufficiency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>Weak mu agonism, weak delta agonism</td>
<td>Pro-drug: activation through CYP2D6</td>
<td>Yes</td>
</tr>
<tr>
<td>Tramadol</td>
<td>Weak mu agonism, Monoamine reuptake inhibition</td>
<td>Pro-drug: activation through CYP2D6 and CYP3A4</td>
<td>Yes</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>Partial mu agonism, kappa antagonism</td>
<td>CYP3A4, glucuronidation</td>
<td>No</td>
</tr>
<tr>
<td>Morphine</td>
<td>Mu agonism, weak kappa agonism</td>
<td>Mainly glucuronidation, active metabolites</td>
<td>Yes</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>Mu agonism, kappa agonism</td>
<td>CYP3A4, CYP2D6, active metabolites</td>
<td>Yes</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>Mu agonism</td>
<td>CYP3A4</td>
<td>No</td>
</tr>
</tbody>
</table>

CYP = Cytochrome P450. Sources: Trescot et al., 2008; Miotto et al., 2017; Abdulla et al., 2013; Ickowicz et al., 2009; Al-Tawil et al., 2013; Olkkola et al., 2013; Kress & Kress, 2009.

2.4 PHARMACOLOGICAL TREATMENT OF PAIN IN OLD AGE

The Finnish Current Care Guidelines set reduction of pain, improved ability to function, and improved quality of life as the main goals of chronic pain management (Finnish Medical Society Duodecim, 2017b). The basis of pain management should be non-pharmacological, consisting of treatment methods such as exercise, physical therapy, and cognitive-behavioural therapy. Although some of these methods, especially resistance, endurance, and balance exercise, can be important in treating and preventing pain in old age (Abdulla et al., 2013), the focus of this summary of recommendations by the American and British Geriatrics Societies (AGS and BGS) is on the pharmacological treatment of pain with analgesics (Ickowicz et al., 2009; Abdulla et al., 2013). Both guidelines note the low overall quality of evidence for their recommendations, as older adults with comorbidities are rarely included in RCTs of pain treatment.

As older adults are a heterogeneous population and age-adjusted dose recommendations do not exist for most drugs, analgesics should be prescribed on an individual basis (Ickowicz et al., 2009; Abdulla et al., 2013). Comorbidities and co-medications should be considered when choosing an analgesic. The starting dose should be low and titrating to the response should be slow. Combining drugs with complementary mechanisms of action can be advantageous, but generally, only one drug should be started at a time, allowing for the assessment of its effect. In addition, the oral route should be preferred when possible.
Paracetamol is recommended as the first-line analgesic due to its safety profile (Ickowicz et al., 2009; Abdulla et al., 2013). It is also recommended for pain due to knee and hip osteoarthritis despite its possible low efficacy (McAlindon et al., 2014; National Institute for Health and Care Excellence, 2014; Finnish Medical Society Duodecim, 2018; Leopoldino et al., 2019). Dose reductions to 2 grams or less per day are recommended in cases of malnutrition, hepatic insufficiency, and in patients with alcohol use disorder (Ickowicz et al., 2009; Abdulla et al., 2013).

If treatment with paracetamol is insufficient, NSAIDs can be considered for short-term therapy, especially for inflammatory pain (Ickowicz et al., 2009; Abdulla et al., 2013). For musculoskeletal pain, topical NSAIDs are preferred over their orally administered versions due to their safety. Bleeding, renal, and cardiovascular risk factors, including the effects of co-medication, need to be taken into account if oral NSAIDs are considered and treatment should commence with the lowest effective dose for the shortest possible duration. Proton-pump inhibitors (PPIs) should be co-prescribed in patients with an elevated risk of gastrointestinal bleeding.

For moderate-to-severe pain, opioids may be required (Ickowicz et al., 2009; Abdulla et al., 2013). Especially for patients at risk of NSAID-related events, opioids may be preferred, but careful selection of patients, slow titration, and close monitoring are needed. The choice of the opioid agent should be made on an individual level, considering comorbidities, co-medications, cause of pain, pain severity, previous opioid use (i.e. level of tolerance), CYP genotype, previous ADEs, and patient preference (see also Table 3). Short-term use of opioids has been associated with a reduction in pain intensity and better physical functioning but with poorer mental health functioning in older adults (Papaleontiou et al., 2010). Long-term use for non-malignant pain does not seem to confer more benefits than harms, however (Chou et al., 2015; Busse et al., 2018). Sedation and nausea are worse around treatment initiation and dose escalation but may subside within 2 to 3 days. Cognitive ADEs may take longer to resolve. As there is no tolerance to constipation, laxatives should be co-prescribed if their need is anticipated. Opioid therapy should be reviewed regularly for both efficacy and tolerability and titrated down from high doses before ending drug use to avoid withdrawal symptoms.

**Pharmacological treatment of pain in Alzheimer’s disease**

In addition to the challenges in pain assessment, the AGS and BGS guidelines do not differentiate pain treatment between those with cognitive disorders and those without (Ickowicz et al., 2009; Abdulla et al., 2013). However, pain assessment does affect treatment monitoring and thus can be more difficult in individuals with AD (Scherder et al., 2009). Similarly, ADEs can be more challenging to distinguish from other symptoms. Persons with AD are more likely to be frail, have more comorbidities, and use more drugs than their peers, all of which should be taken into account when making treatment decisions about analgesics.
In addition, expectation-induced analgesia, i.e. the placebo effect of analgesics may be reduced in AD (Scherder et al., 2009). This may be due to the importance of the prefrontal lobes in analgesic responses: a decreased placebo effect has been reported in persons with AD whose prefrontal executive functions are impaired (Benedetti et al., 2006; Palermo et al., 2019). This may lead to lower responsiveness to analgesics, but the clinical implications of the possibility require further research (Scherder et al., 2009).

2.4.1 Analgesic use among community-dwelling persons with and without cognitive disorders

Due to the problems in pain recognition and communication in persons with AD, there has long been a suspicion that they may be receiving inadequate analgesic treatment (Scherder and Bouma, 1997; Morrison and Siu, 2000). In previous studies, individuals with cognitive disorders have received opioids for post-operative pain less frequently and at lower doses (Morrison and Siu, 2000; Adunsky et al., 2002; Sieber et al., 2011; Jensen-Dahm et al., 2016). Similarly, in care facilities for the aged, individuals with cognitive impairment have been less likely to use analgesics as compared to the other residents (Tan et al., 2015).

In studies among community dwellers with cognitive disorders, however, analgesic use patterns have varied (Table 4). In older, interview-based estimates of prevalence, individuals with cognitive disorders used significantly fewer analgesics in the recent past (Schmader et al., 1998; Mantyselka et al., 2004). In more recent register-based studies with longer follow-up times, analgesic and opioid use prevalences have been similar or even higher among individuals with cognitive disorders (Bell et al., 2011; Hoffmann et al., 2014; Jensen-Dahm et al., 2015; Shen et al., 2018). There are notable differences between the studies in the analgesics in use: US- and Denmark-based studies report significantly higher annual prevalences of opioid use in comparison to Finland (Bell et al., 2011; Jensen-Dahm et al., 2015; Shen et al., 2018). These may be actual differences in prescribing practices between the countries but they may also reflect what kind of drug use is attainable from the used databases. For example, codeine products were not reimbursed in Finland in 2005 and thus data on their use was not available for Bell et al. Similarly, the most frequently used analgesic in the study of Hoffman et al. (2014) was metamizole, an uncommon analgesic in most countries with an unknown mode of action and a recognised increased risk for agranulocytosis (Hoffmann et al., 2015). The relative frequency of metamizole use is likely influenced by both German prescribing patterns, its availability as a liquid, and the fact that paracetamol use data is not available in the utilised insurance claims data.
Table 4. Studies on the prevalence of analgesic use among community dwellers with cognitive disorders compared to other older adults.

<table>
<thead>
<tr>
<th>Study (country)</th>
<th>Data source, years of data collection</th>
<th>Cognitive disorder type (N)</th>
<th>Comparison persons (N)</th>
<th>Definition and measure of analgesic use</th>
<th>Analgesic use prevalence among persons with cognitive disorders</th>
<th>Analgesic use prevalence among comparison persons</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Interview-based studies</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Schmader et al., 1998 (USA)</td>
<td>Cohort of persons ≥65 years 1991–1994</td>
<td>Unspecified (100)</td>
<td>Cognitively intact (303)</td>
<td>Use during 2 weeks prior to the interview. OTC drugs included</td>
<td>Analgesics: 44%</td>
<td>Analgesics: 65%</td>
</tr>
<tr>
<td>Mäntyselkä et al., 2004 (Finland)</td>
<td>Population-based health survey of persons ≥75 years 1998</td>
<td>Unspecified (77)</td>
<td>Other older adults (446)</td>
<td>Use during 30 days before the interview. OTC drugs included</td>
<td>Analgesics: 33%</td>
<td>Analgesics: 47%</td>
</tr>
<tr>
<td>Haasum et al., 2011 (Sweden)</td>
<td>Random sample cohort 2001–2004</td>
<td>Unspecified (119)</td>
<td>Other older adults (2199)</td>
<td>Regular and as-required use at the time of interview. OTC drugs included.</td>
<td>Analgesics: 36.1% Paracetamol: 24.4% NSAIDs: 5.9% Opioids: 14.3%</td>
<td>Analgesics: 24.3% Paracetamol: 15.4% NSAIDs: 12.0 Opioids: 8.0%</td>
</tr>
</tbody>
</table>

(Continued)
Table 4 (continued)

<table>
<thead>
<tr>
<th>Nordic register-based studies</th>
<th></th>
<th>AD (28,093)</th>
<th>Age-, sex- and region of residence matched controls (28,093)</th>
<th>≥1 dispensed opioid during a year</th>
<th>Opioids: 3.6%</th>
<th>Opioids: 4.6%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bell et al., 2011 (Finland)</td>
<td>Nationwide healthcare registers 2005</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jensen-Dahm et al., 2014 (Denmark)</td>
<td>Nationwide healthcare registers 2010</td>
<td>Unspecified (19,407)</td>
<td>All other community dwellers ≥65 years (844,402)</td>
<td>≥1 dispensed opioid during a year</td>
<td>Opioids: 27.5%</td>
<td>Opioids: 16.9%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Insurance claims-based studies</th>
<th></th>
<th>Unspecified (1,848)</th>
<th>Age- and sex-matched controls (7,935)</th>
<th>≥1 prescription during the year of cognitive disorder diagnosis. No paracetamol</th>
<th>Analgesics: 47.5%</th>
<th>Analgesics: 44.7%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hoffman et al., 2014* (Germany)</td>
<td>Gmünder ErsatzKasse 2005–2006</td>
<td></td>
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</tr>
<tr>
<td>Shen et al., 2018 (USA)</td>
<td>Medicare sample survey 2006–2013</td>
<td>Unspecified, with chronic pain (530)</td>
<td>Other beneficiaries with chronic pain (5902)</td>
<td>≥1 prescription/ reported use within the calendar year of the survey</td>
<td>Opioids: 32.8%</td>
<td>Opioids: 33.4%</td>
</tr>
</tbody>
</table>

AD = Alzheimer’s disease; OTC = Over-the-counter; NSAIDs = Non-steroidal anti-inflammatory drugs. *Proportion of community dwellers in Hoffman et al was 80% among persons with dementia and 97% among controls (analgesic use according to dwelling-status not reported).
Long-term analgesic use has been less extensively studied among community dwellers with cognitive disorders. Gallini et al., (2013) examined the persistent use of analgesics among persons with AD by considering those using analgesics in ≥2 consecutive study visits (6 months apart). In their study, the prevalence of analgesic use at any visit was 26% and 13% on consecutive visits. However, the study did not include a comparison group and they did not specify which analgesics were used. In other studies investigating factors related to long-term opioid use, dementia has been found to have an inverse association in Norway and USA (Mellbye et al., 2014; Oh et al., 2019). In contrast, Kostev et al. (2015) found dementia to be associated with a decreased risk of treatment discontinuation in a German setting.

**Analgesic treatment efficacy among persons with cognitive disorders**

The effect of analgesics on pain or other outcomes, including BPSDs, among persons with cognitive disorders has not been studied extensively (Husebo et al., 2016). Five studies were identified, these included two RCTs and three crossover trials (Manfredi et al., 2003; Buffum et al., 2004; Chibnall et al., 2005; Husebo et al., 2011; Erdal et al., 2018) (Table 5). All of these studies had been conducted among nursing home residents with heterogeneous treatment schemes and outcome measures. Most studies were randomised (four out of five) and double-blinded (four out of five).

Buffum et al (2004) and Chibnall et al (2005) studied the effects of paracetamol on various neuropsychiatric symptoms with a crossover design. Neither of these studies found an effect as compared to placebo when assessing agitation, but Chibnall et al. described positive effects in the intervention phase in terms of social interaction. It is important to note that the dose of paracetamol in the study of Buffum et al. may have been too low, as noted by the authors. In the third crossover study conducted by Manfredi et al. (2003), oxycodone or morphine was used in the active phase of the trial. Overall, they found no differences in overall measures of agitation but reported that there was less agitation in participants aged ≥85 years (N = 13).

Two RCTs on the effects of analgesic treatment schemes were conducted in Norwegian nursing homes (Husebo et al., 2011; Erdal et al., 2018) (Table 5). Husebo et al. (2011) implemented a stepwise pain treatment protocol where treatment was progressively increased from the participants’ pre-trial analgesics. Participants were treated with paracetamol at the maximum dose, adding morphine or buprenorphine if the participant was already on paracetamol 3 grams/day before the trial, as well as adding pregabalin if the pain was deemed to be neuropathic. The results of this trial have been described in multiple publications. Overall, agitation was reduced with the intervention as compared to usual care. More specifically, decreases were most pronounced in verbally agitated behaviours, as well as in the most common agitation symptoms, e.g. general restlessness (Husebo et al., 2014). Moreover, psychotic symptoms were reduced in those patients with symptoms at baseline (Habiger et al., 2016) and mood-related symptoms, such as apathy were also improved (Husebo et
The intervention reduced pain and elevated ADL function in those treated with paracetamol (Sandvik et al., 2014).

The second RCT, from the same research group, studied the effects of paracetamol and transdermal buprenorphine on residents with depressive symptoms (Erdal et al., 2018). A 13-week intervention did not yield positive effects on depressive symptoms as compared to placebo, and there was a high dropout rate due to psychiatric and neurological ADEs of buprenorphine. Another analysis of the same study found a positive effect on sleep parameters after one week of treatment, but these were not sustained throughout the whole 13-week study (Blytt et al., 2018a; Blytt et al., 2018b).

Overall, very little research has been conducted on how efficacious analgesics are among persons with dementia and whether their use reduces pain or BPSDs. Most of the available evidence points to some benefit especially for high dose paracetamol, but the effects of opioids have been more heterogeneous. Only Chibnall et al. (2005) studied the effects of analgesics on psychotropic drug use; they did not find any difference in as-needed drugs in the intervention phase. Moreover, it does not seem that there are any population-based studies nor any studies on community dwellers with cognitive disorders.
<table>
<thead>
<tr>
<th>Study (country)</th>
<th>Control; blinding</th>
<th>Setting</th>
<th>Inclusion criteria</th>
<th>N</th>
<th>Intervention</th>
<th>Outcome (instrument)</th>
<th>Result compared to control</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Randomised controlled trials</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
| Husebo et al., 2011 (Norway) | Usual care; open-label | 60 nursing home units | A moderate-to-severe CD, BPSDs | 352 | 8-week Stepwise Protocol:  
Step 1: paracetamol (max 3 g/day) or, if already receiving treatment, adjusted to either  
Step 2: morphine, max 20 mg/day,  
Step 3: buprenorphine TD, max 10 µg/h, or  
Step 4: pregabalin, max 300 mg/day | Agitation (CMAI) | Reduction in agitation |
| Erdal et al., 2018 (Norway) | Placebo; double-blinded | 47 nursing homes | A CD, depressive symptoms. No severe pain | 162 | 13-week paracetamol (3g/day) or added buprenorphine TD (10µg/h) if already on paracetamol | Depressive symptoms (Cornell Scale) | Increase in depressive symptoms |
| **Crossover trials** |
| Manfredi et al., 2003 (USA) | Placebo; double-blinded (not randomised) | 1 nursing home | An advanced CD, severe agitation | 47 | 8-week long-acting oxycodone 20 mg/day or long-acting morphine 20 mg/day | Agitation (CMAI) | No difference in agitation |
| Buffum et al., 2004 (USA) | Placebo; double-blinded (randomised) | 3 nursing homes | Severe CD, painful condition | 39 | 4-week paracetamol 2600 mg/day with placebo as-needed or placebo with paracetamol as-needed | Discomfort (DS-DAT) | No difference in discomfort |
| Chibnall et al., 2005 (USA) | Placebo; double-blinded (randomised) | 4 nursing home units | A moderate-to-severe CD | 25 | 4-week paracetamol 3 g/day | Behavioural symptoms (DCM, CMAI); use of as-needed psychotropics | Increased social interaction. No difference in agitation or use of psychotropics |

BPSDs = Behavioural and psychological symptoms of dementia; CD = cognitive disorder; CMAI = Cohen-Mansfield agitation inventory; DCM = Dementia Care Mapping; DS-DAT = Discomfort Scale -Dementia of the Alzheimer Type; TD = transdermal.
2.5 ADVERSE DRUG EVENTS ASSOCIATED WITH OPIOIDS

Previous research has identified the fear of adverse effects as a barrier to the use of opioids among individuals with cognitive disorders (Chandler et al., 2016). Many adverse effects, such as confusion are believed to be more frequent among persons with AD as compared to other older adults. Similarly, many severe adverse outcomes, e.g. falls and fractures, delirium, and infections such as pneumonia are common in AD and have been associated with opioid use (Rudolph et al., 2010; Tolppanen et al., 2013; Oh et al., 2017). The emphasis in this section will be placed on studies assessing pneumonia related to opioid use.

2.5.1 Pneumonia

Persons with AD have an increased risk for infections, such as pneumonia and urinary tract infections due to their impaired immunological responses (Livingston et al., 2017). Pneumonia is one of the most frequent reasons for hospitalisations and is linked to the higher mortality in this population (Mitchell et al., 2009; Rudolph et al., 2010; Foley et al., 2015). Despite the importance of pneumonia for AD prognosis, drug use has not been studied extensively as a risk factor for pneumonia. Nonetheless, due to the respiratory effects of opioids, they have been suspected as increasing the risk for pneumonia (Reid et al., 2011).

The effects of opioids on the respiratory system include depression of the respiratory rate, amplitude, and reflex responses, but also reduced upper airway dysfunction (Pattinson, 2008; Van Ryswyk and Antic, 2016). A suppression of the central cough reflex is a well-known effect of opioids. This impairment of the cough reflex reduces airway clearance and predisposes users to pathogens (Mandell and Niederman, 2019). Microaspiration of oropharyngeal secretions may play a major role in the pathogenesis of many types of pneumonia, but macroaspiration is necessary to develop the so-called aspiration pneumonia (Cillóniz et al., 2018; Mandell and Niederman, 2019). In addition to impairment of the cough reflex, opioids may make it easier for gastric contents to gain access to the lung by inducing gastro-oesophageal reflux via oesophageal dysmotility (Kraichely et al., 2010). Moreover, swallowing problems are frequent among persons with AD (Seçil et al., 2016) and cognitive disorders are a strong risk factor for aspiration pneumonia (van der Maarel-Wierink et al., 2011; Bosch et al., 2012). However, the effects of opioids on aspiration have not been studied in this population.

Another proposed mechanism to account for the link between opioids and pneumonia is opioid-induced immunosuppression (Plein and Rittner, 2017). Opioids have been demonstrated to reduce macrophage, lymphocyte and natural killer cell activity in animal and human models, and this may be one potential mechanism. However, not all opioids have displayed these properties and this contrast has been utilised in epidemiological research to test the immunosuppressive hypothesis.

Five previously conducted observational studies on opioids and the risk of pneumonia were identified: three case-control studies (Dublin et al., 2011; Wiese et
al., 2018; Edelman et al., 2019), one cohort study (Vozoris et al., 2016) and one case-crossover study (Wiese et al., 2016) (Table 6). All of these have been conducted in North America in heterogeneous populations: among persons with rheumatoid arthritis or COPD, among older health insurance clients and Medicare recipients, and among veterans with and without human immunodeficiency virus (HIV). Only Vozoris et al. (2016) and Dublin et al. (2011) included only persons over 65 years. Moreover, the main outcome has varied: in their 2016 study Wiese et al. investigated hospitalisation for serious infections and in their 2018 study, the examined invasive pneumococcal diseases. Thus, all variants of exposure, such as different doses, were not reported for the association with pneumonia in these studies.

A new-user design was utilised by Dublin et al. (2011) and Vozoris et al. (2016) and, in the sensitivity analyses conducted by Wiese et al. (2016 and 2018). Only Edelman et al. (2019) considered different opioid doses with respect to the outcome of pneumonia. However, Edelman et al. did not report the associated risk for pneumonia outside of their classification for immunosuppressive status. Similarly, only Dublin et al. reported the associated risk according to the duration of use.

In case-control studies, current opioid use has been associated with a 38% to 54% increased risk as compared to non-use (Dublin et al., 2011; Wiese et al., 2018) (Table 6). The risk was highest at the beginning of use (OR 3.24, 95% CI 1.64–6.39) and non-significant after two weeks (Dublin et al., 2011). In the case-crossover study, an incident rate ratio of 1.22 (95% CI 0.99-1.51) was found for hospitalisations for pneumonia (Wiese et al., 2016). Higher doses have also been associated with a higher risk of pneumonia (Dublin et al., 2011; Edelman et al., 2019), although the dose-response relationship was not consistent in the study of Dublin et al (2011). The risk associated with different opioid strength categories has not been studied previously. Those opioids classified as being immunosuppressive have been associated with a higher risk in comparison to non-immunosuppressive opioids (Dublin et al., 2011; Edelman et al., 2019).

Overall, published studies investigating the association between opioid use and pneumonia have been heterogeneous in design, study population, outcomes, and exposure measures. No studies have been conducted outside of North America or among persons with cognitive disorders. Risk estimates for the duration of use, different doses, or different opioid strength categories have either not been reported or have been reported in single studies. Moreover, studies conducted in middle-aged adults are not generalisable to individuals aged 75 years or more.
Table 6. Studies on opioid use and the risk of pneumonia-related outcomes.

<table>
<thead>
<tr>
<th>Study (country)</th>
<th>Data source</th>
<th>Study population (N)</th>
<th>Mean age, % of women</th>
<th>Definition and measure of opioid use</th>
<th>Risk of pneumonia compared to non-use</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Adjusted odds ratio (95% confidence interval)</td>
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<tr>
<td>Case-control studies</td>
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<tr>
<td>Dublin et al., 2011 (USA)</td>
<td>Group Health database 2001–2003</td>
<td>1039 cases of pneumonia (2022 matched controls)</td>
<td>Cases: median age: 77 years, 49.5% Controls: median age: 77 years, 49.1%</td>
<td>Current use: ≥ 1 prescription fills 5–60 days before the outcome Non-use: no fills 5–365 days before the outcome Immunosuppressive / not immunosuppressive*</td>
<td>Current opioid use: 1.38 (1.08–1.76) Current use which began: 5–14 days before: 3.24 (1.64–6.39) 15–30 days before: 1.28 (0.72–2.29) 31–90 days before: 1.24 (0.78–1.99) ≥ 91 days before: 1.27 (0.91–1.77) Current use, dose of &lt;20 MME/day: 1.05 (0.71–1.56) 20–50 MME/day: 2.30 (1.10–4.83) &gt;50 MME/day: 1.37 (0.64–2.92) Immunosuppressive: 1.88 (1.26–2.79) not immunosuppressive: 1.23 (0.89–1.69)</td>
</tr>
<tr>
<td>Wiese et al., 2018 (USA)</td>
<td>Tennessee Medicaid 1995–2014</td>
<td>1233 cases of invasive pneumococcal diseases (911 pneumonias) (24,399 matched controls)</td>
<td>Cases: not reported, 59.4% Controls: not reported, 68.6%</td>
<td>Current use: prescription fill overlapping outcome date Non-use: no fill within 182 days before the outcome</td>
<td>Current opioid use: 1.54 (1.26–1.88)</td>
</tr>
</tbody>
</table>
**Table 6 (continued)**

<table>
<thead>
<tr>
<th>Study</th>
<th>Health Care System</th>
<th>Study Population</th>
<th>Cases/Controls</th>
<th>Hospitalisation</th>
<th>Incidence of Pneumonia</th>
<th>Inpatient Stay</th>
<th>Prescription Use</th>
<th>Adjusted Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edelman et al., 2019 (USA)</td>
<td>Veterans Health Administration 2000–2012</td>
<td>Veterans with HIV (14,906) Uninfected veterans (10,486)</td>
<td>4246 cases with incident pneumonia requiring hospitalisation and 21,146 matched controls</td>
<td>Cases: 55 years, 1.1%</td>
<td>Current use: prescription fills 5–60 days before the outcome</td>
<td>Controls: 55 years, 1.1%</td>
<td>Non-use: no fills 5–365 days before the outcome</td>
<td>Immunosuppressive/ not immunosuppressive*</td>
</tr>
<tr>
<td>Vozoris et al., 2016 (Canada)</td>
<td>Ontario health administrative data 2007–2012</td>
<td>89,224 incident opioid users ≥66 years with COPD 41,930 opioid non-users ≥66 years with COPD</td>
<td>Opioid users: 77 years, 47.4%</td>
<td>Opioid user: any opioid dispensing</td>
<td>Emergency room visits for COPD or pneumonia: 1.14 (1.00–1.29) Hospitalisations for COPD or pneumonia: 1.08 (0.97–1.21)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wiese et al., 2016 (USA)</td>
<td>Tennessee Medicaid 1995–2009</td>
<td>1,790 patients with rheumatoid arthritis with at least 1 hospitalisation for a serious infection</td>
<td>Not reported</td>
<td>Current use: the time between prescription fill and the end of the supply</td>
<td>Hospitalisation for pneumonia: 1.22 (0.99–1.51)</td>
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</table>

COPD = Chronic Obstructive Pulmonary Disease; HIV = Human Immunodeficiency Virus; MME = Morphine Milligram Equivalents. *Immunosuppressive opioids included codeine, morphine, fentanyl (and methadone in Dublin et al.); non-immunosuppressives included hydrocodone, oxycodone, hydromorphone, tramadol.
2.5.2 Other severe outcomes associated with opioid use

Due to the common adverse effects of opioids such as sedation, dizziness, and confusion especially when treatment is initiated or the dose is increased, their use has been suspected to lead to an increased risk for falls and fractures (Abdulla et al., 2013). Opioids have been associated with an increased risk for falls in meta-analyses of observational studies among older adults (Park et al., 2015; Seppälä et al., 2018). Perttilä et al. (2017) investigated factors associated with falls in an exercise-based intervention study in persons with AD and opioid use was identified as a strong predictor for falls. Similarly, two meta-analyses of observational studies have found an increased risk for fractures among opioid users (Teng et al., 2015; Ping et al., 2017), which was especially high for hip fractures. Among individuals with AD, a doubled risk for hip fractures was found among incident opioid users as compared to non-users in a register-based study (Taipale et al., 2018). The risk was elevated only at the beginning of opioid use, indicating a possible sedation-based mechanism for fractures in this population.

Opioid-induced delirium has also been reported (Guerard and Cleary, 2017; Şenel et al., 2017). The mechanisms behind opioid deliriogenesis include increased dopaminergic, glutaminergic, and anticholinergic activity (Maldonado, 2018). In their systematic review, Clegg and Young (2011) stated that there was moderate-quality evidence to suggest that opioids would be associated with a more than 2-fold increased risk of delirium in medical and surgical patients, including persons with cognitive disorders. Results on specific opioids were heterogeneous, but a higher risk was found for pethidine as compared to the other opioids. A more recent systematic review on surgical patients, including persons with cognitive disorders, found a higher risk for delirium associated with meperidine and tramadol as compared to other opioids, although the evidence was not strong (Swart et al., 2017). None of the included studies in these reviews was conducted exclusively in individuals with cognitive disorders or in outpatient settings.

Older adults seem to be at an increased risk for traffic injuries associated with opioid use (Monárrez-Espinó et al., 2013, 2016). A meta-analysis of observational studies found an increased risk of traffic injuries among older drivers (Monárrez-Espinó et al., 2013). In a more recent population-based case-control study new, but also frequent opioid use, was associated with a higher risk of road traffic crashes among people aged 50 to 80 years (Monárrez-Espinó et al., 2016). The higher risk associated with new opioid use may be explained by the fact that tolerance has not developed to the cognitive ADEs as will occur with a longer duration of use (Young-McCaughan and Miaskowski, 2001).

The cognitive effects of opioids have also led to a hypothesis of opioid-related cognitive decline or increased incidence of cognitive disorders. Brain autopsy studies have linked high-dose opioid use with higher concentrations of plaque- and fibril-forming peptides, but not with actual neuropathological changes (Dublin et al., 2017; Flanagan et al., 2017). A US cohort study found an association between high-dose opioid use and the risk of cognitive disorders (Dublin et al., 2015). However, the
authors suggest this was due to residual confounding. Similarly, a Finnish register-based case-control study did not find any associations between opioid use, longer duration of use, or high cumulative dose and the risk of AD (Taipale et al., 2017c).

The respiratory effects of opioids may also predispose to sleep-disordered breathing (Yue and Guilleminault, 2010; Van Ryswyk and Antic, 2016). This includes obstructive and central sleep apnea. The higher incidence of obstructive sleep apnea among opioid users may be due to an opioid-induced reduction in airway muscle activation, whereas central sleep apnea may be due to the reduced respiratory response to hypercapnia and hypoxia (Van Ryswyk and Antic, 2016). Opioid-induced sleep-disordered breathing appears to be dose-dependent and possibly not evident at low doses. Obstructive and central sleep apneas are more common among older adults and those with cognitive disorders than among younger adults (Bombois et al., 2010). Older adults could thus theoretically have a higher risk of opioid-induced apnea.

Due to opioid-induced dependency and effects on the reward system of the brain, opioids are well known as causing addiction (Pathan and Williams, 2012). Fear of addiction has been recognised as a common barrier to opioid prescribing and use (Chandler et al., 2016). According to a limited number of studies, opioid addiction may be rarer among older than among younger adults (Papaleontiou et al., 2010). Nonetheless, studies on intentional or unintentional opioid misuse are rare among older adults and therefore, it is difficult to estimate the prevalence of misuse (Maree et al., 2016). In the US, rates of opioid poisonings have increased among those over 60 years old in the past decade (West et al., 2015; West and Dart, 2016). However, most of these incidents have been due to unintentional misuse. The prevalence of unintentional misuse among persons with cognitive disorders could be a topic for future research.
3 AIMS OF THE STUDY

The overall aim of this thesis was to investigate the prevalence of analgesic use and outcomes associated with incident opioid use among community-dwellers with AD.

The study-specific aims were to investigate:

1. the prevalence of analgesic use within 6 months after the AD diagnosis in comparison with matched persons without AD and to identify the factors associated with the use of analgesics (Study I);

2. the prevalence of long-term opioid use for non-malignant pain in comparison with matched persons without AD and to examine which factors are associated with long-term use (Study II);

3. the impact of opioid initiation on the prevalence of antipsychotic, benzodiazepine and related drug and antidepressant use (Study III and additional data);

4. the association between incident opioid use and hospital-treated pneumonia (Study IV).
4 SUBJECTS AND METHODS

4.1 STUDY COHORT AND DATA SOURCES

This thesis is part of the nationwide Medication Use and Alzheimer’s disease (MEDALZ) cohort (Tolppanen et al., 2016b). The cohort includes all community dwellers who received diagnoses of AD in 2005-2011, residing in Finland (N = 70,718). In addition, the cohort comprises up to four comparison persons without AD, who were matched for age, sex, and hospital district at the diagnosis date of the AD case. All data for MEDALZ were collected from several nationwide registers (Table 7). Data on persons diagnosed with AD were retrieved from the Special Reimbursement Register, maintained by the Social Insurance Institution (SII). The Special Reimbursement Register consisting of data on entitlement to higher reimbursement of drugs for specific chronic illnesses, such as AD. The cohort of matched comparison persons was identified from SII registers including all residents. In this thesis, only one, the best matching person, was gathered for each person with AD (N = 70,718, studies I and II). Comparison persons were not allowed to have a diagnosis of AD or antidementia drug purchases before or at the matching date or in the following year. Furthermore, comparison persons needed to be alive and outside institutional care during the month of the matching date. If a comparison person was diagnosed later with AD, their follow-up as comparison persons was censored.

Finnish Current Care Guidelines for cognitive disorders recommend initiating treatment with antidementia drugs when AD is diagnosed, in the absence of contraindications (Finnish Medical Society Duodecim, 2010). To be entitled to antidementia drug reimbursement from the SII, a person must fulfil predefined diagnostic criteria, which are based on the NINCDS-ADRDA (McKhann et al., 1984) and DSM-IV standards (American Psychiatric Association, 1994) and have a mild or moderate stage of AD. These criteria include significant progressive impairment of cognition and a decline in social skills and activities of daily living in at least the previous three months. Impairment is assessed by patient and caregiver interviews and neuropsychological tests. A differential diagnosis is formed through clinical assessment, laboratory tests, and computed tomography or magnetic resonance scan. Mixed cases of AD with other cognitive disorders are also entitled to a special reimbursement if the symptoms are mainly caused by AD. The diagnosis of AD is required to be confirmed by a geriatrician or a neurologist. A diagnostic statement describing the clinical findings is sent to the SII for evaluation and reimbursement is granted if the criteria are fulfilled. Persons with dementia related to Parkinson’s disease have been entitled to reimbursement for rivastigmine since 2007; these persons were excluded from the MEDALZ cohort. Compared to the population-based Cardiovascular Risk Factors, Aging and Dementia (CAIDE) cohort (Solomon et al., 2014), the Special Reimbursement Register has high positive predictive value for AD (97.1, 95% confidence interval, CI 84.7–99.9) but somewhat lower sensitivity.
(63.5, 95% CI 49.0–76.4). It should be noted, however, that the CAIDE study may have included persons with early-stage AD who were not yet eligible for reimbursement, thus resulting in lower sensitivity estimates.

Table 7. Data sources utilised in this thesis.

<table>
<thead>
<tr>
<th>Special Reimbursement Register</th>
<th>Prescription Register</th>
<th>Hospital Discharge Register</th>
<th>Statistics Finland</th>
</tr>
</thead>
<tbody>
<tr>
<td>SII</td>
<td>SII</td>
<td>THL</td>
<td>Statistics Finland</td>
</tr>
</tbody>
</table>

Register holder

Data on entitlement to special reimbursement due to chronic diseases

Purchase data of reimbursed prescription drugs

Data on hospital stays

Data on hospital census data on socioeconomic indices

Data collected (years available)

AD diagnosis (2005–2011);
Comorbidities (1972–2015)

Dates of purchases; ATC codes; Number of purchased items; Dose in DDDs; Drug strength; Dosage form; Nordic article number (1995–2015)

Diagnoses of pneumonia; Comorbidities; Procedures; Dates (1972–2015)


SII = Social Insurance Institution; THL = National Institute of Health and Welfare; AD = Alzheimer’s disease; ATC = Anatomical Therapeutic Chemical; DDD = Defined Daily Dose.

Drug use data in this thesis was extracted from the Prescription Register, maintained by the SII. The register includes all reimbursed purchases of prescription drugs from Finnish pharmacies since 1995 (Furu et al., 2010). It does not include drugs used in hospitals or public nursing homes, non-reimbursed medicines, or over-the-counter (OTC) drugs. Data on drug purchases in the Prescription Register are classified according to WHO’s Anatomical Therapeutic Chemical (ATC) codes (WHO Collaborating Center for Drug Statistics Methodology, Norwegian Institute of Public Health). ATC codes are the gold standard for classifying drug substances for drug utilisation monitoring. The Prescription Register data includes dates of purchases, ATC codes, number of dispensed packages, drug strength, dosage form, and package-specific Nordic article number (VNR). The amount of the drug purchased is registered as defined daily dose (DDD), which is assumed to be the average maintenance dose per day for a drug being used for its main indication in adults (WHO Collaborating Center for Drug Statistics Methodology, Norwegian Institute
of Public Health). In this thesis, data from the register were collected until 2012 in studies I, II and III and until 2015 in study IV.

Information on inpatient hospital days was collected from the Hospital Discharge Register. The register includes data on hospital stays, medical procedures, dates of care and discharge diagnoses since 1972 (according to the International Classification of Diseases (ICD) codes, versions 8, 9 and 10). Procedures are classified according to the Nordic Medico-Statistical Committee Classification (NOMESCO) codes. The Hospital Discharge Register has been utilised for research for many decades and several validation studies have been conducted on various diagnoses in the register (Sund, 2012). Similarly to the drug use data, data on hospital days were collected until 2012 for studies I, II and III and until 2015 for study IV.

The Special Reimbursement Register, which was utilised for identifying persons with AD, was further used to collect data on chronic comorbidities, such as cardiovascular diseases. Similarly to AD, in order to be entitled to higher reimbursement for disease-specific drugs, applicants must meet pre-specified diagnostic criteria. Applications for special reimbursement can be sought for primary, secondary or tertiary care. Data in the register have been collected since 1972.

Data on socioeconomic status were received from Statistics Finland, where these data have been collected from population censuses since 1970. In this thesis, the highest occupational status in middle age was utilised (recorded when participants were 45 to 55 years old).

In addition to the above-mentioned registers, dates of death were collected from the SII. In Finland, all residents are given personal identification numbers (PINs). Data from these different registers were linked through PINs by the register holders and were pseudonymised prior to entrusting it to our research group.

### 4.2 ANALGESIC EXPOSURE

Analgesics in this study were classified into three main categories: paracetamol (N02BE01), oral NSAIDs (M01A, excluding glucosamine) and opioids (N02A) (Table 8). NSAIDs were further classified into non-selective NSAIDs and coxibs in study I. Opioids were classified according to their relative pharmacological efficacies and potencies into mild opioids, partial agonists and strong opioids, and according to a previous definition of immunosuppressive status (study IV) (Dublin et al., 2011; Wiese et al., 2018) (Table 8). In study IV, morphine equivalent doses were calculated according to the equivalency ratio with respect to morphine devised by Svendsen et al. and by drug form (Table 9) (Svendsen et al., 2011).
Table 8. Definitions and classifications of analgesics used in this thesis. Sources: Dublin et al., 2016, Wiese et al., 2018.

<table>
<thead>
<tr>
<th>Class of drugs</th>
<th>ATC code (substance, if applicable)</th>
<th>Exclusion</th>
<th>Data not available in the Prescription register</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paracetamol</td>
<td>N02BE01</td>
<td></td>
<td>OTC use; non-reimbursed purchases prior to 2010</td>
</tr>
<tr>
<td>NSAI Ds</td>
<td>M01A</td>
<td>M01AX05 (glucosamine)</td>
<td>OTC use of: M01AE01 (ibuprofen); M01AE03 (ketoprofen); M01AE14 (dextibuprofen) prior to June 2008 Non-reimbursed purchases of: M01AE52 (naproxen and esomeprazole);</td>
</tr>
<tr>
<td>Non-selective NSAI Ds</td>
<td>MO1AB (acetic acid derivatives and related substances); MO1AC (oxicams); MO1AE (propionic acid derivatives) MO1AG (fenamates)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coxibs</td>
<td>M01AH01 (celecoxib); M01AH05 (etoricoxib)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opioids</td>
<td>N02A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weak opioids</td>
<td>N02AA59 (codeine)*; N02AX02 (tramadol)</td>
<td></td>
<td>Non-reimbursed purchases of: N02AJ06 (codeine/paracetamol effervescent tablet); N02AJ08 (ibuprofen/codeine tablet); N02AJ06 (codeine/paracetamol tablet prior to 2010)</td>
</tr>
<tr>
<td>Partial agonists</td>
<td>N02AE01 (buprenorphine)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strong opioids</td>
<td>N02AA01 (morphine); N02AA03 (hydromorphone); N02AA05 (oxycodeine); N02AB03 (fentanyl); N02AC04 (dextropropoxyphene); N02AD01 (pentazocine)</td>
<td></td>
<td>Non-reimbursed purchases of: N02AA55 (oxycodeine/naloxone)</td>
</tr>
<tr>
<td>Opioids according to their immunosuppressive status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immunosuppressive opioids</td>
<td>N02AB03 (fentanyl); N02AA01 (morphine); N02AA59 (codeine)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-immunosuppressive opioids</td>
<td>N02AX02 (tramadol); N02AA05 (oxycodeine)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*All other codes for codeine analgesics were recoded to N02AA59. ATC = Anatomical Therapeutic Chemical; NSAI Ds = non-steroidal anti-inflammatory drugs; OTC = over-the-counter.
Table 9. Equianalgesic ratios of opioids with respect to morphine (Svendsen et al., 2011).

<table>
<thead>
<tr>
<th>Opioid agent (ATC code)</th>
<th>Administration routes</th>
<th>Equianalgesic ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine (N02AA59)</td>
<td>Oral</td>
<td>0.1</td>
</tr>
<tr>
<td>Tramadol (N02AX02)</td>
<td>Oral, parenteral, rectal</td>
<td>0.2</td>
</tr>
<tr>
<td>Buprenorphine (N02AE01)</td>
<td>Transdermal</td>
<td>110</td>
</tr>
<tr>
<td></td>
<td>Sublingual, parenteral</td>
<td>50</td>
</tr>
<tr>
<td>Morphine (N02AA01)</td>
<td>Oral</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Parenteral</td>
<td>3</td>
</tr>
<tr>
<td>Hydromorphone (N02AA03)</td>
<td>Oral</td>
<td>6</td>
</tr>
<tr>
<td>Oxycodone (N02AA05)</td>
<td>Oral</td>
<td>1.5</td>
</tr>
<tr>
<td></td>
<td>Parenteral</td>
<td>3</td>
</tr>
<tr>
<td>Fentanyl (N02AB03)</td>
<td>Transdermal</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Intranasal, sublingual</td>
<td>50</td>
</tr>
<tr>
<td>Dextropropoxyphene (N02AC04)</td>
<td>Oral</td>
<td>0.15</td>
</tr>
<tr>
<td>Pentazocine (N02AD01)</td>
<td>Oral</td>
<td>0.387</td>
</tr>
</tbody>
</table>

ATC = Anatomical Therapeutic Chemical.

4.2.1 Modelling of drug use

The data extracted from the Prescription Register were utilised to construct estimated drug use periods, i.e. estimations of when continuous drug use started and ended, for each person as well as recording the ATC code. These analyses were undertaken utilising a mathematical modelling method, ‘From prescriptions to drug use periods’, PRE2DUP (Tanskanen et al., 2015).

The overall functioning of the PRE2DUP method is described in Figure 4 and in more detail in Tanskanen et al., 2015. Input data for modelling include purchase data (i.e. substance, date, the amount in DDD) and hospital care periods. A set of global parameters controlled joining of all drug use periods: the longest refill time (restricted to 300 days), the maximum length of a single purchase (150 days), and longest duration of continuous hospital stay included in a drug use period (30 days). Moreover, as the Prescription Register data does not include information on the prescribed dose, expert-defined parameters were designed for ATC codes and individual drug packages as defined by their VNR number. The more specific VNR-level parameters were used instead of ATC-level parameters when they were available. These parameters included limits for the highest, lowest and typical dosage. The highest and lowest possible doses in continuous use were defined based on dosage form, assumed pattern of use among older persons, number of units, divisibility and storage life. For analgesics, the most precise VNR-based parameters
were utilised, including fixed changing schedules for transdermal products. Overall, expert-defined parameters were applied to prevent unrealistically long drug use periods and to provide clinical and pharmaceutical rigour for the method.

Figure 4. An overview of the PRE2DUP modelling of drug use periods (Tanskanen et al. 2015).

For a single purchase, PRE2DUP adopts the dose from an individual’s other drug use period of the same drug, if one exists (Tanskanen et al., 2015). The second-line option was to use the most common refill length, which was calculated from the entire study population, based on the specific VNR number. If the most common refill time length was not available, the method used the expert-defined typical dosage parameters for VNR numbers or for ATC codes.

For multiple purchases, PRE2DUP calculated temporal sliding averages of daily dose (Tanskanen et al., 2015). In addition, the pre-processing phase also calculated statistics for personal regularity of purchases, for each drug and person. Information on the purchased amount of drug, calculated daily dose and individual purchase pattern (e.g. regularity and stockpiling) were utilised to create expected refill lengths for each purchase. Hospital days were excluded from dosage calculations, but hospitalisations did not necessarily end the drug use periods. If the derived calculated daily dose was lower than the preset lower limit, the drug use period was ended. If the calculated refill length reached the next purchase, the drug use period was continued. The drug use periods were terminated after calculating the duration of the last purchase. The process of applying and reapplying data-driven parameters into preliminary drug use periods was iterated in the core process of the method until the results remained stable (Figure 4).

If an expected refill length was shorter than the time until the next purchase, PRE2DUP applied a test for stockpiling (Tanskanen et al., 2015). To observe a stockpiling event, the method compared the sliding average of the current purchase with a sliding average of the previous purchase and the following purchase. If the sliding average was lower than the previous or the following one, the method calculated duration with the current and previous purchases taken together.

When examining the use of any opioids or any NSAIDs, overlapping drug use periods of different opioids or NSAIDs were combined. For example, during a period of any opioid use, a person could change between different opioid substances and use multiple opioids concomitantly. Similar combinations were made for different opioid categories.
In study II, a comparison of the use of oral or transdermal drug administration routes was conducted. Each package of opioids was coded as either one of these formulations, utilising VNR numbers. Drug use periods of oral forms together and transdermal forms together were combined to obtain the duration of “any oral opioid” and “any transdermal opioid” use.

In study IV, a dose-specific analysis was conducted utilising administration route-specific data. In this analysis, DDDs per day were converted into morphine milligram equivalents (MMEs) per day (Table 9). If multiple opioids were used simultaneously, the converted doses were summed together to acquire a total opioid dose.

4.3 STUDY DESIGNS

4.3.1 Prevalence of analgesic use (Study I)

In study I, the prevalence of analgesic use was investigated during a period of 180 days after the AD diagnosis. Persons were defined as analgesic users if their drug use periods were included in this timeframe. Concomitant use of 2 or more analgesics was defined as at least 30 days of overlapping drug use periods.

All persons diagnosed with AD in 2005–2011 (N = 70,718) and one age-, sex and region of residence-matched comparison person without AD for each were included in this study. The AD diagnosis or the corresponding matching date was considered as the index date, from which data on comorbidities and other drug use were collected. Persons were excluded if they had ≥120-day hospital and/or long-term care facility stays during the follow-up or if they died within 2 months of the beginning of the follow-up (Table 10). These exclusions were done to ensure sufficient follow-up data for analgesic use. After exclusions, matching was retained and thus, 67,215 persons with AD and 67,215 persons without AD were included in the analyses.
Table 10. Study exclusions and persons with and without Alzheimer’s disease (AD) included in the analyses.

<table>
<thead>
<tr>
<th>Study</th>
<th>Initial study sample</th>
<th>Study-specific exclusion criteria</th>
<th>Loss of follow-up due to long-term hospitalisation or institutionalisation or death</th>
<th>Active cancer treatment</th>
<th>Opioid use during wash-out</th>
<th>Study-specific exclusion criteria</th>
<th>Loss due to matching</th>
<th>Final study sample</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study I</td>
<td>Persons diagnosed with AD in 2005-2011 n = 70,718</td>
<td>not applied</td>
<td>2,373</td>
<td>1,171</td>
<td>3,641</td>
<td>not applied</td>
<td>1,130</td>
<td>67,215</td>
</tr>
<tr>
<td>Study II</td>
<td>Persons diagnosed with AD in 2005–2011 n = 70,718</td>
<td>not applied</td>
<td>555</td>
<td>714</td>
<td>4,087</td>
<td>not applied</td>
<td>2,332</td>
<td>67,215</td>
</tr>
<tr>
<td>Study III</td>
<td>Persons diagnosed with AD in 2010 or 2011, n = 23,100</td>
<td>not applied</td>
<td>126</td>
<td>436</td>
<td>863</td>
<td>101</td>
<td>3,327 opioid initiators</td>
<td>5,623 opioid users</td>
</tr>
<tr>
<td>Study IV</td>
<td>Persons diagnosed with AD in 2010 or 2011, n = 23,100</td>
<td>not applied</td>
<td>126</td>
<td>436</td>
<td>863</td>
<td>101</td>
<td>3,327 opioid initiators</td>
<td>5,623 opioid users</td>
</tr>
</tbody>
</table>

Opioid initiation before December 31, 2012 n = 3,916

Loss due to matching 1,130

Opioid initiation before December 31, 2015 n = 7,730

Final study sample 62,074 (13,111 opioid users) 62,074 (16,659 opioid users) 3,327 opioid initiators 3,325 matched opioid non-initiators 5,623 opioid users 5,623 matched opioid non-users
4.3.2 Long-term opioid use (Study II)

All persons diagnosed with AD in 2005–2011 (N = 70,718) and one comparison person without AD for each were included in study II, similarly to study I (Table 10). Long-term use of opioids was defined as ≥180 days and short-term use <180 days of continuous use of any opioid, as in the previous studies (Gallini et al., 2013; Busse et al., 2015; Barnett et al., 2017). A limit of six months was chosen in preference to another common definition, three months, as 90 days is the maximum one-time purchase of reimbursed drugs in Finland. Therefore, drug use can be more reliably modelled for use periods longer than 90 days. Persons with at least one long-term use period were classified as long-term users of opioids. The type of the first opioid in long-term use was analyzed at the start of the long-term use or at AD diagnosis for prevalent users. Concomitant use of 2 or more opioids was defined as at least 90 days of continuous overlap between any opioid use periods. A 90-day concomitant use period was applied to avoid misclassification of opioid switching as concomitant use.

Persons with active cancer were excluded to focus on non-malignant pain treatment with opioids. Active cancer was defined as a diagnosis of cancer in the Hospital Discharge Register or anticancer/antineoplastic drug use ongoing within the previous 12 months (Table 11). Anticancer drugs used for the treatment of cancer in clinical practice were defined according to drugs on the market in Finland in 2015. This definition was constructed in co-operation with an Adjunct Professor of Oncology, (LP). The definition was also utilised in studies III and IV (see below).
Table 11. Drug purchases from Prescription register and diagnoses from Hospital Discharge register data utilised in the definition of active cancer in studies II, III and IV.

<table>
<thead>
<tr>
<th>Data</th>
<th>Codes</th>
<th>Exclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATC codes for anticancer or antineoplastic drugs (name of the agent)</td>
<td>L01 (antineoplastic agents); L02 (endocrine therapy); L03AA (colony stimulating factors); L03AB01 (interferon alfa natural); L03AB04 (interferon alfa-2a); L03AB05 (interferon alfa-2b); L03AC (interleukins); L03AX (other immunostimulants); L04AA10 (sirolimus); L04AA18 (everolimus); L04AA34 (alemtuzumab); L04AX02 (thalidomide); L04AX03 or L01BA01 (methotrexate)</td>
<td>L03AX13 (glatiramer acetate); For L04AX03 or L01BA01 (methotrexate): persons with a special reimbursement for rheumatoid arthritis.</td>
</tr>
<tr>
<td>ICD-10 codes for discharge diagnoses related to malignant neoplasms</td>
<td>C00–C97</td>
<td></td>
</tr>
<tr>
<td>NOMESCO codes of surgical procedures related to cancer</td>
<td>AAG50, AX, HA0, PJO, QA0, QB0, QC0, QD0, QW0, QX0, WA, WB, WC, WD, WE, WF0, WFO, ZX0</td>
<td></td>
</tr>
</tbody>
</table>

ATC = Anatomical Therapeutic Chemical; ICD-10= International Classification of Diseases, version 10; NOMESCO = Nordic Medico-Statistical Committee Classification of Surgical Procedures

In addition to active cancer, persons in long-term care for the entire follow-up were excluded (Table 10). Follow-up ended because of ≥90 days of hospitalisation or institutionalisation, death, or the end of the study period (December 31, 2012), whichever came first.

4.3.3 Impact of opioid initiation on the prevalence of antipsychotic, benzodiazepine and related drug and antidepressant use (Study III and additional analyses)

The analyses in study III were restricted to those diagnosed with AD in 2010 or 2011 (n = 23,100), due to inconsistent reimbursement of codeine combination products before 2010 to avoid errors in exposure classification. Only persons with AD were included in this study; persons with an opioid initiation were matched with non-initiators at the date of opioid initiation according to age, sex and time since the AD diagnosis (±90 days). A washout period, in which no modelled opioid use was allowed before opioid initiation, was defined as six months. Moreover, persons with long-term hospitalisations of over six months prior to the washout were excluded from study III (Table 10). Follow-up began six months before opioid initiation. After opioid initiation, the subjects were followed up for six months, or until death, less than ten days of follow-up per month, or the end of the study period (December 31, 2012), whichever came first.
Prevalences of psychotropic drug use were measured before and after opioid initiation. Psychotropic drugs included antipsychotics, BZDRs, and, additionally to previously published results, antidepressants. Measures were made in 30-day periods at six months before and six months after opioid initiation and prevalences of opioid initiators were compared to opioid non-initiators with AD with interrupted time series analyses (Figure 5) (Wagner et al., 2002; Penfold and Zhang, 2013). Interrupted time series analysis makes it possible to estimate pre- and post-intervention trends and to detect a change in the level of an outcome measure (i.e. antipsychotic, BZDR, or antidepressant use) after an intervention (i.e. opioid initiation). It measures the outcome repeatedly over the follow-up period both before and after the intervention. The method accounts for existing trends in the outcome measure, i.e. a rising trend of the prevalence of psychotropic drug use due to AD progression. Thus, the findings reflect the impact of the intervention and possibly other simultaneous changes. In addition to pre- and post-intervention periods, the 30 days following opioid initiation were defined as an intervention period to measure its immediate effects.

![Figure 5. Interrupted time series analyses as a function of time and outcome. The outcome in this study refers to the prevalences of antipsychotic, benzodiazepine and related drug (BZDR) and antidepressant use and intervention to opioid initiation (Wagner et al. 2002; Vidal et al 2008).](image)

### 4.3.4 Incident opioid use and the risk of hospital-treated pneumonia (Study IV)

Study IV investigated the association between incident opioid use and hospital-treated pneumonia (referred to as pneumonia from here on). The study restricted the analyses into those individuals diagnosed with AD in 2010 or 2011 (n = 23,100) and
did not include persons without AD. Persons who were new users of opioids were matched with non-users on the first day of opioid use (index date), where follow-up was started. Matching criteria were age (±2 years), sex and time since AD diagnosis (±90 days). The study applied a new-user design to avoid prevalent user bias (Ray, 2003). In observational research, prevalent users can be referred to as ‘survivors’ of drug use, e.g. persons who experience adverse effects of a drug are more likely to discontinue using it. Thus, including prevalent users could decrease the impact of the exposure and bias the effect towards the null. A washout of one year was therefore applied, and opioid users within the washout period were excluded from the study (Table 10). Similarly, persons who were hospitalised for >50% of the washout period or had >90 days hospitalisation at the end of the washout period were excluded, due to the lack of data about their drug use during the hospital stay. Finally, persons with active cancer within a year or pneumonia six months before opioid initiation were excluded. These exclusion criteria were also applied to opioid non-users. The follow-up after opioid initiation was censored to death, >90 days of hospitalisation/institutionalisation, incident pneumonia, after 1000 days or end of the study period (December 31, 2015), whichever came first.

The Hospital Discharge Register was utilised for identifying diagnoses of pneumonia, thus excluding only community-treated cases. The ICD-10 codes gathered to define a diagnosis of pneumonia are displayed in Table 12. Only the first recorded pneumonia for each person was considered after the diagnosis of AD, to exclude treatment of the original disease.

Table 12. International Classification of Diseases (ICD) 10 codes and categorization of diagnoses utilised in the definition of pneumonia in study IV.

<table>
<thead>
<tr>
<th>ICD-10 codes</th>
<th>Pneumonia due to</th>
</tr>
</thead>
<tbody>
<tr>
<td>J10.0</td>
<td>influenza due to other identified influenza virus</td>
</tr>
<tr>
<td>J11.0</td>
<td>influenza due to unidentified influenza virus</td>
</tr>
<tr>
<td>J12.0</td>
<td>viral infection, not elsewhere classified</td>
</tr>
<tr>
<td>J13</td>
<td>Streptococcus pneumoniae</td>
</tr>
<tr>
<td>J14</td>
<td>Hemophilus influenzae</td>
</tr>
<tr>
<td>J15</td>
<td>bacteria, not elsewhere classified</td>
</tr>
<tr>
<td>J16</td>
<td>other infectious organisms, not elsewhere classified</td>
</tr>
<tr>
<td>J18</td>
<td>unspecified organism</td>
</tr>
<tr>
<td>J69.0</td>
<td>pneumonitis due to solids and liquids</td>
</tr>
</tbody>
</table>

Study IV also targeted unmeasured, time-invariant confounding factors, e.g. lifestyle factors, such as smoking status, via sensitivity analyses with a self-controlled case-crossover design. The case-crossover design utilises within-person comparisons of transient exposure and non-exposure, eliminating inter-individual confounders (Maclure et al., 2012) (Figure 6).
All opioid users without a washout period and who had pneumonia during the follow-up were included in the case-crossover analysis. Persons with pneumonia 120 days prior to the first pneumonia after AD diagnosis were excluded to ensure that we were handling actual new cases. Those with a >90 days’ long-term care period during the follow-up and/or active cancer were excluded. The case period was defined as 1–14 days before the date of first pneumonia, and two control periods were applied: 31–45 and 60–74 days before the event. A minimum follow-up of 2/3 of both windows in outpatient care was required to allow an individual to be included in these analyses. The prevalence of opioid use between the case and control periods was compared with conditional logistic regression and was adjusted for time-dependent use of antipsychotics, BZDRs, immunosuppressants for nonmalignant diseases and oral corticosteroids (see section on Covariates for details).

### 4.4 COVARIATES

Data on comorbidities in this thesis were collected from the Special Reimbursement and Hospital Discharge Registers, and covariate drug use from the Prescription Register modelled with PRE2DUP method (Table 13).
Table 13. Covariates utilised in this thesis.

<table>
<thead>
<tr>
<th>Covariates collected from the Special Reimbursement Register</th>
<th>Reimbursement codes and definition, if multiple</th>
<th>Studies utilising the covariate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any cardiovascular disease</td>
<td>201 (chronic heart failure), 205 (chronic arterial hypertension), 206 (coronary artery disease), and/or 207 (chronic arrhythmia)</td>
<td>I, II, III, IV</td>
</tr>
<tr>
<td>Asthma and/or COPD</td>
<td>203</td>
<td>I, II, IV</td>
</tr>
<tr>
<td>Diabetes</td>
<td>103</td>
<td>I, II, III, IV</td>
</tr>
<tr>
<td>History of cancer</td>
<td>115 (breast cancer), 116 (prostate cancer), 117 (leukemia), 128 (gynecological cancers), 130 (other malignant neoplasms)</td>
<td>I</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>202 (rheumatoid arthritis and connective tissue diseases)</td>
<td>I, II, III, IV</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Covariates collected from the Hospital Discharge Register</th>
<th>ICD codes or definition</th>
<th>Studies utilising the covariate</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of hip fracture</td>
<td>Diagnoses at any time point before the index date</td>
<td>I, II, III, IV</td>
</tr>
<tr>
<td></td>
<td>ICD-10: S72.0, S72.1, and S72.2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ICD-9: 820</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ICD-8: 82000, 82001, 82010, 82011, 82090, 82091</td>
<td></td>
</tr>
<tr>
<td>History of schizophrenia</td>
<td>Diagnosis of schizophrenia or schizotypal disorder at least 5 years prior to AD diagnosis</td>
<td>III</td>
</tr>
<tr>
<td></td>
<td>ICD-10: F20-F29</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ICD-9: 295, 297, 298, 3010, 3012</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ICD-8: 295, 297, 298, 29999, 30100, 30120</td>
<td></td>
</tr>
<tr>
<td>History of stroke</td>
<td>Diagnoses before the index date</td>
<td>IV</td>
</tr>
<tr>
<td></td>
<td>ICD-10: I60–I64</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ICD-8: 430–434</td>
<td></td>
</tr>
</tbody>
</table>

(Continued)
Table 13 (continued).

<table>
<thead>
<tr>
<th>History of substance abuse</th>
<th>Diagnoses of alcohol or narcotic use or alcoholic pancreatitis before the index date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ICD-10: F10–F19, K86.0</td>
</tr>
<tr>
<td></td>
<td>ICD-9: 291, 292, 303, 304, 305</td>
</tr>
<tr>
<td></td>
<td>ICD-8: 291, 303, 304 or hospital admission reasons related to alcohol/drug/narcotic abuse or addiction (33, 71–75)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Recent hospital care</th>
<th>Hospital care during the last 14 days prior to the index date (yes/no)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IV</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Covariates collected from the Prescription Register</th>
<th>ATC codes or definition</th>
<th>Studies utilising the covariate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of drugs in use</td>
<td>Categorized as 0 to 4, 5 to 9, or ≥10</td>
<td>II</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>History of bisphosphonate use (M05BA, M05BB)</td>
<td>I, II, III</td>
</tr>
<tr>
<td>History of long-term BZDR use</td>
<td>≥365 days of continuous use of BZDRs(N05BA, N05CD, N05CF) prior to the index date</td>
<td>II</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>N06A</td>
<td>I, IV</td>
</tr>
<tr>
<td>Antiepileptics</td>
<td>N03A</td>
<td>IV</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>N05A, excluding lithium</td>
<td>I, IV</td>
</tr>
<tr>
<td>Benzodiazepines and related drugs</td>
<td>N05BA, N05CD, and N05CF</td>
<td>I, IV</td>
</tr>
<tr>
<td>Immunosuppressants for non-malignant diseases</td>
<td>L04A</td>
<td>IV</td>
</tr>
<tr>
<td>Proton-pump inhibitors</td>
<td>A02BC</td>
<td>IV</td>
</tr>
<tr>
<td>Oral corticosteroids</td>
<td>H02AB</td>
<td>IV</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Covariates collected from Statistics Finland</th>
<th>Definition</th>
<th>Studies utilising the covariate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Socioeconomic status</td>
<td>Highest occupational position recorded in population census for study persons when they were 45 to 55 years old</td>
<td>I, II, III, IV</td>
</tr>
</tbody>
</table>

ATC = Anatomical Therapeutic Chemical; ICD = International Classification of Diseases; COPD = Chronic obstructive pulmonary disease; BZDRs = Benzodiazepines and related drugs.
All utilised covariates were selected for study-specific aims and were measured at study-specific time points. In study I, AD diagnosis, or the corresponding date (index date) was utilised as the measuring point for non-drug use covariates (Table 13). Covariate drug use was measured within 180 days after the index date. For comorbidities, a diagnosis prior to the index date was required. All covariates were chosen according to their relevance to analgesic use as potential associated factors (e.g., rheumatoid arthritis) or as relative contraindications (e.g., cardiovascular disease for NSAIDs).

Similarly, the date of AD diagnosis or the corresponding date was the measuring point for covariates in study II. In addition to the covariates utilised in study I, a history of substance abuse and a history of long-term BZDR use were considered in study II.

In study III, the covariates were measured at opioid initiation and at the corresponding matching date for matched opioid non-initiators. The covariates were collected to describe the differences between opioid initiators and non-initiators in potential opioid use-related factors. The history of schizophrenia was measured 5 years or more before AD diagnosis to exclude misdiagnoses due to prodromal symptoms of AD.

In study IV, covariates describe factors potentially related to pneumonia risk. Non-time variant data were measured at opioid initiation or at the corresponding matching date. Time-variant data, i.e. other drug use, were collected in a period of 14 days prior to the matching.

4.5 STATISTICAL ANALYSES

Descriptive analyses in this thesis were completed using percentages or percentage points (pps) with P values or 95% confidence intervals (CIs). Categorical variables were compared with the Chi-Squared test.

All statistical analyses were performed using the SAS statistical software (versions 9.3 and 9.4; SAS Institute Inc., Cary, North Carolina, USA).

4.5.1 Prevalence of analgesic use (Study I)

In study I, conditional logistic regression analyses were utilised to evaluate factors associated with analgesic use and the use of different analgesic categories. Thus, opioid use was compared with non-use of opioids, NSAID use with non-use of NSAIDs and any analgesic use with the non-use of analgesics. The results were expressed as ORs and their 95% CIs. Factors included in the adjusted models were AD, age (<80 years or ≥80 years), sex, socioeconomic status (high, medium, low, or unknown), year of diagnosis (from 2005 to 2011), asthma/COPD, cardiovascular disease, diabetes, history of cancer, history of hip fracture, osteoporosis and rheumatoid arthritis and other connective tissue diseases.
4.5.2 Long-term opioid use (Study II)

To investigate factors associated with long-term opioid use in study II, a logistic regression analysis was undertaken. The model compared long-term opioid users with short-term opioid users. Factors included in the multivariable analyses were AD, age (<80 years or ≥80 years), sex, socioeconomic status (high, medium, low, or unknown), asthma/chronic obstructive pulmonary disease, cardiovascular disease, diabetes, history of hip fracture, osteoporosis, rheumatoid arthritis, history of substance abuse, and long-term use of BZDRs.

4.5.3 Impact of opioid initiation on the prevalence of antipsychotic and benzodiazepine and related drug use (Study III and additional analyses)

In study III, prevalences of psychotropic drug uses were analyzed before and after opioid initiation. Time periods of 30 days in the six months before, in the month of opioid initiation and in the six months after the initiation were utilised to define a pre-opioid segment, an opioid initiation, and a post-opioid segment with the values being analysed with segmented linear regression models. Regression coefficients for each segment were calculated to express the change in the prevalences of antipsychotic, BZDR, and antidepressant use (Penfold and Zhang, 2013). Both cohorts were first analyzed separately and then by examining the difference in rates, i.e. by subtracting the prevalence of antipsychotic, BZDR, or antidepressant use of opioid initiators from the prevalence of the non-initiators for every time period. All analyses for opioids were carried out according to the intention-to-treat principle.

The autocorrelation of the time points was estimated utilising a Durbin–Watson test (Penfold and Zhang, 2013). Autocorrelation refers to the dependency of regression residuals over the measured time points. For the results of the Durbin–Watson test, p < 0.05 was considered to indicate statistically significant serial autocorrelation. To increase the reliability of the test, the number of measured time periods was increased in a sensitivity analysis. A total of 24 time periods were created and analysed in 15-day intervals. All time series analyses were performed in autoregressive forms.

4.5.4 Incident opioid use and the risk of pneumonia (Study IV)

In the main analyses for study IV, the risk of pneumonia was evaluated comparing opioid users to non-users with Cox proportional hazard models. Multivariable analyses were adjusted for possible predictors of pneumonia (Torres et al., 2013): cardiovascular disease, diabetes, asthma/COPD, rheumatoid arthritis, baseline use of antidepressants, antipsychotics, PPIs, BZDRs, immunosuppressants for nonmalignant diseases, oral corticosteroids and antiepileptics, history of stroke, hip fracture and substance abuse, socioeconomic status and discharge from hospital care in the last 7 days. A subanalysis categorized opioid use according to the duration of use as ≤60 days, 61–180 days, 181–365 days, and 366–1000 days of exposure. Similarly,
the risk associated with the use of opioids in the different potency categories was evaluated by comparing buprenorphine and strong opioid use to mild opioid use and again by comparing all categories against non-use. Persons initiating opioid use with two or more opioids of different categories were excluded from these subanalyses. Persons were also censored if they later started concomitant use or switched the opioid category. Further dose-response analyses were undertaken by comparing the risk of doses of ≤50 and >50 MME per day and by comparing both dose categories to non-use. The dose of 50 MME was selected as a limit, as the Centers for Disease Control guidelines recommend careful reassessing of individual benefits and risks of opioid treatment, if a dose of >50 MME is prescribed (Dowell et al., 2016). Sensitivity analyses with 40 and 60 MME were also conducted. The proportional hazards assumptions were tested with Kaplan-Meier curves. Accordingly, the main analysis was restricted to the first 1000 days of use and the subanalyses to the first 250 days of use due to the sparsity of data with a longer follow-up time. Moreover, the regression analyses included a robust variance estimator, which accounted for clustering within the matched design.

In intention-to-treat (ITT) analyses, the impact of informative censoring was assessed, i.e. if drug use was discontinued due to adverse effects that would lead to the studied outcome. In these analyses, opioid initiators were considered as users for 180 days regardless of possible discontinuation of use or hospitalisations due to all causes other than pneumonia. The follow-up ended when the subject experienced pneumonia, death, or was still alive at the end of the study, whichever occurred first. For comparison, as-treated analyses were constructed, in which the comparison of users with non-users was restricted similarly to the first 180 days of follow-up.

### 4.6 ETHICAL CONSIDERATIONS

All data utilised in this thesis were pseudonymized by the register holders prior to being transferred to the research group and the study participants were not contacted in any way. Therefore, according to Finnish legislation, an ethics committee approval is not required. The study protocol for MEDALZ was approved by the register holders and SII, THL and Statistics Finland have permitted the use of the data.

I analyzed and saved these data in password-protected computers and did not share them with unauthorized persons. All personal data were only reported in aggregated form and thus individual study participants cannot be identified.
5 RESULTS

5.1 PREVALENCE OF ANALGESIC USE AMONG PERSONS WITH AND WITHOUT ALZHEIMER’S DISEASE AND RELATED FACTORS (STUDY I)

Analgesics were used by 34.9% of persons with AD and 33.5% without AD, respectively (Figure 7). Paracetamol was the most common analgesic utilised in both groups, being used by 25.0% of persons with AD and by 19.1% of persons without AD. NSAIDs were more frequently used by persons without AD (17.4%) as compared with persons with AD (13.3%). Opioid use was slightly more frequent among persons without AD (8.3%) than among persons with AD (7.1%).

![Analgesic use prevalence by persons with and without Alzheimer's disease (AD), with 95% confidence intervals. NSAIDs = Non-steroidal anti-inflammatory drugs.](image)

Figure 7. Analgesic use prevalence by persons with and without Alzheimer's disease (AD), with 95% confidence intervals. NSAIDs = Non-steroidal anti-inflammatory drugs.

AD was not associated with analgesic use in the adjusted logistic regression model (aOR 1.02, 95% CI 1.00–1.04), but was inversely associated with NSAID and opioid use (aOR 0.71, 95% CI 0.69–0.73 and 0.79, 95% CI 0.75–0.82) (Figure 8). A later calendar year of diagnosis was associated with an increased odds for both any analgesic use and opioid use. For NSAID use this association was inverted.
Figure 8. Factors associated with a) any analgesic, b) non-steroidal anti-inflammatory drug (NSAID) and c) opioid use. Adjusted for above-mentioned factors and socioeconomic status. COPD = Chronic obstructive pulmonary disease; OR = odds ratio.
5.2 PREVALENCE OF LONG-TERM OPIOID USE AMONG PERSONS WITH AND WITHOUT ALZHEIMER’S DISEASE AND RELATED FACTORS (STUDY II)

The prevalence of long-term opioid use among persons with AD was 7.2%, as compared to 8.7% among persons without AD (p ≤ 0.0001). With respect to the opioid users, 34.2% of persons with and 32.3% without AD used opioids in the long-term (p = 0.0004). The class of mild opioids was the most frequent class of opioids which initiated long-term use among both persons with and without AD (42.0% of long-term opioid users with AD, 95% CI 40.6–43.5% vs 65.6% of those without AD, 95% CI 64.3–66.9% (Table 14). The most frequent first opioid agent in long-term use, however, was buprenorphine for persons with AD whereas it was codeine for persons without AD. Long-term opioid users with AD started long-term use with strong opioids more frequently than persons without AD.

Among opioid users, the prevalence of long-term transdermal opioid use was 13.2% among persons with and 5.5% among persons without AD (p ≤ 0.0001). The prevalence of at least one transdermal opioid purchase within the long-term use period was higher among persons with AD than among those without AD (59.0%, 95% CI 57.6–60.5% vs 35.1%, 95% CI 33.8–36.4%, respectively).

Table 14. First opioid analgesic in long-term use among long-term opioid users with and without Alzheimer’s disease (AD).

<table>
<thead>
<tr>
<th>First opioid analgesic in long-term use</th>
<th>Long-term opioid users with AD, % (95% CI)</th>
<th>Long-term opioid users without AD, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Codeine</td>
<td>30.5 (29.2–31.9)</td>
<td>48.6 (47.3–50.0)</td>
</tr>
<tr>
<td>Tramadol</td>
<td>11.5 (10.8–12.5)</td>
<td>17.0 (16.0–18.0)</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>35.4 (34.0–36.8)</td>
<td>14.5 (13.6–15.5)</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>8.1 (7.3–8.9)</td>
<td>4.3 (3.8–4.9)</td>
</tr>
<tr>
<td>Oxycodone</td>
<td>3.8 (3.3–4.4)</td>
<td>2.7 (2.3–3.1)</td>
</tr>
<tr>
<td>Other strong opioids</td>
<td>0.1 (0.1–0.3)</td>
<td>0.4 (0.3–0.6)</td>
</tr>
<tr>
<td>Combination of 2 or more opioids</td>
<td>10.6 (9.8–11.6)</td>
<td>12.5 (11.6–13.4)</td>
</tr>
</tbody>
</table>

CI = Confidence interval.

AD was associated with long-term opioid use in the logistic regression model (aOR 1.07, 95% CI 1.02–1.12) as compared with short-term use. Among persons with AD,
the only associated comorbidity was rheumatoid arthritis, whereas among persons without AD, all of the studied comorbidities were associated with long-term use of opioids (Figure 9). Long-term opioid use was associated with a history of long-term use of BZDRs in both groups.

![Long-term versus short term use of opioids](image)

Figure 9. Factors associated with long-term use of opioids compared with short-term use among persons with and without Alzheimer’s disease (AD). Adjusted for above-mentioned factors and socioeconomic status.

### 5.3 IMPACT OF OPIOID INITIATION ON PSYCHOTROPIC DRUG USE AMONG PERSONS WITH ALZHEIMER’S DISEASE (STUDY III AND ADDITIONAL ANALYSES)

Among opioid initiators, the prevalence of antipsychotic use was 13.3% six months before opioid initiation, 18.3% at opioid initiation, and 17.3% six months after opioid initiation (Figure 10a). After accounting for the pre-opioid rate, antipsychotic use decreased by 0.3 pps per month after opioid initiation (95% CI 0.1–0.5 pps) (Table 15). In a segmented regression analysis comparing the prevalence of antipsychotic use...
between opioid initiators and non-initiators, opioid initiation resulted in a decrease in the post-opioid segment (0.5 pps per month, 0.3–0.8).

The prevalence of BZDR use among opioid initiators was 27.1% when assessed at six months before opioid initiation, 27.3% at opioid initiation, and 26.9% six months after the opioid initiation (Figure 10b). By taking the pre-opioid rate into account, the prevalence of BZDR use decreased by 0.4 pps per month after opioid initiation (95% CI 0.2–0.7 pps) and 0.4 pps (0.1-0.7) comparing the prevalences of opioid initiators and non-initiators (Table 15).

The prevalence of antidepressant use among opioid initiators was 25.8% six months before opioid initiation, 29.8% at opioid initiation, and 31.0% six months after opioid initiation (Figure 10c). After accounting for the pre-opioid rate, antidepressant use increased by 0.2 pps (95% CI 0.0-0.3) per month in the post-opioid segment (Table 15). Similarly, there was a small increase in the post-opioid trend when opioid initiators were compared to non-initiators.

In sensitivity analyses, the autocorrelation was tested in time periods of 15 days, creating a total of 24 time periods. The test expressed a weak positive autocorrelation for some of the analyses, but the models did not adjust for it.
Figure 10. a) Antipsychotic, b) benzodiazepine and related drug (BZDR) and c) antidepressant use among opioid initiators (grey bars) and non-initiators (white) in relation to opioid initiation or corresponding date (day 0).
Table 15. Parameter estimates with 95% confidence intervals (CIs) for antipsychotic, benzodiazepine and related drug (BZDR) and antidepressant use prevalence trends among persons with Alzheimer's disease initiating and not initiating opioid use.

<table>
<thead>
<tr>
<th>Parameter estimates</th>
<th>Pre-opioid initiation trend</th>
<th>95% CI</th>
<th>Change in level</th>
<th>95% CI</th>
<th>Post-opioid initiation trend accounting for the pre-opioid trend</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prevalences among opioid initiators</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antipsychotic use</td>
<td>0.66</td>
<td>0.57 to 0.75</td>
<td>2.15</td>
<td>1.70 to 2.60</td>
<td>-0.27</td>
<td>-0.48 to -0.07</td>
</tr>
<tr>
<td>BZDR use</td>
<td>0.10</td>
<td>-0.01 to 0.20</td>
<td>1.86</td>
<td>1.33 to 2.38</td>
<td>-0.42</td>
<td>-0.66 to -0.18</td>
</tr>
<tr>
<td>Antidepressant use</td>
<td>0.38</td>
<td>0.03 to 0.32</td>
<td>2.14</td>
<td>1.83 to 2.44</td>
<td>0.19</td>
<td>0.04 to 0.34</td>
</tr>
<tr>
<td><strong>Prevalences among opioid non-initiators</strong></td>
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</tr>
<tr>
<td>Antipsychotic use</td>
<td>0.62</td>
<td>0.50 to 0.74</td>
<td>0.30</td>
<td>-0.29 to 0.89</td>
<td>0.22</td>
<td>-0.49 to 0.05</td>
</tr>
<tr>
<td>BZDR use</td>
<td>0.03</td>
<td>-0.06 to 0.1</td>
<td>0.29</td>
<td>-0.12 to 0.71</td>
<td>-0.06</td>
<td>-0.25 to 0.13</td>
</tr>
<tr>
<td>Antidepressant use</td>
<td>0.29</td>
<td>0.22 to 0.36</td>
<td>0.34</td>
<td>0.01 to 0.69</td>
<td>-0.07</td>
<td>-0.24 to 0.10</td>
</tr>
<tr>
<td><strong>Differences in prevalences between opioid initiators and non-initiators</strong></td>
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<tr>
<td>Antipsychotic use</td>
<td>0.03</td>
<td>-0.15 to 0.22</td>
<td>1.85</td>
<td>0.94 to 2.76</td>
<td>-0.50</td>
<td>-0.91 to -0.09</td>
</tr>
<tr>
<td>BZDR use</td>
<td>0.07</td>
<td>-0.06 to 0.20</td>
<td>1.57</td>
<td>0.92 to 2.21</td>
<td>-0.36</td>
<td>-0.65 to -0.07</td>
</tr>
<tr>
<td>Antidepressant use</td>
<td>0.09</td>
<td>-0.00 to 0.19</td>
<td>1.79</td>
<td>1.30 to 2.28</td>
<td>0.26</td>
<td>0.02 to 0.50</td>
</tr>
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</table>
5.4 OPIOID USE AND THE ASSOCIATED RISK OF HOSPITAL-TREATED PNEUMONIA AMONG PERSONS WITH ALZHEIMER’S DISEASE (STUDY IV)

The pneumonia rate per 100 person-years was 11.03 (95% CI 10.89–11.16) among opioid users and 6.35 (95% CI 6.30–6.40) among non-users; a difference of 4.68 cases of pneumonia per 100 person-years (Figure 11). Opioid use was associated with an increased risk of pneumonia as compared to non-use in the Cox regression model (adjusted hazard ratio, aHR 1.34, 95% CI 1.14–1.57) (Figure 12). An increased risk was observed during the first two months of use (aHR 2.58, 95% CI 1.87–3.55), but it attenuated after 60 days.

When compared to mild opioids, buprenorphine was not associated with a higher risk of pneumonia (aHR 1.20, 95% 0.83–1.76), but strong opioids were linked with a higher risk (aHR 1.84, 95% CI 1.15–2.97). When compared to non-use, all opioid strength categories were associated with a higher risk of (Figure 12). Moreover, the risk was higher for those using ≥50 MME/day (aHR 2.03, 95% CI 1.24–3.31), as compared to those using <50 MME/day. Immunosuppressive opioids were associated with a lower pneumonia risk when compared to their non-immunosuppressive counterparts (aHR 0.58, 95% CI 0.36–0.93).

![Figure 11. Opioid use and the incidence rates of pneumonia per 100 person-years among persons with Alzheimer’s disease. MME = morphine milligram equivalents.](image-url)
Figure 12. Opioid use and the associated risk of hospital-treated pneumonia. MME = morphine milligram equivalents. The reference is non-user in all analyses.

Altogether 3,736 opioid users were included in case-crossover analyses. The odds of opioid use were significantly higher in the case windows than in the control windows regardless of the observed time periods (Table 16). Adjusting for the use of antipsychotics, BZDRs, immunosuppressants and oral corticosteroids somewhat decreased the ORs.
Table 16. Results of the case-crossover sensitivity analysis. The odds ratio of using an opioid in the case window compared to control windows.

<table>
<thead>
<tr>
<th></th>
<th>Case window: 1-14 days before pneumonia</th>
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<tbody>
<tr>
<td></td>
<td>Unadjusted odds ratio (95% CI)</td>
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<tr>
<td>Control window 1:</td>
<td></td>
</tr>
<tr>
<td>31–45 days before</td>
<td>2.91 (1.95–4.34)</td>
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<tr>
<td>pneumonia</td>
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<tr>
<td>Control window 2:</td>
<td></td>
</tr>
<tr>
<td>61-74 days before</td>
<td>2.74 (1.95–3.84)</td>
</tr>
<tr>
<td>pneumonia</td>
<td></td>
</tr>
</tbody>
</table>

CI = Confidence Interval. Adjusted for the use of antipsychotics, benzodiazepines and related drugs, immunosuppressants and oral corticosteroids.

5.5 SUMMARY OF RESULTS

To summarize, in studies with both persons with and without AD, those with AD used more analgesics and especially paracetamol, but less NSAIDs and opioids than their comparison persons in the first 6 months after the index date. Similarly to their comparison persons, a third of opioid users with AD were long-term users of opioids and a strong association was found between long-term use and transdermal opioids. In studies with only persons with AD, opioid initiation was associated with decreasing trends in antipsychotic and BZDR use, but not in the use of antidepressants. Finally, opioid use was associated with a 34% increased risk for hospital-treated pneumonia as compared to non-use and a dose-dependent risk increase was found.
6 DISCUSSION

6.1 PREVALENCE OF ANALGESIC USE AND ASSOCIATED FACTORS (STUDY I)

Approximately every third individual, either with or without AD was using analgesics. This value is comparable to previous Finnish studies among the general older population, although the inclusion of OTC drugs in interview-based studies increases the prevalence (Pitkälä et al., 2002; Pokela et al., 2010). These results highlight the high frequency of pain among older adults and that it is commonly treated with analgesics (Abdulla et al., 2013).

When examining the values of those persons with cognitive disorders, our findings are comparable to previous studies investigating overall analgesic use (Schmader et al., 1998; Mantyselkä et al., 2004; Haasum et al., 2011; Hoffmann et al., 2014), even though the different studies have had dissimilar lengths of observation. Previously, the lower frequency of analgesic use among persons with cognitive disorders has led to concerns of under-treatment of pain, but the results of the present study do not indicate there is a similar problem among community-dwellers with AD.

Concerning the types of analgesics, Haasum et al. (2011) found persons with cognitive disorders used more commonly paracetamol and were less likely to use NSAIDs, similarly to this study. Opioid use, in contrast, has been much more common in studies originating from Sweden, Denmark, and USA (Haasum et al., 2011; Jensen-Dahm et al., 2015; Shen et al., 2018). Among the general population, opioid use is similarly less frequent in Finland than in these countries (Hamunen et al., 2009; Bosetti et al., 2019), which may contribute to small absolute differences in opioid use prevalence between those with and without AD.

In the logistic regression analysis, AD was not associated with analgesic use but it was inversely associated with NSAID and opioid use. All of the studied comorbidities and older age were associated with any analgesic and opioid use, whereas only the presence of osteoporosis or rheumatoid arthritis was associated with NSAID use. These results may be an indication that prescribers are more cautious of NSAID use among older and possibly more vulnerable persons, as recommended in pain treatment guidelines (Ickowicz et al., 2009; Abdulla et al., 2013). This is supported by the finding that paracetamol use, which is considered safer, was more frequently being taken by persons with AD as compared to those without AD. In contrast, the inflammatory pain caused by rheumatoid arthritis may respond better to NSAIDs than paracetamol (Day and Graham, 2013). However, it is important to note that NSAID use is not recommended among older adults, especially for long-term treatment due to the risk of severe harm (Abdulla et al., 2013). Differences in opioid use between the two groups were less profound and mostly due to the consumption of weak opioids like codeine and also of tramadol. There
may be multiple reasons for less weak opioid use among persons with AD. Both codeine and tramadol frequently cause ADEs such as constipation, confusion, and dizziness (Grond and Sablotzki, 2004; Abdulla et al., 2013). Both drugs require CYP2D6 for their metabolic activation, a fact reflected in both drug-drug interactions and genetic variations in efficacy (Trescot et al., 2008). Moreover, due to tramadol’s unique pharmacology, its use with other serotonergic drugs, which is common among persons with AD (Laitinen et al., 2015; Puranen et al., 2017), may increase the risk for ADEs (Grond and Sablotzki, 2004).

Another important finding from this study is the temporal trends for analgesic, NSAID, and opioid use. Both the decrease in NSAID and increase in opioid use reflect national trends among older Finns (Kristensen et al., 2019; Social Insurance Institution, 2019). Similarly, opioid use has significantly increased since 2003 among Finnish nursing home residents, including those with cognitive disorders (Roitto et al., 2019). It should be noted, however, that the Prescription Register has limitations in this comparison. For example, some products containing paracetamol and combinations of paracetamol and codeine regained reimbursement status during 2009, strongly strengthening these trends. Regardless of these limitations, the trends persist. In addition to reimbursement changes, transdermal buprenorphine products became available in 2008, and their appearance may have increased opioid use among persons with AD, as swallowing difficulties are common in this population (Seçil et al., 2016). Moreover, it is possible that these trends are at least partly attributable to the increased attention being paid to both harms of NSAID use and the presence of pain among persons with AD.

As far as we are aware, this is the first study which has investigated the nationwide prevalence of analgesics among persons with a verified diagnosis of AD. Overall, the results of this study indicate that morbidities such as AD have an important role in the choice for analgesics used by older adults. While this study was not able to assess the appropriateness of the analgesic therapy, no gross undertreatment of persons with AD was found at least when they are compared to persons without AD. Moreover, the common use of paracetamol and decreasing use of NSAIDs over time indicate increased adherence to guidelines for pain among older adults (Ickowicz et al., 2009; Abdulla et al., 2013).

6.2 PREVALENCE OF LONG-TERM OPIOID USE AND ASSOCIATED FACTORS (STUDY II)

In study II, approximately one-third of opioid users with or without AD were long-term users of opioids. Chronic pain is common among older adults, and this likely to be the case also in persons with AD (Abdulla et al., 2013). Frequently, those older adults who report chronic pain have very persistent pain (Karttunen et al., 2015). This may be reflected in this study in the relatively high rates of long-term use of opioids. In their smaller cohort study, Gallini et al. (2013) also found that more than a third of opioid users with AD were using opioids for 6 months or longer. Population-based
studies investigating factors related to long-term opioid use have yielded conflicting results on the role of cognitive disorders (Mellbye et al., 2014; Kostev et al., 2015; Oh et al., 2019). This may be due to the low numbers of persons with cognitive disorders in these studies, or it may also reflect actual differences in prescribing patterns.

Nonetheless, results from meta-analyses do not support the long-term use of opioids (Chou et al., 2015; Els et al., 2017; Busse et al., 2018). This is due to insufficient evidence for benefits whereas there is strong evidence about frequent harms. The AGS guidelines state that opioid therapy may be prescribed for persistent pain as part of a multimodal strategy in properly selected and monitored patients (Ickowicz et al., 2009). As we did not have data on pain, its intensity or type, or on possible non-pharmacological treatment, the appropriateness of opioid therapy cannot be assessed here. However, as the rather high rates of long-term opioid use may constitute a worrisome signal, this phenomenon should be studied further.

Another important finding in this study was that among persons with AD, long-term opioid use was strongly correlated with the use of transdermal opioids, i.e. buprenorphine and fentanyl. Similar results have also been found among the general population (Gallagher et al., 2009; Lalic et al., 2018). Due to their pharmacokinetics, i.e. the slow emergence of the therapeutic effect, both fentanyl and buprenorphine are indicated for non-acute pain (Kress, 2009; Nelson and Schwaner, 2009). Transdermal administration may be advantageous due to the problems in swallowing oral medicines frequently experienced by persons with AD (Secil et al., 2016). Treatment schemes of transdermal opioids, i.e. a change every 3 days (fentanyl) or every 7 days (buprenorphine), provide additional benefits for those participating in patient care, for example in home care and in residential care units (Abdulla et al., 2013). In addition, neither drug requires dose reductions in cases of renal insufficiency. However, transdermal opioids have a longer half-life than their orally administered counterparts, which may be problematic if the patient experiences ADEs (Thompson et al., 1998). It should also be noted that the absorption of transdermal opioids may be impaired if the person is cachectic and the therapeutic effect can be difficult to predict (Heiskanen et al., 2009). Moreover, according to published research, cognitive impairment is a risk factor for initiating transdermal fentanyl in opioid-naive patients (Dosa et al., 2009; Fain et al., 2017). This practice is not recommended due to the risk for acute respiratory failure (United States Food and Drug Administration, 2007).

The somewhat more common long-term opioid use among persons with AD compared to non-AD population in this study may indicate problems in pain assessment and monitoring of the effects of the opioids. In contrast to persons with AD, all of the studied comorbidities were associated with long-term opioid use among those subjects without AD. Thus, AD itself may be the most important risk factor for long-term use in these persons. In addition, transdermal opioids may be a risk factor for persistent use among persons with AD and patients should be assessed regularly for ADEs and efficacy, similarly to the recommendation for the other opioids. Furthermore, strong associations with long-term use of BZDRs and opioids

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may be a cause for concern, as this combination may additively increase sedation and the subsequent associated ADEs (American Geriatrics Society, 2019). These results further underline the importance of regular pain and medication assessment among persons with AD.

6.3 IMPACT OF OPIOID INITIATION ON PSYCHOTROPIC DRUG USE (STUDY III AND ADDITIONAL ANALYSES)

Overall, psychotropic drug use was very common in this study population, especially among those individuals who initiated opioid use. Opioid initiation was associated with a decreasing trend in antipsychotic and BZDR drug use, although the change was rather small. The largest differences are seen in comparison to the pre-opioid trend: opioid initiation seems to blunt this ascending trend, especially for antipsychotics. To the best of our knowledge, there are no previous observational studies on how analgesic initiation affects psychotropic drug use among persons with cognitive disorders. Similarly, previously decreasing trends of psychotropic drugs have been observed after antidementia drug initiation (Vidal et al., 2008; Lachaine et al., 2013; Martinez et al., 2013). The report of Chibnall et al. (2003) seems to be unique in having investigated the effect of an analgesic, paracetamol, on as-required psychotropic drugs (Table 5). In contrast to the results found in this study, these investigators did not find an effect for the intervention as compared to placebo. However, these are two very dissimilar studies, and their results may not be truly comparable.

When BPSDs have been investigated as an outcome, in general, analgesics have produced positive effects in previous interventional studies, but not all interventions have been beneficial for all outcomes (Manfredi et al., 2003; Buffum et al., 2004; Chibnall et al., 2005; Husebo et al., 2011; Erdal et al., 2018). Similarly, the association between pain and BPSDs is strongest for depression, agitation, and aggression, whereas the evidence is lacking for other symptoms (van Dalen-Kok et al., 2015). Adequate pain management is emphasised in multiple guidelines of BPSD treatment, along with treatment of the other underlying causes (Doody et al., 2001; APA Work Group on Alzheimer’s Disease and other Dementias, 2007; Finnish Medical Society Duodecim, 2017a; National Institute for Health and Care Excellence, 2018). Our findings provide further support for the importance of pain assessment and treatment among persons with AD, especially those with BPSDs. Observational pain assessment tools need to be applied when assessing pain among patients with moderate-to-severe cognitive disorders (Corbett et al., 2012).

We found that opioid initiation was associated with an increasing trend of antidepressant use. These results may indicate that opioid initiation does not result in a decrease in depressive symptoms among persons with cognitive disorders, as exemplified by Erdal et al. (2018). Moreover, neuropathic pain may be treated with some antidepressants, which could partly explain the increase in these drugs after opioid initiation (Finnish Medical Society Duodecim, 2017b). Unfortunately, due to
relatively small numbers of opioid initiators, the effect on individual drugs could not
be analysed. Similarly, it was not possible to analyse the effects of specific opioids.

It is important to bear in mind the limitations of this study. Owing to its
observational nature, simultaneous events could underlie the observed effect of
opioid initiation. The decrease in antipsychotic and BZDR use could reflect the
concern over using these drugs in combination with opioids, as concomitant use is
not recommended (American Geriatrics Society, 2019). This seems unlikely,
however, as use of all psychotropic drugs was significantly more frequent among
opioid initiators than in non-initiators. The greatest increases in psychotropic drug
use are seen in the month of opioid initiation, at odds with this interpretation. This
increase in the level is concerning, as concomitant use should be critically evaluated.
Some of the decrease in antipsychotic and BZDR use after opioid initiation could be
explained by regression to the mean, i.e. prevalences of use returning toward the
average after an initial jump. This is partly controlled for by our application of the
interrupted time series method, where measures are taken at multiple times during
multiple months. Phenomena such as cohort-based drug use may also not be very
susceptible to regression toward the mean in this case, as psychotropic drug use
frequently only increases as AD progresses (Orsel et al., 2018). Moreover, one would
expect this phenomenon to be evident for all psychotropic drugs, but no such
decrease was apparent in the prevalence of antidepressant use. Nonetheless, the
results of this study need to be confirmed in future studies.

6.4 OPIOID USE AND RISK OF HOSPITAL-TREATED
PNEUMONIA (STUDY IV)

In study IV, opioid users were at an increased risk for hospital-treated pneumonia
when compared to non-users. This is similar to previous studies on the association
among older adults (Dublin et al., 2011; Vozoris et al., 2016). Persons with cognitive
disorders are at a high risk of pneumonia (van der Maarel-Wierink et al., 2011), which
may be further increased due to their opioid use.

Despite the findings of this study, the mechanisms underlying possible opioid-
induced pneumonia are not clear. However, disruption of airway clearance through
cough reflex suppression and CNS and respiratory system depression have been
frequently suspected (Yamanaka and Sadikot, 2013). Similarly, other CNS
depressants, such as antipsychotics, antiepileptics, and BZDRs have been associated
with an increased risk for pneumonia among persons with AD (Tolppanen et al.
2016a; Koponen, et al., 2016; Taipale et al., 2017a; Tolppanen, et al., 2017; Taipale et al.,
2019). However, cause-specific analyses were not carried out, as the aetiology of
pneumonia was not recorded in most cases. One interesting topic for further study
would be to examine whether the association would be stronger for certain types of
pneumonia, e.g. aspiration pneumonia.

In this study, the risk of pneumonia was highest in the first two months of opioid
use but also increased during the first two to six months. Dublin et al. (2011) also
reported a higher risk for pneumonia in the first two weeks of opioid use. It should be noted that the numbers of longer-term users may have not been sufficient to reveal the associations. Another explanation may be that those who continued opioid use for longer periods developed tolerance to the sedative or respiratory system impairment associated with opioids.

The findings of this study indicate that there was a dose-response relationship i.e. the risk of pneumonia was higher among those using doses of 50 MME or more. Similarly, a higher risk for pneumonia associated with higher opioid doses has been found previously (Dublin et al., 2011; Edelman et al., 2019) as well as for other serious infections (Wiese et al., 2016, 2018). In this study, strong opioid use was associated with a higher risk compared to weak opioid use, which similarly points to a dose-related response in the risk of pneumonia.

As far as we are aware, this is the first study to show an increased risk of pneumonia among transdermal buprenorphine users. Although studies I and II demonstrated that the use of this form of buprenorphine was rather common in this aged population, its safety has not been fully evaluated among persons with cognitive disorders (Erdal et al., 2019). In RCT settings, especially neurological and psychiatric ADEs were previously found to be common among transdermal buprenorphine users with a cognitive disorder (Erdal et al., 2018). The safety issues of buprenorphine and other opioids warrant therefore further assessment.

This study did not replicate results from previous research, where opioids with immunosuppressive properties have been associated with an increased risk of pneumonia as compared to non-immunosuppressive opioids (Dublin et al., 2011; Wiese et al., 2016, 2018; Edelman et al., 2019). There may be multiple reasons for this discrepancy. First of all, the populations in these studies were considerably different. Only two of the previous studies were conducted among older adults (Dublin et al., 2011; Vozoris et al., 2016). Ageing affects several elements of the immune system (Simon et al., 2015), which may be further impaired by AD. Therefore, opioids may affect the immune system of persons with AD differently and opioid-induced immunosuppression could have a smaller role in those individuals. Secondly, all previous studies were conducted in North America. Hence, the opioids used in these previous studies were different drug substances and opioid doses were higher. Moreover, the utilised data sources are not as inclusive as the Finnish nationwide registers, which reduces the generalisability of previous results (Wettermark et al., 2013). Illicit drug use is common among prescription opioid users in the US, which may obscure the effects of the investigated prescription opioid exposures (Dowell et al., 2016). Finally, the validity of an immunosuppressive/non-immunosuppressive opioid dichotomisation is unclear and may require more research.

The overall findings of this study emphasise the recommendations of pain treatment for older adults (Ickowicz et al., 2009; Abdulla et al., 2013). According to clinical guidelines, the initiation of opioid treatment for non-malignant pain needs to be weighed against possible adverse events, including the risk of pneumonia. However, opioids remain an important component of multimodal strategies to treat
moderate-to-severe pain. Nonetheless, initial doses should be kept low and doses of the opioids should be up-titrated slowly. Concomitant use of other CNS depressants, such as BZDRs and antipsychotics, should be avoided.

Similarly, other interventions for pneumonia prevention may be of importance if opioid therapy is indicated among persons with AD. These include improved oral hygiene, improving mobility and nutritional status, smoking cessation, and provision of influenza and pneumococcal vaccinations (Torres et al., 2013; Faverio et al., 2014; Komiya et al., 2015). Specifically, to avoid aspiration pneumonia, an upright position while eating and additionally, practicing coughing and swallowing exercises could be potential preventive measures (Ebihara and Ebihara, 2011; Mandell and Niederman, 2019).

6.5 METHODOLOGICAL CONSIDERATIONS

6.5.1 Data sources

A major strength of this study was its access to many high quality registers. All of these registers are nationwide and have been previously utilised in pharmacoepidemiological research, as have their Nordic counterparts (Furu et al., 2010; Wettermark et al., 2013). The MEDALZ cohort includes data from several registers spanning years to decades (Tolppanen et al., 2016b). Due to their nationwide, inclusive nature, these registers offer complete follow-up for all persons in the cohort and there is no bias due to socioeconomic exclusivity. Thus, the results are generalisable to all community-dwelling persons with AD.

Persons with AD were identified from the Special Reimbursement Register, where 97% of recipients have been estimated to have AD (Solomon et al., 2014). To the best of our knowledge, a similar nationwide cohort of clinically verified AD cases does not exist anywhere else in the world. The diagnosis is based on explicit, predefined criteria based on international standards (McKhann et al., 1984; American Psychiatric Association, 1994). However, as compared to the CAIDE study cohort, the sensitivity of the Special Reimbursement Register was lower, 64% (Solomon et al., 2014). This could be due to persons with early AD, who did not yet fulfil the SII criteria in the CAIDE study. This was partly controlled for by only including comparison persons who did not receive a diagnosis for AD or any purchase of antidementia drugs in the subsequent 12 months after matching (Taipale et al., 2014b). Moreover, mixed cases with pathologies from other types of cognitive disorders present were included in the MEDALZ cohort, if AD was considered as the main contributor to their symptoms.

An additional limitation to utilising the Special Reimbursement Register is that it does not define the severity of AD. It was therefore impossible to carry out sub-analyses at different stages of the disease. The time since AD diagnosis was utilised as a proxy measure for the severity of AD, which decreased some of the confounding related to disease severity. For diseases utilised as covariates in this thesis, the SII-required criteria may vary in relation to time and milder cases of common diseases,
such as hypertension, are not available from the register. Similarly to all health care-based data, undiagnosed health states cannot, by definition, be recorded.

The Prescription Register was utilised for estimating drug use in this thesis. Nordic prescription databases have been utilised for pharmacoepidemiological research for decades (Wettermark et al., 2013). A major strength is that register-based data are not prone to recall bias, which can be a problem in interview-based studies. This would be expected to be particularly problematic when examining persons with cognitive disorders. Moreover, drug dispensing data offer better estimates of actual drug use than prescriptions, that can be left undispensed (Pottegård et al., 2014). The method utilised for drug exposure estimation, PRE2DUP, has been previously validated using interview- (Taipale et al., 2016) and expert opinion-based measures (Tanskanen et al., 2017) as golden standards.

There are important limitations to utilising register-based estimates of drug use. Importantly, as-needed and infrequent drug use is more difficult to estimate (Taipale et al., 2016). For example, it is likely that these drug use patterns are more frequent for analgesics than for many drugs used to treat chronic diseases. Similarly, the Prescription Register in Finland only includes reimbursed drugs, therefore it has no data about OTC drugs and some analgesic products (Table 8). This is reflected in low agreement between register- and interview-based measures of use for NSAIDs and paracetamol (Cohen’s kappa 0.37, 95% CI 0.23–0.50 and 0.25, 95% CI 0.12–0.38, respectively). For opioids, the interview did not include enough users to allow us to conduct a similar comparison (N = 16). Moreover, until 2006, a fixed deductible of 10 euros was in place in Finland, and purchases below this sum were not recorded in the register. The prevalence of analgesic use was thus likely underestimated in study I as well as for estimates prior to 2010, in study II. Restrictions in follow-up reduced the effect of non-reimbursed codeine products in studies III and IV, and some, less commonly used opioids remained unmeasured. This would lead to a reduced observed effect of opioid initiation. A further effort was made to minimize the unmeasured use of drugs in hospitals by censoring persons with long-term care periods.

The Hospital Discharge Register is also widely utilised in research and has been validated for the identification of several diseases (Sund, 2012). It should be noted, that the validity of the diagnosis of hospital-treated pneumonia is currently unknown. Further validation studies would, therefore, be important. By definition, the register only captures hospital-treated pneumonia and our analysis is thus limited to the more severe cases, as are the diagnoses of the covariates.

6.5.2 Study designs

In study I, measures of analgesic use were taken during six months after AD diagnosis or at a matching date and persons were considered users if their use periods were within this timeframe. In comparison to cross-sectional studies, a period prevalence measure from multiple years is not limited by confounding such as seasonal or annual variation in drug use. Similarly, the concomitant use of two or
more analgesics was defined as at least 30 days of overlapping drug use periods. Due to difficulties in determining the end of drug use from register-based data, some of the concomitant use may be switching from one analgesic to another.

In study II, six-month continuous use defined long-term opioid use. Six months was used as a definition due to the reimbursement system, where a six-month use period would require at least two drug purchases. Concomitant use of 2 or more opioids was defined as at least 90 days of continuous overlap between any opioid use periods. A longer overlap compared to study I was utilised because of the long-term nature of the use pattern of interest. As only opioid initiations which began after the index date were considered in this study, it is possible that some persons began a long-term opioid use period prior to this time but were not identified as long-term users due to this restriction. Moreover, as a consequence of higher institutionalisation and mortality among persons with AD, they had shorter follow-up times and thus, fewer possibilities to use opioids in the long term.

In study III, the study design chosen was an interrupted time series analysis. This method strengthens the before-after design by measuring the outcome repeatedly over the follow-up period (Penfold and Zhang, 2013). Moreover, it accounts for pre-existing trends and, in this case, compares the trends to a non-interventional cohort. It is most commonly utilised for investigating the effects of policy changes but can be used to study clinical outcomes and medication use (Wagner et al., 2002; Matowe et al., 2003; Vidal et al., 2008; Penfold and Zhang, 2013). In this study, a washout period of six months was utilised to analyse the effects of opioid initiation, which may not be demonstrable among prevalent users. A longer washout would be likely to further reduce the number of prevalent users but this would be at the expense of losing power in the analysis. Moreover, all analyses in study III were based on intention to treat, as ITT analysis avoids introducing bias resulting from excluding those who discontinue (Gupta, 2011). Whether prolonged opioid therapy would result in a different effect compared to this analysis could not be studied here.

The new-user design was utilised in study IV, applying a washout period of 12 months (Ray, 2003). Although the method reduces the prevalent user bias, a long washout reduces the power in statistical analysis of the results, which may be why it has not been applied in all previous studies investigating opioids and the risk of pneumonia (Dublin et al., 2011; Vozoris et al., 2016; Wiese et al., 2016, 2018; Edelman et al., 2019). Moreover, an additional ITT analysis studied the impact of informative censoring, resulting in a similar risk estimate as the as-treated analysis (Figure 12).

Importantly, observational studies are always susceptible to measured and unmeasured confounding (Etminan and Samii, 2004). Measured confounding can be controlled by a statistical adjustment in multivariable models, which were applied in all of the studies of this thesis. Unmeasured confounding is more difficult to account for, and it is likely that some confounding, especially by indication, still exists i.e. due to pain (Signorello et al., 2002). Furthermore, nationwide health care registers do not include data on many health- or lifestyle-related factors, such as smoking, diet, or functional capacity. Data on pain, type of pain, or severity are not included in the
utilised data sources and analgesic indication can thus not be collected. In study III, the opioid indication is likely to increase the use of psychotropic drugs, which is particularly visible in the first month of opioid use. However, this would bias trends of psychotropic drug use in an upward direction, i.e. towards a null result. In study IV, confounding by pain and pain source would likely lead to an increased risk of pneumonia. Although statistical adjustment of pain-related factors may decrease this bias, it cannot be accounted for fully.

Due to the risks of unmeasured confounding, a case-only design was applied in study IV, which removes the effect of time-invariant, interpersonal confounding (Maclure et al., 2012). In this analysis, the odds of using an opioid was more than 2.5-fold in the time window closer to the outcome after adjusting for other drug use, indicating a significant risk increase for pneumonia when an opioid is being used. Case-crossover studies are prone to bias due to time trends in drug use (Maclure et al., 2012), but it is unlikely that this is a problem with such short intervals between the case and control periods utilised in this study. Furthermore, the case-crossover design does not fully eliminate confounding by indication, but the results of this sensitivity analysis provide more evidence to assess the link between opioid use and pneumonia.
7 CONCLUSIONS

Pain assessment and management should be an important part of the good care of persons with cognitive disorders. Because of the similar prevalences of analgesic use and of long-term opioid use, this study did not find that persons with AD were receiving less frequent analgesic treatment of pain than those without AD. The more frequent use of paracetamol and the less frequent use of NSAIDs are in line with pain treatment guidelines for older adults. These positive findings may be due to the increased attention being paid nowadays to easing pain among persons with cognitive disorders and an awareness of the harms associated with NSAID use among all older adults. Pain assessment and management may be especially important among persons with BPSDs, as pain may be a contributing factor to these symptoms. Pain management may also decrease the use of potentially harmful psychotropic drugs.

However, the frequent long-term use of opioids may be a worrisome signal. Long-term opioid therapy should be regularly assessed in all patients i.e. with or without AD, regardless of the route of opioid administration. Opioid therapy among older adults carries risks which need to be managed, if opioid therapy is nonetheless required. The results of this study underline the importance of the treatment guidelines for pain among older adults: non-pharmacological treatment should be prioritised. If opioid therapy is initiated, low initial doses and careful up-titration should be implemented. Moreover, risk-minimisation strategies to reduce the development of pneumonia may be considered.
8 IMPLICATIONS

8.1 CLINICAL IMPLICATIONS

1. Pain is a common problem experienced by persons with AD. Clinicians and health care systems need to be able to manage pain among the increasing numbers of persons with cognitive disorders. As pain assessment is more difficult among persons with a cognitive impairment, observational pain assessment tools should be used routinely if the patient’s verbal expression capabilities are diminished.

2. Pain management is especially important to consider in those persons experiencing BPSDs. Analgesics should be used alongside non-pharmacological methods of pain treatment, but their adverse effects need to be monitored.

3. Thus far, there are no guidelines for the assessment and treatment of pain among persons with cognitive disorders in Finland. Clinical care guidelines of pain should incorporate updated sections on pain management among older adults, with a special focus on cognitive impairment and frailty.

8.2 RESEARCH IMPLICATIONS

1. Efficacy and safety of opioid use among persons with cognitive disorders need to be studied in both trials and with observational designs.

2. The effects of analgesics and non-pharmacological pain treatment on BPSDs should be clarified. The effects of pain treatment on psychotropic drug use should be studied also with observational data.

3. The effects of opioids on respiratory function and outcomes should be investigated among persons with cognitive disorders. Preventive measures to avoid pneumonia should be examined among opioid users.
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Zis, P. et al. (2017) ‘Depression and chronic pain in the elderly: links and
Pain is a common symptom among persons with Alzheimer’s disease that is frequently treated with analgesics. This thesis examined the prevalence of analgesic use and long-term opioid use in a nationwide sample of persons with Alzheimer’s disease and compared them to matched persons without the disease. The impact of opioid initiation on psychotropic drug use and the association between incident opioid use and hospital-treated pneumonia were also investigated.