

Medication Use and Prognosis of Alzheimer's Disease and Lewy Body Dementia

Hospitalization and Mortality

Ragnhild Djønne Østerhus

Thesis for the degree of Philosophiae Doctor (PhD)
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Abbreviations

AD	Alzheimer's disease
ATC	Anatomical Therapeutic Chemical Classification
CDR-GS	Clinical dementia rating scale – global score
CIRS	Cumulative illness rating scale
CSHR	Cause-specific hazard ratio
DDI	Drug-drug interactions
DLB	Dementia with Lewy bodies
DRP	Drug related problems
DSM	Diagnostic and Statistical Manual for Mental Disorders
HR	Hazard ratio
IRR	Incidence rate ratio
LBD	Lewy body dementia
MMSE	Mini mental status examination
NorGeP	The Norwegian General Practice criteria
NPI	Neuropsychiatric inventory
OR	Odds ratio
PCNE	Pharmaceutical Care Network Europe
PDD	Parkinson's disease with dementia
PIM	Potentially inappropriate medication
REM	Rapid eye movement
SDHR	Sub-distributional hazard ratio

Contents

Abbreviations.....	3
Acknowledgements.....	6
Scientific environment	8
Abstract	9
List of publications	10
1. Introduction	11
1.1 <i>Dementia</i>	12
1.2 <i>Alzheimer’s Disease</i>	13
1.3 <i>Lewy body dementia</i>	15
1.4 <i>Pharmacological treatment in dementia</i>	19
1.5 <i>Prognosis of dementia</i>	22
1.6 <i>Appropriate drug treatment in dementia</i>	25
1.7 <i>Literature search</i>	29
2. Aim and objectives	30
2.1 <i>General aim</i>	30
2.2 <i>Objectives</i>	30
3. Material and methods.....	31
3.1 <i>Subjects and samples</i>	31
3.2 <i>Dementia diagnosis</i>	34
3.3 <i>Ethical considerations</i>	34
3.4 <i>Overview of the samples in the three papers</i>	34
3.5 <i>Clinical assessments</i>	35
3.6 <i>Statistical analyses</i>	38
4. Results	41
4.1 <i>Paper I</i>	41

4.2	<i>Paper II</i>	42
4.3	<i>Paper III</i>	44
5.	Discussion	47
5.1	<i>Introduction</i>	47
5.2	<i>Discussion of method</i>	47
5.3	<i>Discussion of results</i>	56
6.	Conclusions and clinical implications	67
7.	Future research	68
8.	References	70
9.	Paper I-III	81

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Scientific environment

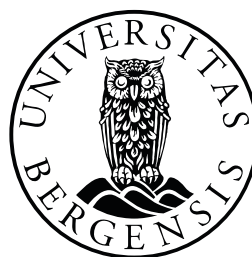
This thesis was conducted at the Centre for Age-Related Medicine, SESAM, Stavanger University Hospital from October 2012 to June 2020 with supervision from Svein Reidar Kjosavik, Dag Aarsland, and Corinna Vossius at SESAM and Arvid Rongve in Helse Fonna, Haugesund. Dag Aarsland was my main supervisor on paper I, while Svein Reidar Kjosavik has been the main supervisor from paper II and further. I have been affiliated with the Department of Clinical Medicine at the University of Bergen and have been a member of the Norwegian PhD School of Pharmacy.

The work has been conducted part-time and was combined with a 50% position as a hospital pharmacist at the Stavanger hospital pharmacy, with two years of maternity leave during this period.

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Abstract

Background: There is no curative treatment available for the cause of dementia, and few drugs are approved for symptomatic treatment. In addition, knowledge about prognosis related to hospitalization and mortality is scarce in patients with dementia. This is especially true for patients with dementia with Lewy bodies and Parkinson's disease dementia. They have many of the same clinical and pathological features and are often referred to as Lewy body dementia. **Aim:** To increase knowledge about pharmacological treatment and prognosis related to hospitalization and mortality in patients with mild Alzheimer's disease and Lewy body dementia. **Methods:** Analysis of data from the DemVest study, a longitudinal cohort study in Western Norway. From March 2005 until April 2007 all consecutive referrals to secondary care outpatient clinics in geriatric medicine and old-age psychiatry with mild dementia were asked to participate. From April 2007 to 2013, only patients with Lewy body dementia were included. The consensus criteria for dementia with Alzheimer's disease, dementia with Lewy bodies and Parkinson's disease dementia were used to set the final clinical dementia diagnosis. The baseline assessment included the recording of present drug treatment, demographic and clinical data assessment of comorbidity and cognition, and a battery of other neuropsychological tests.

Results: Patients with LBD were found to have a significantly shorter time until first hospitalization, more days in the hospital and a shorter survival time after diagnosis compared to AD. Apart from the use of antidementia drugs, 45% of the patients used at least one psychotropic drug; polypharmacy was also identified in 45% of the patients. Few potentially inappropriate medications (n=48) and severe drug-drug interactions (n=4) were identified. **Conclusion and clinical implications:** Having Lewy body dementia was associated with a higher risk of hospitalization and mortality. Polypharmacy and psychotropic drug use were common in mild dementia, but were not found to be associated with hospitalization or mortality. Early diagnosis of dementia may provide opportunities for more streamlined care and appropriate drug use which in turn can potentially improve the prognosis of patients with dementia.

List of publications

Paper I [1]:

Oesterhus, R., et al. (2017). "Potentially inappropriate medications and drug-drug interactions in home-dwelling people with mild dementia." *International Journal of Geriatric Psychiatry* 32(2): 183-192.

Paper II [2]:

Oesterhus, R., et al. (2020). "Risk of Hospitalization in Patients with Alzheimer's Disease and Lewy Body Dementia: Time to and Length of Stay." *J Alzheimers Dis* 74(4): 1221-1230. The publication is available at IOS Press through <http://dx.doi.org/10.3233/JAD-191141>

Paper III [3]:

Oesterhus, R., et al. (2014). "Long-term mortality in a cohort of home-dwelling elderly with mild Alzheimer's disease and Lewy body dementia." *Dementia and Geriatric Cognitive Disorders* 38(3-4): 161-169.

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1. Introduction

In 2012, when this project was initiated, polypharmacy and the potentially negative effects of medication on older people were receiving a lot of attention. A year before, the Norwegian directory of health initiated the patient safety campaign “I trygge hender 24/7”. In this campaign, there were several actions to ensure safer drug treatment. Around the same time, the Norwegian directory of health published national guidance on how to perform a medicine review [4]. Additionally, screening tools to detect inappropriate medications had been published, both nationally and internationally [5, 6]. The importance of appropriate drug therapy was also a focus area in the Dementia Plan 2020 [7], which was published a few years after the project was initiated. The use of psychotropic drugs and problems related to discontinuation were highlighted as challenging areas [7]. However, there were little knowledge about medication use and prognoses related to hospitalization and mortality in home-dwelling people recently diagnosed with dementia. The majority of the published studies included patients from nursing homes, who had more severe dementia. Increased knowledge about the course of the dementia may lead to better utilization of resources in the health care system and enable clinicians to better inform patients and caregivers. Further, receiving a dementia diagnosis may reduce stress in patients and caregivers as a dementia diagnosis leads to professional help which provides knowledge about the disease and treatment options. An early diagnosis may empower people to make decisions related to care and treatment, before the disease has progressed too far [8].

This thesis focuses on aspects related to pharmacological treatment and prognosis in people with Alzheimer’s disease (AD) and Lewy body dementia (LBD), measured by inappropriate drug use, hospitalization and mortality.

1.1 Dementia

Dementia is one of the greatest health care challenges of the 21st century [9]. In 2018, 50 million people were estimated to be living with dementia - a number that is expected to triple by 2050 [10]. Currently, no published epidemiologic studies evaluate the number of people with dementia in Norway. The estimate is believed to be somewhere between 80.000 to 104.000 people [11]. However, a large ongoing prevalence survey is expected to be published in the summer of 2020.

The International Statistical Classifications of Diseases and Related Health Problems (ICD-10), published by the World Health Organization, defines dementia *as a syndrome due to disease of the brain, usually of a chronic or progressive nature* [12]. For a dementia diagnosis, impairment must be present in at least two cognitive domains. Memory is most often impaired, and other frequently affected domains include visuospatial, language, and executive functions. In addition, the impairment must represent a decline from the prior level of function and affect everyday activity. Evaluation of possible dementia requires a medical history and a cognitive and neurologic examination [13].

There is no curative treatment for dementia, and the reason why some people, but not others, develop dementia is unknown, though increasing evidence suggests that many potentially modifiable lifestyle-related factors such as obesity, diabetes, and smoking, increase the risk of dementia. Reducing these risk factors might prevent or delay the development of dementia in some cases [8]. Dementia negatively impacts the persons affected and their families; as the disease progresses, more health and social care is needed, which will have consequences for the health care system [8].

Dementia is a heterogeneous condition and may be caused by different medical and neurological diseases [14]. AD is the most common cause of dementia, followed by vascular dementia and dementia with Lewy bodies (DLB). Mixed dementia is also common and is diagnosed when the boundaries between different forms of dementia are more unclear [8]. DLB together with Parkinson's disease dementia (PDD) are

often referred to as LBD, as both forms of dementia are characterized by Lewy body pathology [15] and share many of the same clinical and pathological features [16].

The focus of this thesis is on AD and LBD. Other forms of dementia will not be further addressed. The terms DLB and PDD will be applied when discussing these diseases specifically, otherwise LBD will be applied, which includes patients with DLB and PDD.

1.2 Alzheimer's Disease

1.2.1 Epidemiology

AD is the most common form of dementia, accounting for 50-75% of all dementia cases [17]. In Europe, the prevalence of AD for those above 65 years is estimated to be 5.1%, with a higher prevalence reported for women than men (7.1% vs 3.3%) [18]. The prevalence increases with age; 1% of individuals between 65-74 years are estimated to have AD, with an increase of up to 22% for those above 85 years [18].

1.2.2 Pathology

The first description of AD was made in 1907 by Aloisius Alzheimer [19], who described the symptoms of a 51-year-old woman. After her death Alzheimer examined the brain and discovered the amyloid plaques and neurofibrillary tangles. These are now the two core pathological hallmarks of AD [20]. Amyloid- β peptides are accumulated into extracellular plaques, while the formation of intraneuronal neurofibrillary tangles is due to hyperphosphorylation and aggregation of the tau protein [20]. These changes develop gradually and lead to synaptic loss and brain atrophy in the affected brain regions [21]. The hippocampus plays an important role in the consolidation of new memories and spatial orientation and is, together with adjacent regions, typically the first region of the brain to be affected by neurofibrillary tangles [21].

1.2.3 Clinical features

AD is characteristic by insidious onset and gradual decline of cognition. Deficits in memory and executive function are the most typical presenting symptoms of AD [9].

A more atypical presentation is a non-amnesic presentation where problems related to language, visual, practical or executive problems are more prominent than the memory impairment [9]. Atypical presentation, with relatively preserved memory at disease debut, is present in approximately 6–14% of all AD cases [22].

Non-cognitive symptoms such as neuropsychiatric symptoms are frequent in patients with AD [23], even at the mild stage [24]. Neuropsychiatric symptoms include for example delusions, hallucinations, agitation/aggression, dysphoria, anxiety, euphoria, apathy, disinhibition, irritability/lability, aberrant motor activity, appetite disorder, sleep disorder [25]. In AD, apathy is the most common neuropsychiatric symptom, followed closely by depression, aggression and anxiety [23].

1.2.4 Diagnostic criteria

The National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) proposed the first diagnostic criteria for AD in 1984 [26] and revised them in 2011 [27]. The 1984 criteria have been applied in several pathological studies, and the sensitivity and specificity have been found to be 81% and 70%, respectively, when one is distinguishing between AD and no dementia [28]. However, the criteria have been found to be less accurate when one is distinguishing between different types of dementia (23-88%) [20]. In 1984, pathological changes could not be measured in vivo. Therefore, a definite diagnosis of AD was possible only after death, and the 1984 criteria focused only on clinical symptoms [26]. The 2011 criteria include clinical symptoms, but combine them with biomarkers of AD pathology ($A\beta_{42}$, total tau and phosphorylated tau), which are found in the cerebrospinal fluid [27]. These biomarkers have made it possible to diagnose AD pathology in vivo. In addition, the new criteria have enabled the diagnosis of AD prior to onset of dementia [27].

1.3 Lewy body dementia

1.3.1 Epidemiology

Dementia with Lewy bodies

There are no robust epidemiological studies of DLB, but the disease is considered the second most common neurodegenerative dementia disorder [29]. In the community, DLB has been estimated to account for 4.2% of all dementia cases, and to account for 7.5% of all dementia cases known to secondary care [29]. However, the reported proportion of DLB among patients with dementia has a wide range (0-23%). Studies including more specific instruments and biomarkers to identify DLB, including dopamine transporter imaging and screening for rapid eye movement (REM) sleep behavior disorder, have reported more narrow estimates (10-24%) [15, 29].

Parkinson's disease with dementia

Among all dementia cases, the proportion of PDD is estimated to be 3-4% [30]. In addition, mild cognitive impairment is common in Parkinson's disease, and often progress to dementia [31]. The prevalence of PDD in patients with Parkinson's disease is believed to be around 25%, and the risk of developing PDD increases with age [15].

1.3.2 Pathology

LBD is characterized by Lewy bodies which are spherical aggregates of protein that accumulate in the neurons of the brain. The protein alpha-synuclein is the major constituent of Lewy bodies [15]. Lewy bodies are found in the substantia nigra and the brainstem ganglia, as well as in the limbic structures and neocortex. Additionally, pathological features of AD may be present in patients with PDD and DLB [15].

1.3.3 Clinical features

As in AD, the onset is insidious and there is a gradual development of symptoms [32, 33]. LBD may be challenging to diagnose in the early stage due to difficulties in differentiating between DLB and AD, and to detect in a timely manner when patients with Parkinson's disease develop cognitive impairment [15].

Dementia with Lewy bodies

Early symptoms of DLB may be deficits related to attention, executive function, and visual processing. Memory impairment, which is one of the primary symptoms of AD, is not always present in the early stage of DLB [32]. Core clinical features of DLB are fluctuating cognition, visual hallucinations, Parkinsonism, and REM-sleep behavior disorder [16].

Cognitive fluctuations can also be present in other forms of dementia, but are more frequent in patients with DLB [16] and have been reported to be present in almost 50% of patients with DLB at the time of diagnosis [34, 35]. Fluctuations in DLB can manifest in many different ways and occur spontaneously [16]. The fluctuations can last anywhere from a few minutes to several days. In between these fluctuating episodes, the patient often function normally [36]. Hallucinations are more common in patients with DLB, as compared to patients with AD [24]. The hallucinations are often well formed and often feature children or animals [15]. REM-sleep behavior disorder occurs in around 20% of patients with DLB [37] and is characterized by dream-enactment due to loss of normal muscle atonia during REM-sleep. The dreams are often realistic and scary and the reenactment may cause harm to the patient or sleep partner [38].

Supportive clinical features are severe neuroleptic sensitivity [16] which can occur in some patients with DLB treated with antipsychotics [39]. This features is characterized by sudden onset of sedation, increased confusion, rigidity, and immobility, potentially causing death within a few days or weeks [40].

Antipsychotics act on dopamine D2 receptors and the density of these receptors has been found to be significantly reduced with increasing Lewy body pathology and is suggested to explain the neuroleptic sensitivity [41]. Other supportive clinical features include severe autonomic dysfunction, e.g. orthostatic hypotension, postural instability, repeated falls, syncope, apathy, anxiety, systematized delusions, excessive daytime sleepiness and depression [16].

Parkinson's disease with dementia

Parkinson's disease is characterized by motor symptoms such as resting tremor, bradykinesia, rigidity and postural instability [42]. The presence of dementia in addition to well-established Parkinson's disease are the two core features of PDD. Associated clinical features in PDD are deficits in cognitive features related to attention, visuospatial functions, executive functions, and memory. The core function of language is largely preserved, but problems with word finding and reduced understanding of complex sentences may be present [33]. Behavioral features include apathy, hallucinations, delusions, personality changes and excessive daytime sleepiness [33].

Impairment of attention is an early and prominent symptom with fluctuations similar to DLB [43] and is associated with impairment in everyday activities [44]. Neuropsychiatric symptoms are frequent [45] and apathy, impairment of attention and visuospatial function is often more prominent in patients with PDD compared to AD patients. Visual hallucinations are often well-formed figures, similar to those experienced by patients with DLB [46].

1.3.4 Diagnostic criteria

Dementia with Lewy bodies

DLB is the most recently defined form of non-AD dementia. DLB is not part of the ICD-10 [12] but is included in the ICD-11 criteria, which have been published, but not yet implemented [47]. In addition, DLB was not included in the Diagnostic and Statistical Manual for Mental Disorders (DSM) before the fifth version, which was published in 2013 [48].

The first diagnostic criteria for DLB were published in 1996 [36], and have since been updated, in 2005 [39] and in 2017 [16]. The first diagnostic criteria were found to have acceptable specificity, but low sensitivity. Therefore, to increase sensitivity, REM-sleep behavior disorder was added as a supportive feature to the 2005 criteria and further included as a core clinical feature in the 2017 criteria. Further,

hypersomnia, typically presented as daytime sleepiness, and hyposmia, partial loss of sense of smell were added as supportive features to the 2017 criteria [16].

Severe neuroleptic sensitivity was listed as a suggestive feature in the 2005 criteria and then changed to a supportive feature in the 2017 criteria. There was a black-box warning issued by the US Food and Drug Administration in 2008 about the use of all antipsychotics to elderly people [49]. This has reduced the prescribing of antipsychotics to patients with DLB; therefore, its diagnostic usefulness is limited [16]. A definite diagnosis of DLB is not possible as there are no direct measure of alpha-synuclein pathology [32]. In the 2017 criteria, the suggestive features were replaced with indicative and supportive biomarkers. Presence of indicative biomarkers have shown to increase diagnostic specificity in DLB, while supportive symptoms and biomarkers carry less diagnostic weight, but may be important when making clinical decisions [16].

A clinical diagnosis of DLB is diagnosed as either probably or possible, depending on which clinical features are present. In the latest version, probable DLB is diagnosed if the patient has two or more core clinical features or has one core clinical feature and one or more indicative biomarkers. Possible DLB is diagnosed if one core clinical feature is present, but there are no indicative biomarkers. Possible DLB can also be diagnosed if at least one indicative biomarker is present, even though no core clinical features are present [16].

Parkinson's disease with dementia

The International Parkinson and Movement Disorder Society has provided clinical diagnostic criteria for probable and possible PDD [33]. According to these criteria, the core feature of Parkinson's disease and dementia must be present in both probable and possible PDD [33]. Probable PDD is diagnosed if the patient has at least two of the associated clinical features. Having at least one behavioral feature such as apathy or hallucinations, supports the diagnosis, although absence does not exclude probable PDD [33]. Possible PDD is diagnosed when the core symptoms are present and the attention is preserved, but the cognitive impairment is more atypical. For example

having aphasia or if retrieval of memory is not improved when a cue or word related to the information is given. Possible PDD is also diagnosed if the patient has features that make the diagnosis uncertain, e.g., comorbidity that may explain the cognitive impairment, or if the time interval from motor and cognitive symptoms is not known. Behavioral symptoms may be present, but not always [33].

In clinical practice and research studies, DLB and PDD are differentiated from each other in terms of in which order dementia and Parkinsonism occur. A PDD diagnosis should be given if the patient has well-established Parkinson's disease, while a DLB diagnosis should be given if dementia occurs before, simultaneously with or less than one year since the Parkinson's disease diagnosis [16, 33]. As the condition progresses, both conditions and underlying pathological changes become similar and can be more viewed as one condition rather than two different diseases [15].

1.4 Pharmacological treatment in dementia

Currently, no medical cure or disease-modifying treatment are available to treat dementia. Clinical guidelines mainly recommend non-pharmacological treatment such as activities matched to interest or music therapy [8] as first line treatment, and pharmacological treatment should never be used instead of, but rather in combination with non-pharmacological interventions [50, 51]. Pharmacological treatment aims to curb the symptoms of disease progression by maintaining memory and functional abilities, reduce neuropsychiatric symptoms and postpone entry into institutional care settings [50].

1.4.1 Management of cognitive symptoms

The degeneration of selected brain nuclei associated with dementia reduces the production of different neurotransmitters such as acetylcholine, which has been shown to have an impact on attention, memory and learning [52]. Today, four drugs are available, all of which are licensed to have symptomatic effect on cognitive symptoms in dementia. Three of the approved drugs, donepezil, rivastigmine, and galantamine, are cholinesterase inhibitors, which inhibit acetylcholinesterase and

prevent the degradation of acetylcholine. This increases the abundance of freely available acetylcholine in the synaptic cleft for cholinergic neurotransmission resulting in improved cognitive function and activity of daily living [52].

Cholinesterase inhibitors are approved as a pharmacological treatment for patients with mild to moderate forms of AD. Clinical guidelines recommend starting treatment when a diagnosis of mild AD is made [51]. Common side effects are nausea, diarrhea, vomiting, anorexia, and abdominal pain [53]. To reduce the risk of side effects it is recommended that the dosing regimen be started with slow titration over the course of four to eight weeks. If side effects are experienced, the dosage may be lowered, or one could shift to another cholinesterase inhibitor. Although there are some pharmacodynamic differences between the different cholinesterase inhibitors, the efficacy of these drugs appears similar [54].

Rivastigmine is also licensed for patients with PDD, but not for those with DLB. However, degeneration of cholinergic neurons also appears in DLB [55] and cholinesterase inhibitors are recommended as a first-line treatment in patients with PDD and DLB [51, 56]. Meta-analyses report that cholinesterase inhibitors benefit patients with PDD and DLB by improving cognitive function and the activity of daily living [57, 58]. However, high frequencies of side effects, such as nausea, vomiting, anorexia, and tremor, were reported, with a higher frequency in rivastigmine [57].

Glutamate is an excitatory neurotransmitter in the brain that can cause neuronal damage and death by over activating N-methyl D aspartate (NMDA) receptors.

Memantine is an uncompetitive antagonist on the NMDA receptor [59] and is the fourth drug approved for treatment in patients with moderate to severe AD.

Memantine has been found to benefit patients with moderate to severe AD by improving cognition and reducing neuropsychiatric symptoms. Memantine is well tolerated and has few side effects in patients with AD. The main side effect reported is dizziness [60]. Further, combining a cholinesterase inhibitor with memantine is recommended in several countries, particularly as dementia progresses [61]. In patients with LBD, the use of memantine is reported to be safe, though evidence

concerning its benefit is less conclusive [57, 58]. Therefore, there are still uncertainties to whether treatment with memantine could benefit patients with LBD [62].

1.4.2 Management of neuropsychiatric symptoms

The majority of patients with dementia will, at some point during the disease, experience neuropsychiatric symptoms [63], and are common even in the mild stage of dementia [24]. Neuropsychiatric symptoms are assumed to have multifactorial causes. Pain, dehydration and infections are some of the most common causes of neuropsychiatric symptoms [63]. These symptoms are often distressing for the patient, and challenging for the caregiver and may cause the patient to be transferred to institutional care. If neuropsychiatric symptoms are present, a thorough assessment and management of underlying causes and non-pharmacological measures should be performed before initiating any pharmacological treatment [63].

Risperidone is approved for the treatment of aggression in patients with AD in most European countries [64], but there is no other licensed pharmacological treatment for neuropsychiatric symptoms. Nevertheless, psychotropic drugs are frequently prescribed off-label to improve or relieve neuropsychiatric symptoms in dementia [65]. Pharmacological treatment may be necessary if patients still have severe neuropsychiatric symptoms, even after trying non-pharmacological interventions [62].

Donepezil or rivastigmine is recommended to treat severe neuropsychiatric symptoms in patients with LBD [62]. If psychotic symptoms are still present after treatment with cholinesterase inhibitors, the use of antipsychotics may be considered [62]. Antipsychotics have been used to treat hallucinations, but high incidences of severe reactions, such as stroke, pneumonia and reduced survival, were experienced [66]. This especially applies to patients with LBD [67], and there is no evidence to support the use of antipsychotics in these patients [62]. In relation to this, neuroleptic sensitivity was listed as a suggestive feature in the 2005 DLB criteria [39] as described in section 1.3.3 and 1.3.4. In AD, treatment with antipsychotics has been reported to have moderate benefits, but also to cause serious adverse events including

Parkinsonism, sedation, pneumonia, and an increased risk of stroke and death [68, 69].

Before initiating treatment with antipsychotics, it is recommended to cooperate with the patient, their relatives and caregivers to determine if potential benefits outweigh the risk of using antipsychotics [8]. A low dose of quetiapine is considered to be the safest choice for patients with LBD, although evidence concerning the effect is limited [62], while national guidelines recommend a very low dose of clozapine [51]. Clozapine is used to treat psychosis in patients with Parkinson's disease and may potentially be beneficial in LBD. However, no trials have been performed [62]. In patients with AD, risperidone is recommended as first-line pharmacological treatment for severe psychotic symptoms such as hallucinations and delusions [70]. This is in line with the Norwegian national guideline [51].

Depression is common in patients with AD and LBD and has a negative impact on cognition and caregiver stress [8]. Few randomized controlled studies have included patients with dementia and there is not enough evidence to support the use of antidepressants in patients with dementia. Therefore, it is suggested that use be limited to patients with severe and disabling symptoms of depression [71]. If pharmacological treatment is necessary, a selective serotonin-reuptake inhibitor (SSRI) is the preferred choice of drug in both forms of dementia. Further, tricyclic antidepressants should be avoided due to anticholinergic side effects [50, 56].

1.5 Prognosis of dementia

With the expected increase in the number of people with dementia [72], more knowledge about prognosis among various forms of dementia was needed. Increased knowledge about prognosis may empower patients with dementia and their families to make arrangements and timely decisions about treatment, accommodation, and care. Additionally, it may lead to more optimal advice from clinicians [73].

Prognosis is a broad term and consists of several aspects, e.g., quality of life, the activity of daily living, and nursing home placement. Previous studies have

investigated the formal care [74], rate of deterioration of cognition [75], time until nursing home admission [76] and caregiver distress [77], and have shown that DLB patients have poorer prognosis compared to patients with AD. These findings have been confirmed by some studies [78-80], but not by others [81]. However, there are also wide variations within the disease groups, and hence, providing information about prognosis to individual patients may be difficult because of a large variation between patients and the diversity of factors affecting prognosis [82].

This thesis focuses on prognosis related to hospitalization and mortality after a dementia diagnosis. These outcomes will be further addressed in this section.

1.5.1 Hospitalization in dementia

The hospitalization rate in a population is known to increase with age [83]. Patients with dementia are reported to have a higher hospitalization rate compared to people without dementia, regardless of age [84]. Further, evidence from English health records showed that around 50% of all patients with dementia were admitted to a hospital the first year after diagnosis [84].

An episode of hospitalization may be stressful for patients with dementia [85], and they may receive inadequate treatment due to their impaired ability to communicate [13]. Further, an underlying medical condition can exacerbate confusion. This can be challenging to detect in LBD due to fluctuating symptoms related to the disease [82]. In addition, combinations of multimorbidity [86] and severe neuropsychiatric symptoms [87] may challenge the medical treatment and care of patients with dementia. Hospitalization may also increase the risk of discharge to a higher level of care than was required before the hospitalization [88, 89]. Hence, preventing hospitalization should be one of the management goals for patients with dementia.

In 2019, one of the first systematic reviews assessing the hospitalization rate and predictors of hospitalization was published [84]. The review included 34 studies including 277,432 patients with dementia. The majority of the studies included patients with AD or focused on all-cause dementia. Only one study with 194 patients with DLB was included in the review [90].

In relation to the complex clinical features of LBD described in section 1.3.3, one might anticipate that patients with LBD will have a higher admission rate and a longer length of stay. However, comparisons of hospitalizations between patients with AD and LBD are scarce. The majority of them had small sample sizes, short follow-up times and have methodological differences [78, 81, 91]. The largest hospital study included 194 DLB patients. The study that patients with DLB had significantly higher admission rates compared to AD patients and the catchment population. In addition, patients with DLB had almost four more hospital days per person-year compared to AD patients [90].

Pharmacological treatment may affect the risk of hospitalization. A Swedish study reported that patients with dementia, using PIM, had an almost 90% (OR 1.88, 95% CI 1.03-3.34) increased risk of being admitted to hospital within one year compared to those who did not use PIM. [92], while another study found that patients with dementia using four or more medications had increased risk of hospitalization [93]. The use of a cholinesterase inhibitor (HR 0.87, 95% CI 0.67-1.14) and antipsychotics (HR 1.32, 95% CI 0.77-2.27) have been found to reduce and increase the risk of admission, respectively. Although, none of these predictors were statistically significant [94].

More knowledge about hospital admissions in patients with different forms of dementia and what factors affect hospital admissions can hopefully benefit caregivers, patients and their relatives.

1.5.2 Survival and mortality in dementia

There is no medical cure and dementia is a chronic illness, leading to death as described in section 1.4. Therefore, a diagnosis of dementia imposes a great burden on the patient and their relatives and produces concern regarding the duration of time one has before death [73]. Patients with dementia have increased mortality [95]; survival time is decreased compared to the life expectancy of an average population of similar age and gender [96]. Knowledge of survival and predictors of mortality in

various forms of dementia may enable the health care system to better inform patients and relatives, to utilize resources, and plan for future care.

In 2012, a systematic review reported that the survival time in patients with different causes of dementia ranged between one year and almost nine years [96]. This systematic review reported data from more than 11,000 patients, among who 65% (n=6370) had AD, close to 2% (n=186) had DLB and none had PDD [96]. Another review, published a year later [97], reported the median survival time from diagnosis in patients with all-cause dementia or AD as ranging from 3.3 to 6.6 years, which is a smaller range than that reported by Brodaty et al. [96]. Both reviews reported high heterogeneity between the included papers due to a variation in follow-up time and differences related to inclusion criteria and choice of index date. Therefore, they were not able to perform a meta-analysis. Todd et al. did not specify whether and how many of the patients were diagnosed with LBD [97]. Hence, knowledge about survival in different forms of dementia was still scarce when this project was initiated. Age and the male gender were considered predictors of mortality in dementia, but knowledge about specific predictors of mortality in different forms of dementia was limited [97].

1.6 Appropriate drug treatment in dementia

Medications are a central part of care, and optimizing drug prescription has become an important public-health issue worldwide [98]. In Norway, appropriate medication use was a focus in the white Paper on Medicinal Products — Correct Use – Better Health, published in 2015 [99], and in the Dementia Plan 2020 [7]. To ensure appropriate medication in patients with dementia they call for a clearer division of roles and responsibility, adequate professional expertise, and better procedures.

Several terms can be used to describe drug treatment such as inappropriate, good or poor [98]. In this thesis, the term “appropriate drug therapy” has been chosen. To assess the level of appropriateness several aspects should be evaluated. According to Spinewine et al., one should assess the drug treatment based on *what the patient*

wants, scientific and technical rationalism and the general good (family and societal consequences) [98]. Another approach is to focus on drug-related problems (DRP). The Pharmaceutical Care Network Europe Association (PCNE) defines a DRP as *an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes* [100]. PCNE has developed a classification scheme for DRP to be used in research. The classification scheme divides DRP into three primary problems (see figure 1).

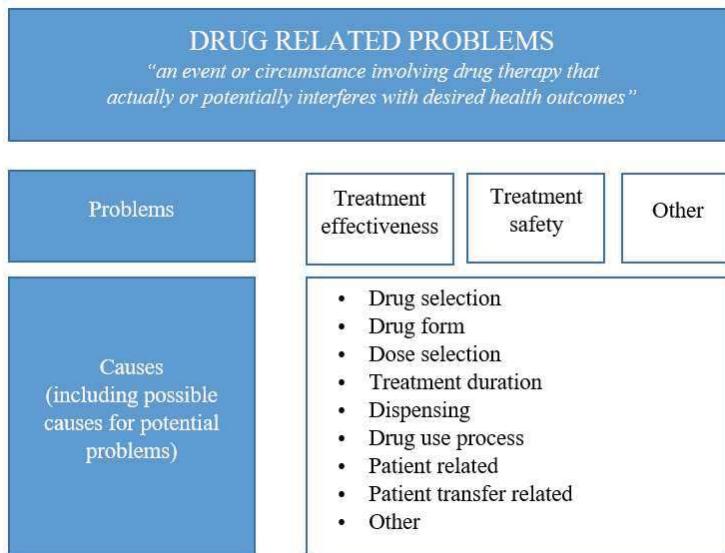


Figure 1: Schematic layout of the PCNE Classification for Drug-Related Problems V9.00. The basic classification [100].

1.6.1 Polypharmacy

Many chronic illnesses, such as dementia, are age-related and the risk of multimorbidity increases with age [86]. Medical treatment of chronic conditions is often managed using guidelines for single conditions. These guidelines aim to improve the clinical outcome, life expectancy, and quality of life. However, they may cause conflicting recommendations for people with more than one medical condition, and may lead to polypharmacy, the simultaneous use of several different drugs [86].

Several definitions of polypharmacy are found in the literature, but the concomitant use of five or more different drugs is often defined as polypharmacy [101].

Polypharmacy is frequent among people over 65 years [102], and among community-dwelling people, polypharmacy is found to be more frequent in people with dementia than without [103]. Polypharmacy may sometimes be appropriate, but each medication may complicate the medication regime and increase the risk of drug-drug interactions (DDI), hospitalization, and mortality [93, 104] leading to inappropriate polypharmacy.

1.6.2 Potentially inappropriate medications and drug interactions

During the last decade an increasing number of papers have focused on *potentially inappropriate medications* (PIM) (figure 2).

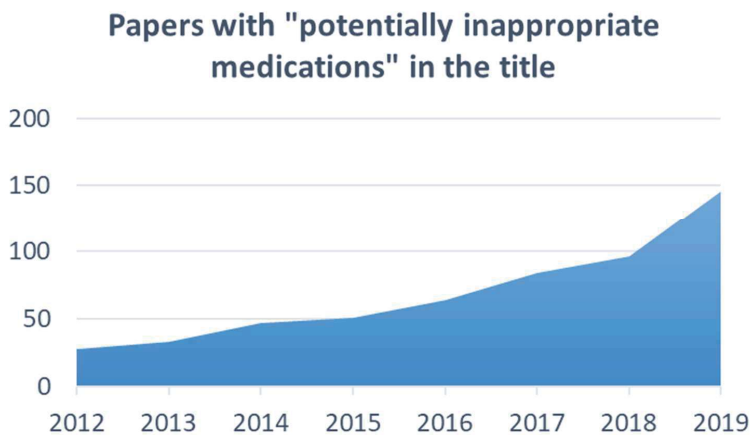


Figure 2: Number of published papers in PubMed with the term "potentially inappropriate medications" in the title.

PIM are drugs whose risks outweigh the benefits of their use or for which safer alternative exist [86] and they may lead to DRP [105]. Polypharmacy is one of the leading risk factors for using PIM [86]. Examples of PIM are benzodiazepines with long-half-lives and antipsychotics, which may be prescribed to treat various neuropsychiatric symptoms, such as hallucinations, aggression and sleep disturbances. Is using benzodiazepines, patients with dementia may experience

increased sedation, impaired cognition, or increased risk of falling [106]. Moreover, the use of antipsychotics is associated with an increased risk of mortality in patients with dementia [107]. In particular, patients with LBD are sensitive to these drugs, as described in sections 1.3.4 and 1.4.2.

Several screening tools have been developed to identify PIM in elderly people, and a recent review identified 36 different screening tools [108]. Screening tools can either be based on specific criteria (explicit) or be judgment-based (implicit). Explicit screening tools can be used without any or little clinical judgment and can be applied without seeing the patient [98]. The Beers Criteria from the US [109] and the STOPP/START criteria from Ireland [110] are among the most cited explicit screening tools. Some of the drugs listed as PIM in these screening tools are unavailable in other countries. Therefore, national screening tools may be more applicable [111]. In Norway, the explicit screening tool Norwegian General Practice (NorGeP) criteria was published in 2009 [6].

Some of the screening tools also contain explicit criteria regarding DDI and drug-disease interactions [108]. A DDI occurs when a drug affects another drug. The interaction leads to changes in the drug's pharmacodynamics or pharmacokinetic properties and may result in an altered therapeutic response. Both PIM and DDI have been associated with increased risk of hospitalization [92, 112]. Identifying PIM and DDI in patients with mild dementia may, therefore, be of vital importance. However the prevalence of PIM and DDI in patients with mild dementia living in the community was not well-described when this project was initiated.

1.6.3 Medication adherence

Medication adherence is an important therapeutic factor and is essential to determining medication effectiveness and safety [113]. Medication adherence is defined by the World Health Organization (WHO) as *the extent to which a person's behavior, corresponds with agreed recommendations from a health care provider* [114].

The definition embraces both over- and under-consumption of medications, the omission of a single-dose or deviation from prescribed time or dose intervals [115]. Multiple prescriptions of medications leading to polypharmacy increase the risk of non-adherence in older people [116]. Other factors that might negatively affect the medication adherence are complex drug regimens that include taking medications at different hours and with specific instructions [116] or problems with opening medicine containers [117]. Patients with dementia have an increased risk of non-adherence [118] probably due to memory loss or impaired executive functions [119]. Low medication adherence may increase the risk of adverse events such as hospitalization and readmission [113]. Therefore, interventions that reduce complexity, such as changing drug formulations from several times a day to extended release formulations or fixed-dose combinations, may have a positive impact on adherence [116].

1.7 Literature search

The comprehensive literature searches for this thesis ended on January 2020. Further, additional references were added when the text in was reviewed in June 2020.

2. Aim and objectives

2.1 General aim

The general aim of this thesis was to increase knowledge about pharmacological treatment and prognosis related to hospitalization and mortality in patients recently diagnosed with AD and LBD.

2.2 Objectives

- 1) To examine the prevalence of polypharmacy, psychotropic drugs, PIM, and DDI and to identify potential variables associated with having PIM and DDI in patients recently diagnosed with mild dementia.
- 2) To examine whether there are differences in hospitalization between patients with AD and LBD and to explore how demographic and disease related variables may explain these differences, as well as to compare hospitalization rates to those of an age-matched general population.
- 3) To examine survival and identify predictors of mortality in patients with AD and LBD and to compare mortality rates with an age- and sex-matched general population.

3. Material and methods

This thesis is based on data from the Dementia Study in Western Norway (DemVest), a longitudinal cohort study of people with mild dementia [120]. It consists of three papers. An overview of these papers is seen in table 1.

Table 1: Overview of the papers included in this thesis

Paper	Design	Inclusion period	Study period	Participants			Analyses
				Group	N	%	
I Theme: Drug treatment	Cross-sectional study	2005-2013	Baseline data	AD	137	55	Simple comparison, Logistic regression
				DLB	78	31	
				Others	36	14	
				Total	251		
II Theme: Hospital admission	Longitudinal study	2005-2013	Baseline and 5 years or date of death	AD	110	55	Simple comparison, Standardization, Negative binomial regression, Competing risk analyses
				DLB	73	36	
				PDD	18	9	
				Total	201		
III Theme: Mortality	Longitudinal study	2005-2007	Baseline until death or end of study (31.12.12)	AD	137	66	Simple comparison, Standardization, Kaplan Meier, Cox regression
				DLB	42	20	
				PDD	11	5	
				Others	19	9	
				Total	209		

AD Alzheimer's disease, DLB Dementia with Lewy bodies, PDD Parkinson's disease with dementia, Others Other forms of dementia

3.1 Subjects and samples

All referrals to outpatient clinics in old-age psychiatry and geriatric medicine were screened for patients with a first-time diagnosis of mild dementia. In addition, neurology clinics were asked to refer patients to the outpatient clinics. The inclusion criterion was a first-time diagnosis of mild dementia. Therefore, the patients had to have a minimum score of 20 on the Mini Mental State Examination (MMSE) [121]

and/or have a global score of ≤ 1 on the Clinical Dementia Rating scale (CDR-GS) [122]. As patients were in the early stage of their disease, the majority of them were living at home. Patients with normal cognition, mild cognitive impairment or moderate and severe dementia defined as MMSE < 20 or CDR-GS=2 were excluded. Additional exclusion criteria were acute delirium or terminal illness, a recent diagnosis of a major somatic illness, or a previous diagnosis of with psychotic or bipolar disorders.

The inclusion process was performed in two periods. The main inclusion period was from March 2005 to April 2007. In this period, 670 subjects were screened, of whom 209 (31%) patients fulfilled the inclusion criteria and 461 (69%) cases were excluded. The reasons for exclusion were moderate or severe dementia (n=166), unwillingness to participate (n=102), mild cognitive impairment (MCI, n=79), normal cognition (n=48), depression and pseudo-dementia (n=24), newly diagnosed somatic or terminal disorder (n=14), bipolar disorder or psychosis (n=11), another neurological disorder (n=7), and delirium (n=4); in six cases there were missing data. The second inclusion period lasted from April 2007 to 2013. In this period only patients with DLB and PDD (n=57) were included in the study. In total, 266 patients completed the baseline assessment. Further, details on the recruitment process and diagnostic procedures are provided in Aarsland et al. [120]. The inclusion process in relation to each paper is illustrated in figure 3.

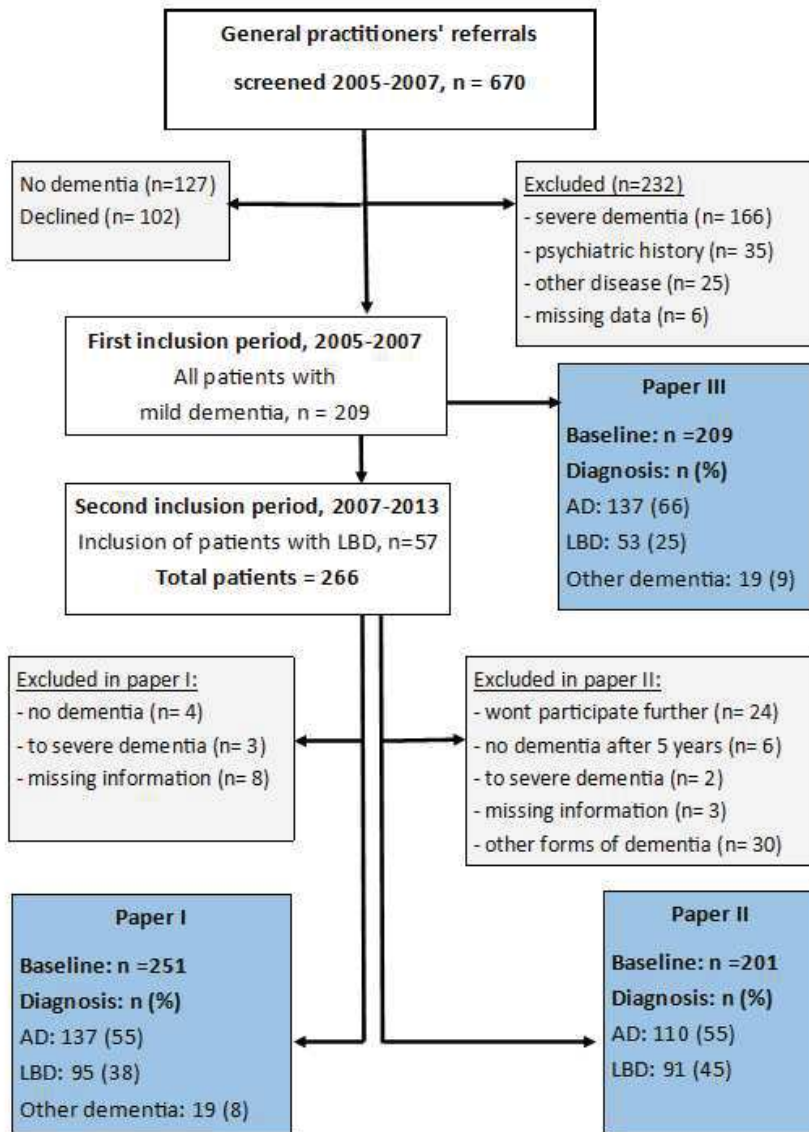


Figure 3: Flowchart of the inclusion process in relation to the papers in this thesis.

3.2 Dementia diagnosis

Dementia was diagnosed according to the Diagnostic and Statistical Manual for Mental Disorders, 4th edition (DSM-IV). The clinical diagnosis of AD, DLB, or PDD was made according to their respective guidelines and consensus criteria [26, 33, 39]. DLB and PDD share many clinical and pathological features [15] and were combined and referred to collectively as LBD in paper II and paper III. In paper I, PDD were grouped with other forms of dementia. In cases of disagreement, the final diagnosis was made as a consensus between specialists in geriatric medicine and geriatric psychiatry. The dementia diagnoses were re-evaluated during the clinical follow-up, which resulted in minor changes between the papers.

3.3 Ethical considerations

The DemVest study was approved by the Regional Committee for Medical and Health Research Ethics in Western Norway (REK ID 2010/633). Detailed information about the study was provided to the patient and caregiver. After the information was provided, written consent was obtained from the participants before their inclusion in the study.

3.4 Overview of the samples in the three papers

The study samples vary between the papers, and may also vary from other papers based on DemVest data. A reason for this is that DemVest is a longitudinal and ongoing study. Therefore, the database is continuously updated with new information, resulting in new versions of the database. Another reason is that some papers are based on final consensus diagnoses from 2017. In this version, 56 patients have pathological diagnoses. The pathological diagnoses showed consistency with the clinical diagnosis in over 80% of the cases, for patients with AD and LBD [123].

3.4.1 Sample of paper I

Paper I included patients from both inclusion periods. Of the 266 patients included, 15 patients were excluded for different reasons (missing information about diagnosis (n=8), mild cognitive impairment (n=4), or moderate dementia (n=3)). Therefore, the study sample consisted of 251 patients, of whom 137 (55%) had AD, 78 (31%) had DLB and 36 (14%) had other forms of dementia.

3.4.2 Sample of paper II

In paper II, all patients with a diagnosis of AD, DLB or PDD were included. Of 266 patients in DemVest, 24 patients did not want to participate, three patients lacked information about baseline MMSE or dementia diagnosis, six patients had mild cognitive impairment and two patients had too-severe dementia at baseline (MMSE<20). In addition, patients with other forms of dementia were excluded (n=30). This resulted in 201 patients included.

3.4.3 Sample of paper III

In the third paper, only patients from the first inclusion period were included, as this cohort was believed to better reflect the general population as compared to the entire cohort. The study sample consisted of 209 patients of whom 137 (66%) had AD and 53 (25%) had LBD (DLB=42 and PDD=11), while 19 (9%) patients had other forms of dementia.

3.5 Clinical assessments

A thorough clinical assessment was conducted at baseline and afterward, annually until death or drop-out. A detailed and comprehensive battery of assessment instruments was applied and the use of standardized and validated instruments was emphasized. The main instruments used in the different papers will be described below.

3.5.1 Cognitive function

The MMSE [121] assesses cognitive functions and was used as a screening test. It focuses on memory, attention, orientation, concentration and constructing ability. The first part requires only vocal response, while the second part contains verbal and written commands and figure copying. The questionnaire is administered directly to the patient.

To stage the severity of dementia, the CDR [122] was applied. The CDR rates the impairment in six cognitive categories, in which memory is weighted the highest. The severity of dementia is presented as a CDR-GS rating of either no dementia (zero), questionable dementia (0.5), mild dementia (1), moderate dementia (2), or severe dementia (3). The total global score was calculated by an online algorithm [124].

3.5.2 Neuropsychiatric symptoms

Neuropsychiatric symptoms were evaluated using the Neuropsychiatric Inventory (NPI) [125]. The inventory assesses twelve neuropsychiatric symptoms frequently occurring in patients with dementia. The assessment scale focuses on symptoms that have been present for the past month. If the symptom is present, the frequency (0-4) and intensity (0-3) of the behavior are determined. Frequency and intensity are multiplied to provide an item score for each symptom (0-12). Thereafter, a sum score is calculated by summing the item scores (0-144). The questionnaire was proxy rated by a next of kin and symptoms were considered to be present if the frequency x intensity score was greater than zero.

3.5.3 Depression

In paper III, the Montgomery and Aasberg depression rating scale (MADRS) was applied to assess depression [126]. The scale consists of ten questions, rated from zero to six. The score from each question is summed up to provide a total score (0-60). The total score is found to be a valid measure of the severity of depression, even in patients with mild dementia [127].

3.5.4 Physical comorbidity

The cumulative illness rating scale (CIRS) [128] was applied to estimate the patient's total illness burden at baseline. CIRS assesses the degree of impairment in 13 different areas grouped after body systems and provides knowledge about the medical burden and its severity. The assessment was performed retrospectively on baseline data and medical records close to the baseline date. Most of the CIRS assessments were performed by a specialist in geriatric medicine. Later, another geriatrician assessed the remaining missing CIRS score (n=16).

3.5.5 Psychotropic drugs and polypharmacy

Medications were registered and classified according to the Anatomical Therapeutic Chemical classification system (ATC) [129]. Opioids (N02A), antipsychotics (N05A), anxiolytics (N05B), hypnotics and sedatives (N05C), antidepressants (N06A), and antidementia drugs (N06D) were classified as psychotropic drugs. Most anxiolytics (N05B) and hypnotics (N05C) are benzodiazepines. Non-benzodiazepine sleeping pills (N05CF) also act via benzodiazepine receptors and were therefore classified together with N05BA and N05CD as benzodiazepines. Polypharmacy and psychotropic polypharmacy were defined as the concomitant use of five or more drugs [101] and the use of three or more centrally active drugs [6], respectively. The analysis was performed without knowledge of whether the medication was scheduled or taken pro re nata. Data on adherence to a prescribed medication and use of over-the-counter drugs and dietary supplements was also lacking.

3.5.6 Classification of potentially inappropriate medications and drug-drug interactions

The NorGeP criteria were applied to assess the use of PIM. The NorGeP criteria consist of a list of pharmacologically inappropriate prescriptions for people over the age of 70 years; the list consists of 36 criteria, with 21 being single drugs and 15 being drug-drug combinations [6].

DDI were identified using a prescription and expedition support database (FEST) maintained by the Norwegian Medicines Agency [130]. The applied interaction

database uses a three-point scale to classify DDI: 1) “Drug interaction only of academic interest”, 2) “Clinicians need to take precautions”, and 3) “Drugs should not be combined”.

3.6 Statistical analyses

Statistical analyses were performed using IBM SPSS Statistics versions 20, 23 and 24. In paper III some analyses were performed in R version 3.4.

3.6.1 Descriptive statistics

Baseline and demographic variables were presented as counts and percentages of categorical variables, means and standard deviations (SD) for normal distributed continuous variables and medians and interquartile ranges (IQR) for non-normal continuous variables.

3.6.2 Simple comparison

Comparison between groups was performed using Pearson Chi-square tests or Fisher’s exact test if over 20% of the cells had expected count less than 5, independent samples t-test, or Mann-Whitney U tests as appropriate. The distribution of the data was checked using Kolmogorov-Smirnov statistics and simple scatter plots to determine whether parametric or non-parametric methods were most applicable. $P < 0.05$ was considered statistically significant.

3.6.3 Standardization

In papers II and III, the observed number of admissions and deaths were standardized and compared to a reference population. Paper II standardized in relation to age, while paper III standardized in relation to both age and gender. In paper II, a standardized admission ratio (SAR) for the first year after inclusion was estimated and defined as:

$$SAR = \frac{\text{The observed number of admissions in the study population}}{\text{The expected number of admissions in the study population}}$$

SAR was estimated for both planned and unplanned admissions in the age groups 60-74 years and 75 years or older.

In paper III, a standardized mortality ratio (SMR) was estimated and defined as:

$$SMR = \frac{\text{The observed number of deaths in the study population}}{\text{The expected number of deaths in the study population}}$$

In paper II, data about all admissions in the same catchment area in the age group 60 years or older, combined with population statistics from Statistics Norway [131], were used to determine the expected number of admissions in the study population. In paper III, the Norwegian population was applied as the reference population. The death rate for this population was given by Statistics Norway as deaths per 100,000 population, stratified by gender and age for each year between 2005 and 2011 [132]. Rates for 2012 were not available at the time of analysis. Therefore, the 2011 death rates were extrapolated to 2012. Age groups were adjusted each year as the study participants aged throughout the course of the study.

The interpretation of SAR and SMR is the same. A ratio of 1 indicates no difference between patients with dementia and the reference population, while a value higher than one (>1) or less than one (<1) than one indicates that patients in the study population have more or fewer admissions or deaths than the reference population.

3.6.4 Regression models and survival analysis

Logistic regression was applied to assess whether baseline characteristics were associated with having PIM or DDI. Having PIM and having DDI were defined as dependent variables and were dichotomous into either present or absent. First, a univariate model was constructed. Potential confounders were baseline characteristics. Second, a multivariable model was constructed including all potential explanatory variables from the univariate analyses with $p < 0.25$.

Differences in rate and length of hospitalizations between AD and LBD were assessed using negative binomial models, yielding incidence rate ratios (IRR). Similarly, differences in time to first hospitalization were analyzed with the Fine-

Gray competing risk regression model yielding sub-distributional hazard ratios (SDHR). All models were adjusted for factors that could have an impact on hospitalization, such as age, gender, the severity of neuropsychiatric symptoms and depression. The factors were added stepwise. Social factors and comorbidities were included first, followed by dementia-related variables such as the severity of neuropsychiatric symptoms and depression. Lastly, medication variables were adjusted for. To better reflect the cumulative incidences of hospitalizations seen in the community, time under observation was not accounted for in paper II. Additional analyses in which death was treated as a censoring event were published as supplementary results. Treating death as a censoring event yields cause-specific hazard ratios (CSHR) instead of SDHR.

Differences in survival from time of diagnosis were assessed using Kaplan–Meier curves with log rank tests. Cox regression models were applied to explore predictors associated with survival time. Baseline characteristics were included as predictors. As in the logistic regression analysis, univariable models were estimated before a multivariable model including all significant variables from the univariable models. The final Cox regression model was found to be acceptable with regard to multicollinearity and the assumptions of proportional hazards.

4. Results

4.1 Paper I

Nearly all patients (96%) used one or more medications at the time of dementia diagnosis and the median number of medications were four (IQR 2, 6). One or more psychotropic drugs were used by almost 70% of the patients. Excluding antidementia drugs, 45% of the patients were using one or more psychotropic drugs. See table 2 for an overview of the psychotropic drugs used at baseline.

*Table 2: Psychotropic drug use at baseline.
Modified from paper I with DLB and PDD grouped together as LBD.*

	Drug group	Whole sample		AD		LBD		Other dementia		P-value
		N	%	N	%	N	%	N	%	
ATC	Psychotropic drugs*	113	45.0	56	40.9	47	49.5	10	52.6	0.34
N06D	Antidementia	105	41.8	69	50.4	34	35.8	2	10.5	0.001
N06A	Antidepressives	81	32.3	44	32.1	28	29.5	8	42.1	0.56
N05A	Antipsychotics	19	7.6	4	2.9	13	13.7	2	10.5	0.009
N02A	Opioids	9	3.6	4	2.9	5	5.3	0		0.44
N05BA	Benzodiazepines	40	15.9	19	13.9	16	16.8	5	26.3	0.37
N05CD										
N05CF										
	In total	251		137		95		19		

AD Alzheimer's disease, LBD Lewy body dementia. Statistics presented as n (%) and compared using Kruskal-Wallis test. *Antidementia is not included

Polypharmacy was identified in 45% of the patients, while psychotropic polypharmacy was identified in seven patients. PIM were identified in 35 patients (14%). The top three PIM were long-acting benzodiazepines (n=8, 3.2%), combinations with non-steroidal anti-inflammatory drugs (n=7, 2.8%), and psychotropic polypharmacy (n=7, 2.8%). Four cases of severe DDI ("should not be combined") were identified, while the majority of DDI were in the group "take precautions" (n=149). Here, combinations with beta-blocking agents and cholinesterase inhibitors were most frequent (n=23, 9.2%). Use of acetylsalicylic acid

in combination with selective serotonin reuptake inhibitors (n=18, 7.2%) and the use of bisphosphonates in combination with calcium or drugs combined with calcium (n=11, 4.4%) were the second and third most frequent DDI, respectively. There were no significant differences in the number of PIM or DDI between the dementia diagnoses.

Factors significantly associated with having PIM were number of prescribed medications (odds ratio, OR=1.5, 95% CI 1.3-1.8, $p < 0.001$) and being female (OR=2.7, 95% CI 1.1-6.5, $p = 0.021$). While only number of prescribed medications (OR=2.0, 95% CI 1.7-2.5, $p < 0.001$) was associated with having DDI.

4.2 Paper II

Over 77% of the patients were hospitalized during the five-year study period, and the majority were unplanned admissions. Compared to the age-matched general population, both AD and LBD had a higher risk of admission (SAR for AD: unplanned 1.30, planned 1.35; for LBD: unplanned 1.83, planned 2.01). When stratified based on age, patients with LBD in the age group 60-74 years had close to four times as many admissions as the general age-matched population.

Patients with LBD had a significantly shorter time until first hospitalization (median 1.28 years, 95% CI 0.93-1.67) compared to AD (2.32 years, 95% CI 1.74-3.31). Patients with LBD were found to have an increased risk of hospitalization in the unadjusted competing risk model (unadjusted SDHR 1.72, 95% CI 1.25-2.35, $p < 0.001$). After adjusting for demographic variables and somatic comorbidities (SDHR 1.42, 1.01-2.00, $p = 0.046$), and, afterward dementia-related variables (SDHR 1.37, 0.96, -1.95, $p = 0.09$), the difference in risk was reduced. Adjusting for medication-related variables did not substantially affect the SDHR. When death was treated as a censoring event, patients with LBD had an 86% higher hazard of being hospitalized compared to those with AD in the unadjusted analysis (CSHR 1.86, 95% CI 1.35, 2.56, $p < 0.001$). In the fully adjusted model, LBD patients had a 42% higher

hazard, though the difference was no longer significant (CSHR 1.42, 95% CI 0.99, 2.03, $p=0.054$).

Compared to AD, patients with LBD had more unplanned admissions (median 2, IQR 1-3 vs AD: 1, 0-2, $p=0.004$) and more unplanned hospital days (median 7 days, IQR 2-26 vs AD: 2 days, 0-11, $p=0.001$) for the period of five years after the dementia diagnosis. In the unadjusted negative binomial model, LBD patients had 84% more hospital days than AD patients (IRR 1.84, 95% CI 1.22-2.77, $p=0.004$) after five years. After adjustment for demographic variables and somatic comorbidities, the difference in hospital days between LBD and AD was reduced to 63% (IRR 1.63, 1.02- 2.61, $p=0.040$). Further adjustments with dementia-related variables reduced the difference even further, and the difference was no longer statistically significant (IRR 1.53, 0.92, 2.52, $p=0.099$). When differing observation time were allowed for (due to death), the unadjusted IRR for all rates of admission and days in the hospital increased. In the fully adjusted model, patients with LBD had a 42% increased risk of any hospitalization (IRR 1.42, 1.02, 1.98, $p=0.037$).

4.2.1 Additional results

Hospitalization rate per person-year

In paper II, results were presented as rate per one year or rate per five years. Death was not taken into account. However, in the systematic review from Shepherd et al. [84] results were presented per person-year. For purposes of data comparison, additional results are presented in table 3.

Table 3: Mean number of admissions per person-year

Person years	Alzheimer's disease			Lewy body dementia		
	N	mean	95% CI	N	mean	95% CI
		769.7			402.6	
All hospitalizations	306	0.40	0.35-0.44	248	0.62	0.54-0.70
Unplanned	267	0.34	0.31-0.38	201	0.50	0.45-0.55
Planned	39	0.05	0.03-0.07	47	0.12	0.09-0.15

CI Confidence interval, N Number of admissions

4.3 Paper III

The overall median survival time after diagnosis was 6.2 years (95% CI 5.4-6.9). The median survival time after diagnosis for patients with LBD was 4.4 years (95% CI 3.6-5.2), which was significantly shorter than that for patients with AD (6.9 years, 95% CI 6.2-7.6, $p < 0.001$). After five years, the survival rates for AD and LBD, were 68% (95% CI 67.9-68.1) and 34% (95% CI 33.9-34.1), respectively.

Multivariable Cox regression models showed that older age at diagnosis (hazard ratio, HR 1.1, 95% CI 1.0-1.1) and an LBD diagnosis (HR 2.1, 95% CI 1.4-3.3, $p < 0.001$) were factors significantly increasing mortality.

Compared to the age- and sex-matched general population, the study cohort had an 80% higher risk of dying (SMR=1.8, 95% CI 1.6-2.0). Both AD and LBD were found to have higher mortality than the age- and sex-matched general population. The sub-analyses showed that patients with LBD had SMR=2.6 (95% CI 2.1-3.3), while patients with AD had a SMR=1.5 (95% CI 1.3-1.7). In the first year after diagnosis, the SMR was close to one indicating that the mortality rate was equal to that of the general population. At about two to three years after diagnosis the mortality rate increased.

4.3.1 Additional results

Use of psychotropic medications

Paper III reported that pharmaceutical treatments, such as antedementia drugs or the use of antipsychotics were not included because very few patients used antedementia drugs ($n=4$) and none of them used antipsychotics. Meanwhile, in paper I, the use of antedementia and antipsychotics was reported to be 42% and 8%, respectively.

Paper III was the first of the three papers to be published. DemVest is an ongoing study and a reason for this discrepancy might be that some of the data were not plotted or have been updated since the writing of paper III. Additionally, the medical data were not adequately registered. Therefore, before analyses related to paper I could begin, the database had to be reconstructed so that information about drug use

based on ATC could be easily retrieved. Further, the study populations included in paper III and I are not exactly the same. Paper III includes only patients from the first inclusion period (2005-2007), while paper I includes patients from both inclusion periods. This also explains some of the differences in drug treatment between these two papers.

The use of psychotropic drugs was therefore reanalyzed for patients included in paper III (table 4). Significantly more patients with AD were treated with antidementia drugs, and significantly more patients with LBD were treated with antipsychotics. The prescribing practice varied, with three different first-generation antipsychotics (levomepromazine n=2, proklorperazin n=2, haloperidol n=5) and three different second-generation antipsychotics (risperidone n=1, quetiapine n=1, olanzapine n=1) being prescribed. One patient was prescribed lithium.

Table 4: Updated numbers of registered medication used at baseline by patients included in paper III.

		Total		AD		LBD		p-value
Number of drugs in total (median, IQR)		4 (2; 6)		4 (2; 6)		4 (2; 6)		0.27**
		N	%	N	%	N	%	
ATC	Psychotropic drugs*	83	43.7	58	42.3	25	47.2	0.66
N06D	Antidementia	78	41.1	66	48.2	12	22.6	0.002
N06A	Antidepressives	58	30.5	43	31.4	15	28.3	0.81
N05A	Antipsychotics	13	6.8	4	3.1	9	16.9	0.002
N05B	Anxiolytics	15	7.9	10	7.3	5	9.4	0.63
N05C	Sedatives	18	9.5	15	10.9	3	5.6	0.26
N05BA	Benzodiazepines	26	13.7	19	13.9	7	13.2	1.00
N05CD								
N05CF								
		Total	190	137		53		

IQR Interquartile range presented with Q1 and Q3, Statistics presented as n (%) and compared using Pearson Chi-Square test unless otherwise noted.

*Antidementia is not included

**Mann-Whitney test

Predictors of mortality

To examine the relationship between prescribed medication and mortality, a univariate analysis was performed for all medications listed in table 4. Further, a multivariable analysis was performed to determine how medications together with other baseline covariates were associated with death. In paper III only covariates that were significant ($p < 0.05$) in the univariable analysis were included in the multivariable model. In this analysis, all covariates with a $p < 0.25$ were included in a stepwise multivariable model. Both backward and forward elimination (likelihood ratio, LR) were performed, yielding the same result.

In the univariate model, the use of anticholinergics was associated with a reduced risk of mortality, but was not significant (HR 0.76, 95% CI 0.52-1.12, $p=0.17$).

While, the use of antipsychotics was significantly associated with higher mortality (HR 2.05, 95% CI 1.12-3.76, $p=0.020$) in the univariate model. This effect was attenuated in the adjusted model and was no longer significant (HR 1.40, 95% CI 0.70, 2.8, $p=0.34$). In the fully adjusted model a diagnosis of LBD (HR 1.93, 95% CI 1.25–3.00, $p=0.003$), higher age (HR 1.08, 95% CI 1.04–1.11, $p<0.001$), and being male (HR 1.87 95% CI 1.21-2.88, $p=0.005$) remained significant predictors of higher mortality.

5. Discussion

5.1 Introduction

This thesis aimed to investigate the medication use and prognosis of patients recently diagnosed with mild dementia, with a focus on hospitalization and survival time after diagnosis.

In paper I, medication use at the time of diagnosis was explored with a focus on polypharmacy, psychotropic drugs, and adverse drug combinations. This paper provides a snapshot of the drug treatment in patients recently diagnosed with dementia. This paper does not identify the risks of using psychotropic drugs or of polypharmacy. These aspects were included in paper II and in additional results related to paper III (section 4.3.1). Papers II and III are longitudinal studies that investigate whether one dementia diagnosis is more susceptible to hospitalization or death than the other, and compared to the general population, which is relevant to the health care providers and the patient and their relatives.

A critical assessment of the methods applied and how this might have influenced the results is provided in the first section (5.2), while a discussion of the results is provided in the next section (5.3). The findings will be compared to those of previous studies. In addition, similarities and inconsistencies will be discussed, implications for practice will be explored, and conclusions will be made if appropriate.

5.2 Discussion of method

5.2.1 Validity of the DemVest study

Strengths

The DemVest study has been ongoing since 2005 and the majority of the patients have been followed until death. The annual follow-up with repeated measurements has allowed for persistent and repeated analyses from mild to severe dementia.

The study has low attrition for causes other than death. In total 266 patients have performed the baseline assessment. Throughout the years, 24 (9.0%) patients have withdrawn and three (1.1%) have been excluded due to a lack of information. These patients accounted for 10.2% of the total study population. There is a risk of attrition bias when patients who have withdrawn from the study differ from those still remaining. No significant difference was found in the baseline characteristics between patients who withdrew and those who remained in the study, suggesting a low risk of attrition bias. However, this project has no knowledge of the patients' further disease course. In addition, eight patients were first diagnosed with mild dementia, but they did not progress and were diagnosed with mild cognitive impairment after five years and excluded. As a result, 87% of the patients are still included in the study.

Since the start of DemVest in 2005, the diagnostic criteria for AD [27] and DLB [16] have changed, with the addition of supplementary diagnostics and biomarkers in clinical practice. This has led to regular updates of the clinical diagnosis and the three papers use different versions of the clinical diagnoses. The last published paper, paper II, used the final consensus diagnoses where 56 of them are pathological diagnoses. The clinical diagnoses have been found to correlate well with the pathological diagnoses [123]. Out of 20 patients with neuropathological verified LBD, 16 had a clinical diagnosis of LBD (DLB=11, PDD=5), resulting in a sensitivity, specificity, positive predictive value and negative predictive value of 80%, 92%, 84%, and 89%, respectively. For a clinical diagnosis of probable AD, the sensitivity, specificity, positive predictive value and negative predictive value were 81%, 88%, 89%, and 79%, respectively [123].

Change in recruitment

Patients were included from outpatient clinics in the counties of Rogaland and Hordaland over a period of eight years. During the two first years of the study, all patients with a first-time diagnosis of mild dementia were included. After that, only patients with DLB or PDD were included in order to increase the number of patients with these dementia diagnoses and thereby increase the study's statistical power and

robustness. This change in recruitment could potentially lead to selection bias and create two sample groups. However, the recruitment sites and all other selection criteria remained unchanged. Further, an analysis of the baseline characteristics from the LBD patients included in the two time periods was performed and resulted in the detection of no significant differences. Still, this change may cause findings from the total dementia group to have a bias effect due to the skewness between AD and LBD, with LBD being overrepresented. However, this will probably not affect the findings in AD and LBD, individually.

Representativity and generalizability

In relation to the representativity of the DemVest cohort, the literature reports the proportion of AD and PDD among persons with dementia as being around 50-75% and 3-4%, respectively [17, 30] while the proportion of DLB is reported to range between 10-24% [15, 29]. The proportion of different forms of dementia in the DemVest cohort from the two inclusion periods is seen in figure 4.

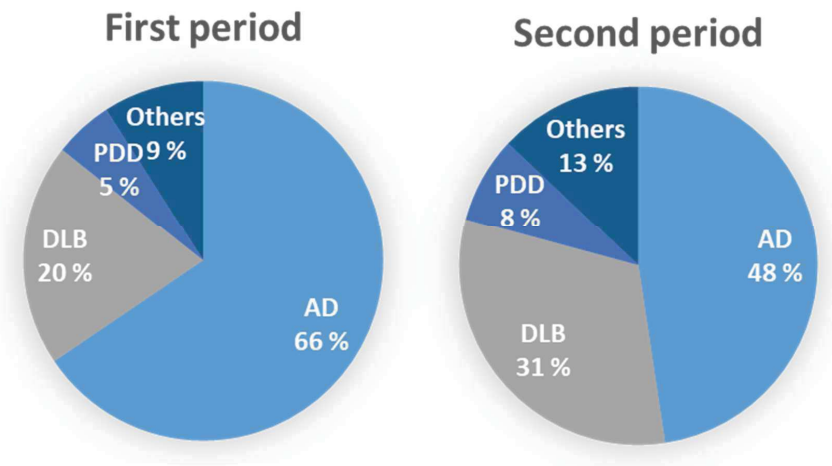


Figure 4: Frequency of different forms of dementia in the DemVest study from the first [3] and second inclusion periods [2].

The first inclusion period from 2005-2007 corresponds relatively well to reported proportions. The frequency of AD and DLB was within the reported range, while the frequency of PDD patients was slightly above. The proportion of DLB was closer to the high end. This may be related to the secondary care often have the ability to perform multiple assessments, which in turn enables them to better detect clinical differences between diagnoses [29]. Another reason might be these outpatient clinics special interest for DLB patients, increasing the likelihood that the characteristic DLB features would be detected. However, all patients screened for inclusion were consecutive referrals and underwent a comprehensive assessment using established diagnostic criteria [120]. In the second inclusion period (after change in the inclusion criteria), the proportion of DLB and PDD increased to 31% and 8%, respectively, according to plan.

The DemVest study is based on referrals from general practitioners and is not a population-based study. Therefore, the study includes only cases known to the health care system. This may lead to a referral bias through the referral of only more severely impaired patients with dementia to the outpatient clinics. This applies especially to patients with DLB who have a more complex clinical picture, with hallucinations, fluctuating cognitions, and REM sleep disturbances. Additionally, patients with less severe symptoms might not have been referred if the symptoms of dementia did not lead to severe enough stress for the patients or caregiver to seek help. However, general practitioners were asked to refer patients with possible dementia even if this might not have been required for medical reasons.

Mild dementia was defined as having an MMSE score of 20 or above or a CDR of 1 or lower. According to Monroe et al., the level of education, language, hearing and vision abilities should be taken into account before using the MMSE to prevent the MMSE score from being biased. Failure to do so may potentially lead to lower MMSE score [133]. In DemVest, all patients were ethnic Norwegians and the median level of education was nine years for both AD and LBD. Some patients probably had impaired vision and/or hearing, but this was likely compensated for by the use of glasses or hearing aids. Therefore, the assumptions are assumed to have been met.

Further, the MMSE has been criticized for not being able to sufficiently detect the cognitive impairment in DLB as it does not directly assess psychiatric, autonomic, or executive functions that often are impaired in these patients [134] and for showing unsatisfactory results in terms of diagnosing patients with PDD [135]. In addition, the same MMSE score might not represent the same disease severity for patients with DLB as compared to patients with AD [134], potentially causing a recruitment bias. Although, there were no significant differences in the CDR at baseline. The CDR captures a broader range of functional deficits due to cognition and may be a more precise and comprehensive measure of dementia severity in LBD. However, the CDR was also designed for use in AD and has not yet been sufficiently tested in DLB [75].

Statistical analysis

DemVest has one of the largest LBD cohorts followed longitudinally in a single study. Still, the number of patients was relatively low and, thus the statistical power to detect significant associations may be limited. As the statistical power and the risk of type II errors are related, studies with low power have a higher risk of making a type II error [136]. Therefore, the recruitment was changed in 2007 to increase the sample size of LBD and thereby the statistical power.

In this project several statistical tests have been performed, which increases the risk of at least one test yielding a false significant result, thereby causing a type I error. To reduce the risk of incorrect conclusions, adjustments for multiple testing can be applied [137]. However, there is no clear-cut when to adjust for multiple testing, as this depends on the study performed. In confirmatory studies adjustments for multiple testing should be applied, while adjustment for multiple testing in explorative studies can cause type II errors [137]. The papers included in this project have reported more preliminary results and are believed to be more akin to exploratory studies than confirmatory studies. Therefore, multiple testing was considered not to be necessary for this project.

5.2.2 Combining DLB and PDD

In this thesis, DLB and PDD were combined and collectively referred to as LBD. A relevant topic is whether this is justified.

They are both defined as alpha-synuclein disorders and are considered part of the LBD spectrum [15]. DLB and PDD differ in the sequence of the onset of dementia and Parkinsonism and possibly levodopa-responsiveness [16], though they share many clinical and neuropathological features [43]. So far, no specific clinical and pathological differences between DLB and PDD have been identified, and as the diseases progress, distinguishing between them becomes difficult [15]. Therefore, DLB and PDD are believed to be related alpha-synucleinopathies with different phenotypic presentations, which are unlikely to affect prognosis and clinical outcomes [138]. In addition, several studies report no statistically significant difference in mortality between the two entities [138, 139].

5.2.3 Choice of index date

Choice of index date differs from study to study in the existing literature. Some studies have used time from first symptom as the index date [140], while others [138, 141], including this project, have applied date of diagnosis as the index date.

Different factors may affect time to diagnosis. Higher education has been found to increase time from symptom onset to diagnosis, regardless of dementia diagnosis [142]. Data from a register study found that five additional years of education increased the time to diagnosis by 10%, but it was not possible to distinguish this effect between different forms of dementia due to low statistical power [142]. Moreover, it might take up to a year after help is sought before a DLB diagnosis is made. Patients with DLB may also have received other diagnoses before being diagnosed with dementia [143]. Findings from DemVest showed that patients with LBD reported a significantly longer time from first symptom to diagnosis compared to patients with AD (three years vs two years). This delay from first symptom to diagnosis may be related to the complex clinical phenotype of LBD with Parkinsonism, hallucinations, fluctuations and sleeping disorders [15]. This time

difference may have led to more patients with LBD being assessed closer to the time of the study outcome, e.g., first hospitalization or death. Additionally, there is still stigma attached to dementia, which may prevent people from seeking help [8]. This may cause patients to die before being diagnosed with dementia, resulting in an underestimation of the true prognosis. Further, the timing of the first symptom also depends on various factors. First, it is affected by the patient's or caregiver's ability to remember. In addition, the time is influenced by their knowledge about dementia and the symptoms related to the disease [96]. Some may even believe the first symptoms to be part of the normal aging process. Using the time from diagnosis as the index date was therefore considered the best choice for assessing prognosis.

5.2.4 Information about drug treatment and medication adherence

Information about drug treatment was retrieved from the patient or family members and was either given orally or based on a written medication list. Information about over-the-counter drugs could not be retrieved. Norway has a relatively strict policy governing which medications can be sold over the counter and outside of the pharmacy. However, non-prescription drugs might be considered inappropriate for some patients.

This project has no information related to medication adherence. Patients with Parkinson's disease often have complex medication regimes, with multiple doses in one day. This complex medication regimen may be difficult to adhere to as the disease progresses. Further, patients with dementia often experience reduced communication skills as the disease progresses [13], which may be why a study reported people with cognitive impairment to report fewer adverse events than people with normal cognition. [144]. In addition, interpreting clinical signs and symptoms related to drug treatment may be difficult when communication skills reduces.

5.2.5 Choice of screening tool for identifying PIM

The NorGeP criteria were applied to assess the prevalence of PIM in paper I. This screening tool consists of 21 single drugs and 15 drug-drug combinations that should be avoided in people above 70 years. It was developed and validated through a three-

round Delphi process [6]. Initially, it was considered to use the second version of the STOP criteria [110]. However, the DemVest study was not initiated to assess medical treatment in patients with dementia and the choice of screening tool had to be based on the information available. Many of the STOPP criteria depend on clinical information, which was not available. This would have led to only parts of the STOPP criteria being applicable. The NorGeP criteria were considered the most optimal choice of screening tool as it was developed in Norway and require no clinical information to be applied.

The prevalence of PIM was fairly low in this project (14%); a higher prevalence might have been found if another screening tool had been applied. Some screening tools include medication that should not be used with specific diseases [109, 110], which the NorGeP criteria does not. This may result in an underestimation of the prevalence of PIM. The prevalence of PIM shows great diversity between different screening tools applied to the same population and there is little correlation across these scoring tools [145]. This implies that more consensus is needed regarding which drugs should be defined as PIM, so that more uniform screening tools can be developed. This would potentially lead to more comparable studies.

The NorGeP criteria have been developed to assess PIM in people above 70 years of age. In paper I, the median age at baseline was 77 years (IQR 71-81), although, some patients were younger than 70 years. The pathological changes in the brain due to dementia make patients with dementia more sensitive to specific drugs such as antipsychotics and drugs with anticholinergic properties [146] and thereby more prone to adverse events. Hence, assessing PIM in patients with dementia who are younger than 70 years may improve drug regimens and reducing the risk of adverse drug events.

When assessing appropriate medication use, several aspects should be considered. Most early screening tools focused on specific drugs, dosages, and duration. However, other aspects, such as the omission of medications, medication monitoring, and drug-disease interactions, should also be considered. During the last decade, both

STOPP and Beer's criteria have been updated and now evaluate more aspects than the original versions (see table 5). The NorGeP criteria evaluate the fewest aspects and have not been updated since their publication in 2009, though a nursing home version was published in 2015 [147].

Table 5: Aspects evaluated in different potentially inappropriate medications screening tools. Modified from Motter et al. [108].

List name	Year	Country	Independent of diagnosis	Dosage	Duration of therapy	Disease-drug interaction	Drug-drug interaction	Duplication	Alternatives therapies	Special considerations of use
Beers Criteria	1997	USA								
STOPP version 1	2008	Ireland								
NorGeP	2009	Norway								
STOPP version 2	2015	Europe								
Beers criteria	2015	USA								
NorGeP-NH	2015	Norway								

The use of screening tools to detect PIM may be relevant to assessing the quality of prescribing and to informing authorities, stakeholders and researchers. Still, many of the screening tools are comprehensive and may be difficult to use at the clinical level [148]. If applying a screening tool, one should choose a tool that, in addition to PIM also identifies drugs that should have been used to increase the clinical impact [149]. If it had been possible, it would have been preferable to perform an advanced medication review [150]. This method includes medication history, clinical information and the patient perspective, which is important when considering appropriate drug treatment.

5.3 Discussion of results

5.3.1 Appropriate drug treatment

This section aims to place the drug treatment in context and compare the findings with others. The best treatment available at the time of diagnosis, in relation to the specific dementia diagnosis, was given to patients in DemVest. However, this study was not originally designed to assess appropriate drug treatment; strengths and limitations related to that will also be discussed.

Polypharmacy and use of psychotropic drugs

The prevalence of polypharmacy in patients with dementia has been found to range from 25-98%, depending on the setting [149]. The prevalence of polypharmacy was 45% in the DemVest cohort at baseline. The PRIME study, a multicenter, prospective study including patients with mild cognitive impairment and dementia, reported that 66% of the study participants were exposed to polypharmacy [151]. These findings are somewhat higher than those found in DemVest. Meanwhile a register study from Denmark reported that the prevalence of polypharmacy in community-dwelling people with dementia was 54.5% [103], which is more in line with the findings in DemVest. Overall, the prevalence of polypharmacy is high in patients with dementia living in community settings. Improving polypharmacy in patients with dementia and multimorbidity may be challenging, but the use of screening tools along with clinical information may lead to more appropriate polypharmacy, especially if possible prescribing omissions are considered [116].

The use of psychotropic drugs in DemVest is generally in line with the use reported in the population-based Cache County Study [152], except for the use of antidementia drugs and benzodiazepines. In DemVest, the use of benzodiazepines was nearly twice as high (16% vs 7.4%), while use of antidementia drugs was nearly three times as high (42% vs 15%). The low use of antidementia drugs in the Cache County study is probably related to Donepezil first being approved for medical use in the United States in 1996 [153]. This was one year after the establishment of the Cache County Study. Some of the differences in the use of benzodiazepines may be attributed to

how benzodiazepines are grouped. In this project, benzodiazepines consist of medications from the following ATC-groups: N05BA, N05CD, and N05CF. However, the Cache County Study does not state how the benzodiazepines were grouped. The PRIME study reported the use of antipsychotics, benzodiazepines and antidementia drugs at baseline to be 25%, 21%, and 62%, respectively [73, 154]. The use of antipsychotics and benzodiazepines was higher compared to DemVest, though the PRIME study reported benzodiazepines only from the ATC group N05BA. The use of antidementia drugs in the PRIME study was in line with the use at follow-up 1 (61%) in DemVest [24]. Compared to DemVest, a study of patients with dementia receiving domiciliary care in Norway [155], reported less use of antidementia drugs (13% vs 42%) and antidepressants (20% vs 32%). The low use of antidementia drugs in that study may be explained by the fact that the majority of patients with dementia (80%) were diagnosed after inclusion [155].

Prevalence of PIM and DDI

When analyses for paper I were executed, no other papers investigating the prevalence of PIM in home-dwelling patients with mild dementia were found. Therefore, the prevalence of PIM was compared to study samples in which the patients were in different stages of their disease, or in which the study was conducted in a different setting [156, 157]. Later, one systematic review from 2015 was found [158]. This systematic review examined the prevalence of PIM in people with cognitive impairment and dementia in different settings. Eight of these studies included people with dementia living in the community [158]. The prevalence of PIM in these eight ranged between 10-56%. Since then, at least three other reviews assessing inappropriate medications in people with dementia have been published. These reviews report that the prevalence of PIM ranges from 14-74% [86, 149, 159].

The systematic review by Patel et al., included seven studies, consisting only of ambulatory home-dwelling people with dementia [159]. Four different tools were applied to detect PIM, none of them applied the NorGeP criteria. This systematic review reported the most narrow range of PIM, ranging from 15% to almost 47%, with a median PIM of 26% [159]. The review was published in 2017 but did not

include papers published after 2015. Since then, a minimum of four additional studies including outpatients with dementia have been published [103, 151, 160, 161] reporting a prevalence of PIM ranging from 21-64%. Correspondingly, the prevalence of PIM in paper I is at the lowest end (14%). The findings of few PIM may be because patients in DemVest were in their early stages of dementia and were not using many medications, though it is most likely due to the selection of screening tool as discussed in section 5.2.5.

There are conflicting results as to whether patients with dementia have higher prevalence of PIM compared to patients without dementia [149]. Some studies report the prevalence to be higher in patients with dementia [92, 103], while other studies report the prevalence of PIM to be higher in patients without dementia [162, 163]. Additionally, some studies report no difference between these two groups [144]. This inconsistency may be explained by differences in study design and the use of different screening tools [149]. Therefore it would have been preferable to apply the NorGeP criteria to a comparison group to be able to more explicitly state whether the prevalence in DemVest was low or high.

Benzodiazepines, and anticholinergic drugs are among the most commonly reported PIM [149]. These drugs may cause cognitive and psychological impairment in patients with dementia [146, 164]. The NorGeP criteria also consider benzodiazepines as a PIM and although they do not specifically indicate anticholinergic drugs, the NorGeP criteria contain drugs with anticholinergic properties such as tricyclic antidepressants and first-generation antihistamines. In line with recent findings, benzodiazepines were the most frequent PIM (n=8) in this project, while four anticholinergic drugs were identified. The prevalence of anticholinergic drugs would probably have been higher if an explicit anticholinergic assessment tool had been applied, but this was beyond the scope of this project.

Paper I reported no difference in PIM use between AD and DLB, and an additional analysis (data not published) showed no difference between patients with AD and LBD. However, a study including more than 2000 patients with AD and 144 patients

with LBD reported that patients with LBD had significantly more PIM than patients with AD [165]. The patients with LBD used more medications compared to AD, which is a risk factor for having PIM. Meanwhile, the difference may also be explained by the choice of screening tool. They applied the Beer's Criteria from 2015 which evaluates more aspects than the NorGeP Criteria (see table 5, section 5.2.5).

A study from Germany reported that the prevalence of DDI in community-dwelling patients with dementia was 35% [166], which is in line with the prevalence of "take precaution" DDI reported in paper I (36%). A Swedish hospital study including patients with dementia, reported that the prevalence of clinically identified DDI to be 43% [167]. The overall findings are comparable with findings in paper I. However, a higher frequency of DDI that should be avoided (7.6%) was reported [167]. The patients included in the Swedish study used more medication compared to patients in DemVest, which may explain some of the differences. Another potential reason may be that the interaction database used ranks interactions differently than the one used in Paper I.

In paper I, the prevalence of DDI in the group "take precaution" was relatively high (36%), but the study had no knowledge of whether dose adjustments already had been made for this group of interactions. If this has not been done, this may be an area for future improvement. In addition, there is a possibility that patients might have had other interactions that have not been identified. Paper I addressed only DDI, but a drug interaction can also be related to other factors, such as food or other diseases. Therefore, this project analyzed just some of all potential drug interactions.

The assessed medication were prescribed between 2005 and 2013 and there is a possibility that the patterns of drug prescribing in Norway might have changed since then. Halvorsen et al. [168] analyzed the trends in prescribed PIM in different Norwegian nursing homes at three different time periods (1997, 2005, and 2011). They applied the nursing home version of the NorGeP criteria [147] and found that the prescribing of several PIM was reduced. However, the overall use of PIM increased in this period, indicating a shift in prescribing pattern [168]. Although the

study is from a setting found to have higher risk of being prescribed PIM [148], the potential change in prescribing patterns may also have taken place among outpatients.

Factors associated with PIM or DDI

In paper I, the female gender was associated with having PIM. This finding is in line with others studies [144, 156, 161]. However, the reasons why the female gender is associated with an increased risk of having PIM are however not known. Lau et al. [163] suggested that the use of estrogen may be a possible reason. They performed additional analyses that removed estrogen, which resulted in no significant difference between men and women [163]. However, the NorGeP criteria do not list estrogen as PIM; therefore, estrogen is not a plausible explanation for this study. Patel et al. [159], suggested that association of the female gender with PIM may be related to women having more complaints related to depression, sleeplessness, and nervousness, which may increase their risk of being prescribed psychotropic drugs such as benzodiazepines and antidepressants. The association between an increased number of drugs used and having PIM and DDI was not surprising, and is in line with other studies including outpatients with dementia [144, 156, 161, 167]. Another study including patients with suspicion of dementia reported that the use of a medication dispenser or the receipt of support with drug administration had a positive effect and reduced the risk of PIM (OR 0.13, 95% CI 0.02, 0.63) [144]. However, information about this was not available in this project.

5.3.2 Hospitalization

Compared to the general population

In paper II, SAR was calculated to compare the hospitalization rate in AD and LBD with the age-matched general population from the catchment area. SAR revealed a higher rate of admissions, for both planned and unplanned admissions in patients with AD and LBD (Planned: AD 1.35, LBD 2.01; Unplanned: AD 1.30, LBD 1.83). These findings are in the same direction as the meta-analysis in Shepherd et al. [84].

Adjusted for age, sex, and physical comorbidity, the meta-analysis gave a pooled relative risk of 1.42 (95% CI 1.21, 1.66) for people with dementia compared to those without [84].

When SAR was divided into age-groups, patients between 60-74 years with LBD had almost four times as many hospitalizations during the first year after diagnosis compared to the general age-matched population. Unfortunately, it was not possible to adjust for sex due to the small sample size. Only admissions that took place during the first 12 months after diagnosis were included in the calculation of SAR. This was done to reduce the competing risk of death. This resulted in a small number of admissions, which may have reduced the strength of the results. Therefore, these results may be regarded as preliminary; several studies with a larger study sample must be conducted before a reliable conclusion can be made.

Differences between patients with AD and LBD

In 2019, the first systematic review reporting on the hospitalization rate in patients with dementia was published [84]. Close to 280,000 patients with dementia were included, but just 194 of the patients had LBD [90]. The reported hospitalization rate ranged between 0.37 and 1.26 per person-year [84]. The findings from the additional analysis (see section 4.2.1) show that findings from paper II is at the lower end, with a hospitalization rate per person-year of 0.40 (95%CI 0.35-0.44) and 0.62 (95%CI 0.54-0.70) for patients with AD and LBD, respectively.

In paper II, patients with LBD were found to have a shorter time until first hospitalization, more admissions, and more unplanned hospital days compared to patients with AD. Other studies report findings in the same direction [81, 90, 91], except for one [78]. These consistent findings indicate that patients with LBD have a poorer prognosis in relation to hospitalization compared to patients with AD.

Factors affecting hospitalization

There is strong evidence that older age affects hospitalization and moderate evidence that physical comorbidity is associated with hospitalizations [84]. This is consistent with findings from paper II showing a reduced SDHR and CSHR after adjustment for these factors. Further, there is moderate evidence that taking seven or more medications is associated with hospitalization [84]. In paper II, adjustments for having polypharmacy did not affect the size of SDHR and CSHR. An explanation for

this may be that polypharmacy, defined as the use of five or more medications is not sufficient to find any association.

Polypharmacy and the use of psychotropic drugs were based on drugs used during the first year; changes in drug regimens were not taken into consideration during the study period and there is a possibility that the drug regimen changed during the follow-up. Further, other drugs than those adjusted for in paper II may be associated with hospitalization. Beta-blockers in combination with other medications were the most frequently reported DDI in Paper I, and it is suspected that use of such drugs may be the underlying cause in many hospitalizations [169]. The use of benzodiazepines has been found to increase the risk of hip fracture among patients with AD [170], which again, leads to hospitalization. None of these drugs were included in the statistical model although it would have been interesting to have analyzed whether and how they were associated with hospitalization. Still, no substantial change was seen on the effect size (SDHR, CSHR) after adjustment for other psychotropic drugs and polypharmacy. More studies are needed to clarify whether the reduction of polypharmacy, psychotropic drugs or PIM is effective in reducing adverse events and thereby potentially preventing hospitalization.

During the five-year study period, patients with LBD spent more time in the hospital compared to patients with AD and the IRR ranged from 1.41 to 1.84 in unadjusted analysis, depending on the outcome. When counting days in hospital, patients with LBD had 53% (IRR 1.53, 95% CI 0.92-2.52) more days in hospital compared to AD, in the fully adjusted negative binomial model but was no longer statistically significant. This may indicate that something else have an impact on hospitalization. Functional impairment shows moderate evidence of being associated with hospitalization [84]. Unfortunately, it was not possible to adjust for functional impairment in paper II. Adjusting for functional impairment would have strengthened the study and could potentially explain some of the increased effect size seen in patients with LBD. The statistical model was arranged to compare rate and risk between LBD and AD. Therefore it is not possible to disentangle the specific variable

effect from each other. To gain knowledge about whether and how specific factors affect hospitalization another set-up should have been chosen

Knowledge about the cause of admission is relevant and may lead to more targeted care, and interventions aiming at reducing these causes may potentially prevent some of the hospitalizations. In patients with AD, frequent causes of admissions have been reported to be related to falls and fall-related injuries, cardiac disease, gastrointestinal system and pneumonia [171]. While, patients with LBD have been reported to be admitted due to neuropsychiatric symptoms, falls and infections [89]. Paper II did not highlight the causes of admission, but falls and fall-related injuries composed the most frequent cause of admission for both dementia diagnoses in DemVest (data not published). Therefore, capturing early signs of infections or those at risk of functional impairment and thereby reducing the risk of falling may prevent hospitalizations.

5.3.3 Survival and mortality

Compared to the general population

In paper III, SMR was calculated to compare mortality in AD and LBD with the age- and sex-matched general population in Norway. Patients with LBD were found to have a mortality rate of 2.6 (SMR 2.6, 95% CI 2.1-3.3), while patients with AD had a mortality rate of 1.5 (SMR 1.5, 95% CI 1.3-1.7) compared to the general population. A study from the US [172], published in 2010, reported similar findings for patients with LBD (SMR 2.42) and AD (SMRprobable AD 1.70, SMRpossible AD 1.84). The findings from this study and paper III were further confirmed by Larsson et al. [139] and Strand et al. [141]. Both report that patients with dementia have higher mortality than the general population. Savica et al. [173] analyzed survival curves in different synucleinopathies. All the synucleinopathies had increased mortality compared to the general population and the difference diverged from the general population approximately two years after diagnosis [173], which are in line with the SMR over time found in paper III. This suggests that, around two years after the dementia diagnosis, something changes that causes the mortality to deviate from the comparison group. The cause of this is not known and should be further explored.

Differences between patients with AD and LBD

Paper III was one of the first published studies on mortality in patients with LBD using the DLB diagnostic criteria from 2005. The main findings were that patients with dementia had higher mortality compared to the general population. Patients with LBD had a significantly shorter survival time than patients with AD, while higher age at baseline and having LBD predicted higher mortality in dementia.

The introduction of the consensus criteria for the diagnosis of DLB in 1996 [36] and the further revision in 2005 [39] which increased the sensitivity of the consensus criteria [174] have probably led to more patient being diagnosed with DLB resulting in larger studies with DLB patients. Additionally, naturalistic data from electronic health records may now be retrieved, which, again, has led to an increasing number of publications on survival in DLB [140]. As a result, the first systematic review and meta-analysis comparing survival in patients with AD and DLB was published in 2019 [95]. Eleven papers were included, including paper III. The baseline characteristics in the meta-analysis are not entirely the same as those reported in paper III as the meta-analysis only included patients with DLB.

The systematic review comprised 20,923 patients with AD and 2029 patients with DLB. The average survival time for AD and DLB was reported to be 5.66 years ($SD\pm 5.32$) and 4.1 years ($SD\pm 4.10$), respectively [95]. A recently published study from a memory clinic in Sweden comparing mortality in LBD with that of the general population, reported a median survival time of 4.1 years (IQR 2.6-6.0) [139], while a Norwegian registry-based prospective study, NorCog, reported that patients with AD have a significantly longer survival time after diagnosis than patient with LBD [141]. Thus, the findings from paper III are very much in line with the most recent published literature. These studies increase the evidence that patients with LBD have a shorter survival time after diagnosis compared to patients with AD. However, the confidence interval in the Swedish study has a substantial range and the survival time reported in the meta-analysis ranged from 1.9 to 5.59 years for DLB patients and 2.29 to 8.3 years for AD patients. Hence, there is still a too-pronounced variation in the reported survival time to be able to provide a precise estimate of survival time to health care

personnel and patients. These heterogeneous results may be due to differences in the choice of index date (see section 5.2.3) or the inclusion of patients at different stages of their dementia.

Factors predicting mortality in dementia

Paper III found that higher age at baseline was a predicting factor for increased mortality, which is in line with published literature. The findings of LBD having increased mortality compared to AD have recently been confirmed in another Norwegian study. Strand et al. [141], reported that patients with LBD have a 71% (HR 1.71, 95% CI 1.33-2.21) higher risk of death than patients with AD, even after adjustment for age, gender, comorbidity, functional impairment, and cognition [141].

The additional finding (section 4.3.1) of the male gender influencing mortality is in line with previous findings [175]. However, Strand et al. [141] found a gender difference only in patients with AD and not in patients with LBD. Most studies have reported on observed mortality and not on life expectancy and the years of life lost, which Strand et al. did [141]. They found that both men and women with dementia had a significantly shorter life expectancy, but women with dementia had significantly more years of life lost than men with dementia when compared to the general population. According to Strand et al., this was believed to be related to the fact that women, in general, live longer and thus lose more years of life [141].

Further established predictors of mortality in dementia are disease severity, comorbidities, and functional impairment [175]. The first two predictors were significantly associated with higher mortality in the univariable analysis in paper III, but did not remain significant in the fully adjusted model. Adjustment for functional impairment was not possible, although it would have been interesting to see how functional impairment was related to mortality as patients with DLB have been reported to have more functional impairment than AD patients at baseline [176], but with no significant difference in rate of functional decline during follow-up [177].

In relation to psychotropic drugs, the use of antidementia drugs indicated lower risk of mortality, but was not statistically significant (see section 4.3.1). Two other studies

reported that the use of cholinesterase inhibitors reduced the risk of mortality in patients with AD [178, 179]. Studies including patients with LBD have not been found, but a positive clinical response to memantine revealed a positive effect on survival time for patients with LBD [180]. The use of antipsychotics is recognized as a predictor of increased mortality [181]. However, this association was not established in this project (see section 4.3.1), nor was it established in a more recent, larger study [140]. Overall, studies report that LBD is associated with increased mortality compared to AD even after adjustment for relevant predictors. This suggests that other factors related to survival still are unknown.

6. Conclusions and clinical implications

The general aim of this thesis was to increase knowledge about pharmacological treatment and prognosis related to hospitalization and mortality in patients recently diagnosed with AD and LBD.

The increased risk of hospitalization, even in mild dementia, should be highlighted. Falls and fall-related injuries seem to be major causes of admission among patients with AD and LBD - causes that are potentially preventable. The reduced survival and higher mortality, which cause a substantial years of life lost should also be emphasized. However, the large range of survival time makes it difficult to inform about individual prognosis. The quality of prescribing seems to be acceptable in relation to PIM and DDI, though clinicians are encouraged to have a regular focus on appropriate drug use.

A dementia diagnosis often leads to symptomatic treatment, mapping of the functional level and the need for help, which, in turn, may reduce the risk of hospitalization and longer survival time. Therefore, a timely and correct diagnosis of dementia may provide optimal care and hopefully improve prognosis in patients with dementia.

7. Future research

Several studies have initiated interventions to reduce PIM and optimize the pharmacological treatment [182, 183]. Due to the naturalistic design of this project, no intervention was performed. Interventions such as medication reviews, use of computerized systems, or interventions related to education or deprescribing have shown positive results in reducing the number of PIM [183]. In a recent systematic Cochrane review, two thirds of the studies examined how interventions, focusing on appropriate polypharmacy, were associated with clinical outcomes related to hospitalization or quality of life. None of them included mortality [182]. Due to design limitations in the included studies, the Cochrane systematic review concluded that there is little evidence of whether interventions focusing on appropriate use of polypharmacy are effective [182]. All the included studies reported outcomes using a quantitative measure. This may not be sufficient to detect an effect regarding appropriate drug treatment. Qualitative methods explore other aspects than quantitative methods do, and may be used to get a deeper insight into, and understanding of, the patients' experience after an intervention. Therefore, combining these methods in future studies may complement the findings and increase evidence.

Patients with dementia, and especially patients with LBD were found to have a high admission rate compared to the general population. Admissions related to falls and fall-related injuries and infections (see section 5.3.2) are frequent in patients with dementia [90, 171], and represent a potentially preventable cause. Future studies should focus on how to identify patients who are at risk of infections or falls. Reducing such hospitalizations may lead to a better quality of life for the patient and reduce health care costs. Further, not all hospitalizations are preventable. Therefore, one should investigate how to reduce unnecessary stress and optimize care for patients with dementia who are hospitalized. Other patient groups such as patients with transient ischemic attack (TIA) or cardiac arrest, have specific treatment loops. A treatment loop specifically aimed at patients with dementia or cognitive impairment may be beneficial for reducing stress at admission.

Currently, there is little knowledge about drug use prior to nursing home admission in patients with dementia in Norway. A planned PhD project will combine data from several central health registers. An important focus of this project will be how psychotropic drug use, and potentially PIM, are associated with institutionalization or death in patients with dementia.

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Potentially inappropriate medications and drug–drug interactions in home-dwelling people with mild dementia

Ragnhild Oesterhus^{1,2}, Dag Aarsland^{1,3}, Hogne Soennesyn¹, Arvid Rongve^{2,4}, Geir Selbaek^{5,6} and Svein R. Kjosavik^{1,7}

¹Centre for Age-Related Medicine, Stavanger University Hospital, Stavanger, Norway

²Department of Clinical Medicine, University of Bergen, Bergen, Norway

³Department of Neurobiology Caring Science and Society, Karolinska Institutet, Stockholm, Sweden

⁴Department of Research and Innovation, Haugesund Hospital, Haugesund, Norway

⁵Vestfold Hospital Trust, Norwegian Advisory Unit on Ageing and Health, Tønsberg, Norway

⁶Centre for Old Age Psychiatric Research, Innlandet Hospital Trust, Ottestad, Norway

⁷Research Unit for General Practice, Uni Research Health, Bergen, Norway

Correspondence to: R. D. Oesterhus, E-mail: rdsalte@gmail.com

Objectives: The objectives of this study were to describe the use of psychotropic drugs among home-dwelling people with mild dementia, to identify potentially inappropriate medications (PIM) and drug–drug interactions (DDI), and to analyze potential variables associated with having PIM and DDI.

Methods: Patients ($n = 251$) with a first-time diagnosis of mild dementia (defined as a mini-mental state examination score >20) were included from outpatient clinics. Prevalence of psychotropic drug use, polypharmacy, and psychotropic polypharmacy were investigated. The prevalence of PIM and DDI were defined using the Norwegian general practice criteria and an interactions database, respectively. Variables associated with having PIM and DDI were assessed using a multivariable logistic regression analysis adjusting for relevant demographic and clinical variables.

Results: Almost 96% of the patients used one or more medications. Polypharmacy was found in 45% of the patients, and nearly 70% of the patients were using one or more psychotropic drugs. Psychotropic polypharmacy was found in seven patients. PIM were identified in 35 patients (14%), while only four severe DDI were found. Female sex and number of medications were significantly associated with having PIM, whereas only number of medications was significantly associated with having DDI.

Conclusion: Few patients had PIM or severe DDI, indicating that the quality of prescribing was acceptable. However, psychotropic drug use was common in home-dwelling people with mild dementia despite limited evidence of benefit in dementia. More knowledge is needed about the potential risks associated with psychotropic drug use and having PIM and DDI in people with mild dementia. Copyright © 2016 John Wiley & Sons, Ltd.

Key words: dementia; psychotropic medications; drug interactions; drug therapy; outpatients; potentially inappropriate medications

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Introduction

Older people are major consumers of prescription medicine (Norwegian Institute of Public Health, 2014), with increased risk of polypharmacy and drug–drug interactions (DDI). This, in combination with decreased drug tolerance due to age-related changes in the

pharmacokinetics and pharmacodynamics, leads the older people to being at high risk of having drug-related problems (Lau *et al.*, 2010). Dementia is one of the most common age-related disorders, and the disease increases the risk of adverse drug reactions (Hajjar *et al.*, 2003). Neuropsychiatric symptoms such as aggression, agitation, sleep disturbances, and hallucinations are frequent

in dementia, and psychotropic drugs such as benzodiazepines and antipsychotics are often used (Hartikainen *et al.*, 2003; Wergeland *et al.*, 2014), despite limited evidence of benefit and high risk for adverse effects (Defrancesco *et al.*, 2015; Schneider *et al.*, 2005).

High drug consumption was found to be a strong predictor of institutionalization (Luppa *et al.*, 2010), and one of five prescriptions to older community-dwelling people has been found to be inappropriate (Opondo *et al.*, 2012). Therefore, older people may benefit from a drug assessment to reduce the number of drugs and especially potentially inappropriate medications (PIM). Screening tools like “the Norwegian general practice” (NORGEP) criteria (Rognstad *et al.*, 2009), “screening tool of older persons’ potentially inappropriate prescriptions” (O’Mahony *et al.*, 2015), and “Beers criteria for PIM use in older adults” (The American Geriatrics Society, 2012) may be used to assess PIM.

Studies investigating the prevalence of PIM in people with dementia are mostly based on patients living in care homes or nursing homes (Bakken *et al.*, 2012; Parsons *et al.*, 2012). The few studies in home-dwelling people with dementia included a combination of home-dwelling and institutionalized patients or patients with different degrees of dementia (Andersen *et al.*, 2011; Lau *et al.*, 2010; Montastruc *et al.*, 2013). Considering the increasing number of people with dementia, with about 50% of them living at home (Hjort and Waaler, 2010), more studies performed in this group are needed. The objectives of this study were to describe the use of psychotropic drugs among home-dwelling people with mild dementia, to identify PIM and DDI, and to analyze potential variables associated with having PIM and DDI.

Methods

Material

This is a cross-sectional study based on a longitudinal cohort on dementia in western Norway, the DemWest study, (Aarsland *et al.*, 2008). From March 2005 to March 2007, home-dwelling patients with a first-time diagnosis of mild dementia (defined as a mini-mental state examination (Folstein *et al.*, 1975) score >20) were consecutively included from geriatric and psychogeriatric outpatient clinics in the counties of Hordaland and Rogaland, Norway. From April 2007 to April 2013, only patients with Parkinson’s disease with dementia and dementia with Lewy bodies (DLB) were included. Patients without dementia, terminal illness, or with previous history of any

psychiatric disorder were excluded. Of the 266 patients included in the study, 15 patients were excluded because of different reasons (missing information about diagnosis ($n=8$), mild cognitive impairment ($n=4$), and moderate dementia ($n=3$)). The study sample therefore consisted of 251 patients, all of whom had available information about drug use.

Ethical issues

The study was approved by the regional committee for medical and health research ethics, REC West. After the study procedure had been explained in detail, written consent to participate was provided by the subjects or next of kin if the patient was unable to consent

Diagnosis and assessment

The diagnosis of dementia was made according to the Diagnostic and Statistical Manual for Mental Disorders, 4th edition (DSM-IV) and classification of dementia according to consensus criteria (Emre *et al.*, 2007; McKeith *et al.*, 2005; McKhann *et al.*, 1984). For a thorough description of the case finding, diagnostic criteria, and diagnostic procedures, please see the work of Aarsland *et al.* (2008). All patients were examined at baseline, and demographic and clinical data were recorded. The diagnosis was re-evaluated during the clinical follow-up, and the final diagnosis was made as a consensus between two experts in geriatric psychiatry and one geriatrician, with pathological verification in 35 of the patients, at the time of writing. Baseline examinations included the following instruments: the mini-mental state examination (Folstein *et al.*, 1975) and the Clinical Dementia Rating Scale (CDR) (Morris, 1997), which were used to measure the cognitive decline. The CDR assesses the impairment in six categories where memory is weighted highest. The global score of CDR was calculated using an online algorithm (National Alzheimer’s Coordinating Center, 2014). A global score of 0 corresponds to no dementia, 0.5 to very mild dementia, 1 to mild dementia, 2 to moderate dementia, and 3 to severe dementia. The total burden of medical illness was quantified using the Cumulative Illness Rating Scale (CIRS) (Linn *et al.*, 1968), which rates 13 domains, including neurological and psychiatric disorders. The severity in each domain ranges from 0 (no impairment) to 4 (extremely severe impairment). The total CIRS score is calculated by adding together the scores in the various domains (range 0–52). The Norwegian-validated version of the neuropsychiatric inventory (Cummings *et al.*, 1994; Selbæk *et al.*, 2008) was

applied to assess neuropsychiatric symptoms occurring in dementia such as visual hallucinations and agitation. The neuropsychiatric inventory assesses both the frequency (0–4) and the intensity (0–3) of 12 neuropsychiatric symptoms. Frequency and intensity are multiplied to give an item score for each symptom (0–12). A sum score is calculated by summing the item scores (0–144).

Drug use and classification

Drug names and dosages at baseline were classified according to the Anatomical Therapeutic Chemical classification system (WHO Collaborating Centre for Drug Statistics Methodology, 2014). Psychotropic drugs were classified into antipsychotics (N05A), anxiolytics (N05B) hypnotics and sedatives (N05C), antidepressants (N06A), and anti-dementia drug (N06D). Most anxiolytics (N05B) and hypnotics (N05C) are benzodiazepines. The non-benzodiazepine sleeping pills (N05CF) also act via benzodiazepine receptors and were therefore classified as benzodiazepines together with N05BA and N05CD. Polypharmacy was defined as the concomitant use of five or more drugs, and psychotropic polypharmacy was defined as the concomitant use of three or more CNS-active drugs. Over-the-counter (OTC) drugs and dietary supplements without an Anatomical Therapeutic Chemical-code were not included in the analysis.

Potentially inappropriate medications and drug–drug interactions

The NORGEF criteria, which were used to classify any PIM, are comprised of 36 explicit statements, including 21 regarding single drugs and 15 regarding drug–drug combinations (Rognstad *et al.*, 2009). To identify possible DDI, a drug interaction database (Norwegian Medicines Agency, 2014) was used. A 3-point scale is employed to classify the DDI into the following categories of increasing severity: (i) “drug interaction only of academic interest”; (ii) “clinicians need to take precautions”; and (iii) “drugs should not be combined.” The prevalence of PIM and DDI is presented at person level and defined as the percentage of participants who was prescribed at least one PIM or DDI, respectively.

Statistical analysis

The statistical analyses were performed using the software program SPSS, Release 22.0.0.0 (IBM, Inc., Chicago, IL, USA). The chi-squared test (Pearson) was applied for

categorical variables (sex, dementia diagnosis, degree of dementia (CDR-GS), and social status). All the other variables were continuous variables and had a non-parametric distribution according to the Kolmogorov–Smirnov test ($p < 0.05$). The Mann–Whitney U -test was therefore applied. $p < 0.05$ was considered statistically significant. To assess potential variables associated with having PIM or DDI, a univariable logistic regression analysis was performed, followed by a multivariable analysis. All variables were analyzed for multicollinearity, and all were found to have acceptable values (variance inflation factor < 2 and tolerance values > 0.6). Variables from the univariable analysis with a $p < 0.25$ were included in the multivariable analysis. The stepwise backward Likelihood Ratio (LR) method was applied. At each step, the least significant variable was removed manually until only variables with $p < 0.05$ remained in the model.

Results

Study sample

The study sample consisted of 251 patients (42% males), with a median age of 77 years (IQR 71–81). Please see Table 1 for demographic and clinical baseline data of the study sample.

Drug use

In the study sample, 96% used one or more medications. The median number of drugs used per patient was 4 (IQR 2–6, Table 1). A total of 173 patients (69%) used at least one psychotropic drug. Polypharmacy was identified in 113 patients (45%) and psychotropic polypharmacy in seven patients (2.8%). Antipsychotics were used by 19 patients (8%), 12 of them diagnosed with DLB. Both anxiolytics and hypnotics–sedatives were used by 26 patients (10%), whereas 40 patients (16%) used benzodiazepines. Anti-dementia drugs were used by 105 patients (42%), while 81 patients (32%) used antidepressants.

Potentially inappropriate medications

Among the 1110 medications reviewed, 48 PIM were found according to the NORGEF criteria, which were accounted for by 35 patients (14%). Five of the patients (2%) had two or more PIM. Medications relevant to 19 of the 36 NORGEF criteria were identified, the most common being long-acting benzodiazepines

Table 1 Demographic and clinical baseline data of the study sample

	Total sample	Without PIM	With PIM	<i>p</i> -value for PIM ^a	Without DDI	With DDI	<i>p</i> -value for DDI ^a
Number of participants (%)	251 (100)	216 (86)	35 (14)	—	148 (59)	103 (41)	—
Age, years, median (IQR)	77 (71–81)	77 (70–81)	79 (73–82)	0.15	75 (70–81)	78 (74–82)	0.003
Sex							
Male, <i>n</i> (%)	105 (42)	96 (91)	9 (9)	0.04	63 (60)	42 (40)	0.78
Female, <i>n</i> (%)	146 (58)	120 (82)	26 (18)	—	85 (58)	61 (42)	—
Diagnosis							
AD, <i>n</i> (%)	137 (55)	119 (87)	18 (13)	0.90	84 (61)	53 (39)	0.71
DLB, <i>n</i> (%)	78 (31)	66 (65)	12 (15)	—	44 (66)	34 (44)	—
Other forms of dementia, <i>n</i> (%) ^b	36 (14)	31 (66)	5 (14)	—	20 (66)	16 (44)	—
Years of education, median (IQR)	9 (7–11)	9 (7–11)	9 (8–10)	0.65	9 (7–11)	8 (7–11)	0.56
MMSE total score, median (IQR)	24 (22–26)	24 (22–26)	24 (22–26)	0.58	24 (22–26)	24 (22–26)	0.89
CDR score ≤1, <i>n</i> (%) ^c	218 (87)	187 (86)	31 (14)	0.49	129 (59)	89 (41)	0.60
CIRS total score, median (IQR) ^d	6 (4–8)	6 (4–7)	7 (4–8)	0.03	5 (4–7)	7 (5–9)	<0.001
Duration of symptoms, years (IQR) ^e	2 (1–3)	2 (1–3)	2 (1–3)	0.76	2 (1–4)	2 (1–3)	0.71
Number of medication per patient, median (IQR)	4 (2–6)	4 (2–5)	7 (2–6)	<0.001	3 (2–4)	6 (5–8)	<0.001
NPI total (intensity × frequency), median (IQR) ^f	15.5 (5–31)	15 (5–32)	20 (6–33)	0.75	15 (5–34)	16.5 (5–29)	0.83
Living with partner ^g	142 (59)	126 (89)	16 (11)	0.20	86 (61)	56 (39)	0.48

^aDifferences in sex, dementia diagnosis, degree of dementia (CDR), and social status were tested with Pearson's chi-squared test for independence. Differences in age, MMSE score, CIRS total score, duration of symptoms, number of medications, years of education, and NPI were tested with Mann-Whitney *U*-test.

^bOther forms of dementia: Parkinson's disease dementia, vascular dementia, frontotemporal dementia and alcoholic dementia.

^cCDR: Missing data for 17 cases. Degree of dementia: 0 = no dementia, 0.5 = mild cognitive impairment, 1 = mild dementia, 2 = moderate severe dementia, and 3 = severe dementia.

^dCIRS (range 0–52): missing data for 18 cases.

^eDuration of symptoms before diagnosis: missing data for 12 cases.

^fNPI (range 0–144): missing data for 21 cases.

^gSocial status: missing data for nine cases.

PIM, potentially inappropriate medications; DDI, drug-drug interactions; IQR, interquartile range; *n*, number of participants; AD, Alzheimer's disease; DLB, dementia with Lewy bodies; MMSE, mini-mental state examination; CDR, clinical dementia rating; CIRS, Cumulative Illness Rating Scale; NPI, neuropsychiatric inventory.

($n=8$, 3.2%), combinations with warfarin ($n=7$, 2.8%), combinations with non-steroidal anti-inflammatory drugs ($n=7$, 2.8%), and psychotropic polypharmacy ($n=7$, 2.8%). Table 2 gives an overview of all the PIM. The patients with PIM were more often women ($p=0.037$), had higher burden of comorbid diseases ($p=0.027$), and used more medications ($p<0.001$) compared with those who did not have PIM (Table 1).

Drug–drug interactions

A total of 191 DDI were identified, accounted for by 103 patients (41%). Two or more DDI were identified in 36 patients (6%) with eight being the maximum number of DDI. Four patients (1.6%) used drugs that “should not be combined” (Table 3). Drug combinations where one should “take precautions” ($n=149$) were used by 90 patients (36%). The three most frequent DDI in this group were “increased risk of bradycardia” (beta blocking agents in combinations with cholinesterase inhibitors, $n=23$, 9.2%), “increased risk of gastrointestinal bleeding” (acetylsalicylic acid in combination with selective serotonin reuptake inhibitors, $n=18$, 7.2%), and impaired absorption of oral bisphosphonates (bisphosphonates in combination with calcium or drugs combined with calcium, $n=11$, 4.4%). Unfavorable drug combinations of “academic interest” ($n=38$) were used by 32 patients (13%). The patients with DDI were older ($p=0.003$), had a higher burden of comorbid diseases ($p<0.001$), and used more medications ($p<0.001$, Table 1).

In both the univariable and in the multivariable analysis of PIM (Table 4), female sex and number of medications were significantly associated with having PIM. In the univariable analysis of DDI, age at baseline, CIRS scores, and number of medications (Table 4) were significantly associated with having DDI. In the multivariable analysis, only number of medications remained significant.

Discussion

Main findings

To our knowledge, this is one of the first studies investigating the prevalence and potential variables of having PIM and DDI in home-dwelling patients with mild dementia. A total of 45% of the study sample had polypharmacy, and although 2/3 of them used psychotropic drugs, only seven patients (2.8%) had

Table 2 Potentially inappropriate medications according to the NORGE criteria identified at baseline

	The NORGE criteria	Number of PIM	Total ($n=251$, %)
1	Amitriptyline	—	—
2	Doxepin	—	—
3	Clomipramine	1	0.4
4	Trimipramine	1	0.4
5	Chlorpromazine ^a	—	—
6	Chlorprothixene	—	—
7	Levomopromazine	2	0.8
8	Prochlorperazine	2	0.8
9	Diazepam	4	1.6
10	Nitrazepam	3	1.2
11	Flunitrazepam	1	0.4
12	Oxazepam > 30 mg/24 t	2	0.8
13	Zopiclone > 7.5 mg/24 t	1	0.4
14	Carisoprodol ^a	—	—
15	Dextropropoxyphene	—	—
16	Theophylline	1	0.4
17	Sotalol	4	1.6
18	Dexchlorfeniramine	—	—
19	Promethazine	—	—
20	Hydroxyzine	—	—
21	Alimemazine	2	0.8
22	Warfarin + NSAID	2	0.8
23	Warfarin + ofloxacin or ciprofloxacin	—	—
24	Warfarin + erythromycin or clarithromycin	—	—
25	Warfarin + SSRI	5	2.0
26	NSAID/Cox-2 selective inhibitor + ACE inhibitor/ARB	2	0.8
27	NSAID + diuretics	2	0.8
28	NSAID + glucocorticoid	—	—
29	NSAID + SSRI	3	1.2
30	Erythromycin or clarithromycin + statins	—	—
31	ACE inhibitor + Potassium or potassium saving diuretics	3	1.2
32	Fluoxetine or fluvoxamine + TCA	—	—
33	Beta blocker + cardio selective calcium antagonist	—	—
34	Diltiazem + lovastatin or simvastatin	—	—
35	Erythromycin or clarithromycin + carbamazepine	—	—
36	Concomitant prescription of three or more drugs within the groups centrally acting analgesics, antipsychotic agents, antidepressants, and/or benzodiazepines	7	2.8
	Total number of potentially inappropriate medications	48	19

^aWithdrawn from the Norwegian market, but can be obtained upon registration exemption.

PIM, potentially inappropriate medications; NSAID, non-steroidal anti-inflammatory drugs; ACE inhibitor, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

psychotropic polypharmacy. The frequency of PIM and serious DDI was also low.

Table 3 Drug–drug interactions identified at baseline in the category “drugs that should not be combined”

Drug 1		Drug 2		Possible clinical consequence
ATC	Substance	ATC	Substance	
N03A F01 B01AA03	Carbamazepine Warfarin	N08C A05 M01A B	Nifedipine Acetic acid derivatives and related substances Escitalopram	Impaired concentration of nifedipine Increased risk of bleeding due to combined inhibition of platelet aggregation and coagulation factors
N05A D01	Haloperidol	N06A B10		Possible increased risk of severe arrhythmias due to QT-prolongation
N06D X02	<i>Ginkgo biloba</i>	B01A A03	Warfarin	Possible increased risk of bleeding

Most of the psychotropic drug used was related to cholinesterase inhibitors, which is an evidence-based treatment for some types of dementia (O'Brien and Burns, 2011). The relatively low percentage (42%) found to be using cholinesterase inhibitors is most likely related to the study design. Many of the patients received the dementia diagnosis in the outpatient clinic on the day of inclusion; thus, the use of these medications was probably not registered at baseline. In the present study, the use of antipsychotics, anxiolytics, and hypnotics–sedatives was low, while the use of antidepressants was high compared with other studies (Hartikainen *et al.*, 2003; Wergeland *et al.*, 2014).

The relatively prevalent use of antidepressants (32%) is likely associated with the high frequency of depression in dementia (Enache *et al.*, 2011). However, recent evidence suggests limited benefits of antidepressants in people with dementia (Banerjee *et al.*, 2011) and an increased risk of falling (Kuschel *et al.*, 2014) and other potentially serious side-effects (Coupland *et al.*, 2011). On the other hand, other studies found that withdrawal of antidepressants in nursing homes leads to worsening of depression in some patients (Bergh *et al.*, 2012) and that treatment with antidepressants decreased agitation among patients having Alzheimer's disease (Porsteinsson *et al.*, 2014). Thus, more research exploring the benefit and harm of antidepressants in people with dementia is warranted.

The patients included in the present study had mild dementia and a relatively low burden of psychiatric and other comorbidities, which may explain the rather infrequent use of the other psychotropic drugs (antipsychotics, hypnotics–sedatives, and anxiolytics). Nevertheless, it is interesting that although the patients are in the early stage of their dementia disease, patients with DLB are those using antipsychotics most frequently. This might be related to the more severe psychotic and other neuropsychiatric symptoms found in

patients with DLB compared with people with other dementia diagnoses (Bjoerke-Bertheussen *et al.*, 2012). This is noteworthy given the high risk for severe adverse reactions related to antipsychotics, which is a key diagnostic feature of DLB (McKeith *et al.*, 2005).

Potentially inappropriate medications

In a review, the prevalence of PIM ranged between 3% and 40% in the older people (Opondo *et al.*, 2012). This review excluded studies including patients with dementia, and the few studies reporting the prevalence of PIM in people with dementia report the prevalence of PIM to vary between 20% and 46%. Thus, the finding of 14% with PIM is in the lower end. Still, these studies cannot be readily compared with the present study because they either use different screening tools, have a mixed study sample where the patients are in different stages of their disease, or the study is conducted in a different setting (Lau *et al.*, 2010; Montastruc *et al.*, 2013; Parsons *et al.*, 2012).

In previous studies, the use of long-acting benzodiazepines was one of the most prevalent PIM (Aparasu and Mort, 2000; Montastruc *et al.*, 2013), which was also true for the present study where seven of 40 patients taking benzodiazepines used long-acting benzodiazepines. Side-effects associated with benzodiazepines include sedation, falls, and cognitive impairment, and the use should be short-term, but often remains chronic (Llorente *et al.*, 2000). Furthermore, a recent systematic review concluded that there is still limited evidence to recommend use of benzodiazepines in people with Alzheimer's disease (Defrancesco *et al.*, 2015). In addition, there is some indication that the use of benzodiazepines increases the risk of developing dementia, although it is debated whether this observation might be due to the

Table 4 Logistic regression analysis: association between potential variables and the risk of having potentially inappropriate medications or drug-drug interactions

Variable	N	Potentially inappropriate medications				Drug-drug interactions			
		Univariable model		Final model		Univariable model		Final model	
		OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95%CI)	p-value	OR (95%CI)	p-value
Age at baseline	251	1.04 (0.99–1.09)	0.15			1.06 (1.02–1.10)	0.001		
Sex									
Male	251	Ref.				Ref.			
Female		2.31 (1.03–5.17)	0.03	2.70 (1.11–6.53)	0.021	1.08 (0.65–1.79)	0.78		
Diagnosis									
AD	251	Ref.	0.90			Ref.	0.71		
DLB		1.20 (0.55–2.65)				1.23 (0.68–2.15)			
Other forms of dementia		1.07 (0.37–3.10)				1.27 (0.60–2.66)			
Years of education	245	1.02 (0.90–1.15)	0.79			0.995 (0.91–1.07)	0.92		
MMSE total score	251	1.04 (0.91–1.20)	0.55			0.996 (0.90–1.10)	0.93		
Degree of dementia (CDR-GS score)									
Very mild dementia	234	Ref.	0.62			Ref.	0.65		
Mild dementia		0.99 (0.46–2.14)				1.18 (0.68–2.05)			
Moderate dementia		0.40 (0.05–3.29)				1.60 (0.55–4.65)			
Comorbidity (CIRS total score)	233	1.14 (1.00–1.31)	0.05			1.24 (1.12–1.38)	<0.001		
Duration of symptoms	239	1.01 (0.86–1.20)	0.89			1.02 (0.91–1.15)	0.70		
Number of medication per patient	251	1.50 (1.29–1.73)	<0.001	1.51 (1.30–1.75)	<0.001	2.06 (1.71–2.48)	<0.001	2.0 (1.7–2.5)	<0.001
NPI total (intensity × frequency)	230	1.00 (0.98–1.03)	0.71			0.998 (0.98–1.01)	0.79		
Living alone	242	1.61 (0.77–3.37)	0.20			1.21 (0.72–2.03)	0.48		

PIM, potentially inappropriate medications; DDI, drug-drug interactions; N, number of participants; OR, odds ratio; CI, confidence interval; AD, Alzheimer's disease; DLB, dementia with Lewy bodies; Other forms of dementia, Parkinson's disease with dementia, frontotemporal dementia, and alcoholic dementia; Ref., reference (OR = 1.0); MMSE, mini-mental state examination (0–30); CIRS, Cumulative Illness Rating Scale (0–52); CDR, Clinical Dementia Rating Scale (0–3); NPI, neuropsychiatric inventory (0–144).

benzodiazepines being used to treat prodromal symptoms of dementia (Zhong *et al.*, 2014).

In studies using the NORGEP criteria, the prevalence of PIM ranged between 18% and 35% in the older people (Bakken *et al.*, 2012; Brekke *et al.*, 2008; Nyborg *et al.*, 2012). These studies were performed both in primary and secondary care, which might explain the differences in prevalence. When comparing the present results with the studies from primary care (Brekke *et al.*, 2008; Nyborg *et al.*, 2012), our patients have few PIM despite the dementia diagnosis. An explanation for this might be the inclusion of younger people in the present study (range 50–92 vs. ≥ 70 years), and therefore, a healthier study sample as comorbidity is known to increase with age.

Drug–drug interactions

Only four patients (1.6%) used drugs that should not be combined. This is in line with a previous nursing home study using the same interaction database. Furthermore, the nursing home study had a greater percentage within the group “clinician should take precautions” (47% compared with 36% in our sample) (Søraas *et al.*, 2014). The difference is most likely due to higher comorbidity in nursing home patients, resulting in higher drug use.

Again, DDI studies are difficult to compare because of differences regarding study sample and setting but most importantly because different drug interaction databases have been used. A drug–drug interaction is either due to a pharmacokinetic interaction or a pharmacodynamic interaction. Not all drug interaction databases assess pharmacodynamic interactions, and different databases also categorize the severity of a DDI differently, which complicates the comparison further.

This study is based on a longitudinal study that began inclusion in 2005. During these years, there has been a focus on reducing the use of psychotropic drugs in people with dementia, especially the use of antipsychotics. Kales *et al.* (2011) found that the use of antipsychotics in people with dementia was reduced after the US Food and Drug Administration warned about increased mortality associated with the use of antipsychotics. Figures from the Norwegian Prescription Database from 2004 until 2013 shows a 32% relative reduction (a 1.6% absolute reduction from 5.1% to 3.5%) in the use of antipsychotics among people aged 65 years and older (Norwegian Institute of Public Health, 2014), which might indicate a change in the prescription pattern.

Strengths and limitations

The strengths of this study include the inclusion of people with mild dementia, the use of a standardized assessment to record clinical and drug use information, and pathological confirmation of the diagnosis in a substantial number of subjects. An additional strength is the use of the NORGEP criteria. When using screening tools to analyze PIM, one should preferably use screening tools developed in the respective area to avoid problems with medication availability, which has been shown to give a large variation in detected PIM (Chang *et al.*, 2011). The NORGEP criteria were therefore considered the most applicable for this study sample because they have been developed in Norway. Even though the NORGEP criteria were developed for patients 70 years or older (Rognstad *et al.*, 2009), we considered them to be applicable to people with dementia, although some in the study sample were younger than 70 years of age. Importantly, the cognitive and functional decline in patients with dementia increases the sensitivity toward certain drugs also used by older people (Lindblad *et al.*, 2006). Several methods have been used to report the comorbidity in previous studies. Some studies use number of drugs as a proxy for comorbidity (Montastruc *et al.*, 2013), while other calculates the number of diseases (Andersen *et al.*, 2011) or reports self-rated health (Lechevallier-Michel *et al.*, 2005). A strength of the present study is the use of CIRS, which is characterized as a reliable and valid tool to assess comorbidity (de Groot *et al.*, 2003) and is found to correlate well with autopsy results (Conwell *et al.*, 1993). The NORGEP criteria do not assess comorbidity, which is a limitation. This might reduce the sensitivity of the screening tool and lead to reduced number of detected PIM compared with other screening tools like screening tool of older persons’ potentially inappropriate prescriptions (O’Mahony *et al.*, 2015) and Beers criteria (The American Geriatrics Society, 2012). Another limitation is that the patients’ drug history does not include information about the duration of the drug treatment and potential changes in drug treatment after baseline, a limitation which is common for this kind of studies. Nor is there any information on OTC drugs and whether the patients are compliant. Many OTC drugs and herbal medicine may lead to PIM and can also lead to serious DDI. In relation to PIM, only non-steroidal anti-inflammatory drugs from the NORGEP criteria are available as an OTC drug; therefore, the impact is most likely minimal. Additionally, this study includes patients recruited from hospital-based outpatient clinics, which may have led

to a selection bias and therefore might not be representative for the general population with mild dementia. This potential bias could lead to an underestimation of the true prevalence of PIM and DDI, but there is also a possibility for overestimating the true prevalence of PIM and DDI if patients with more severe and complex diseases and comorbidity are overrepresented. Another limitation is the change in inclusion after 2007 where only patients with DLB or Parkinson's disease with dementia were included. Although the same recruitment sites and other selection criteria were similar, there is a possibility of creating two sample groups. Furthermore, very few people were found to have PIM, and there is a possibility that this may have resulted in our study not being adequately powered to pick up other predicting factors.

Conclusion

In the present study, few patients with mild dementia were found to have PIM and severe DDI, indicating that the quality of prescribing was acceptable. However, psychotropic drug use was common even in home-dwelling people with mild dementia despite limited evidence of benefit. More knowledge is needed about the potential risks associated with psychotropic drug use and PIM and DDI in people with mild dementia. Such knowledge has the potential to improve care, which could benefit quality of life and function for people with dementia, enabling them to live independently longer.

Conflict of Interest

None declared.

Key points

- People recently diagnosed with dementia were frequently prescribed with psychotropic drugs.
- Potentially inappropriate medications defined by the NORGE criteria were seldom prescribed to patients with mild dementia.

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Authors Contributions

Study design and conduct of data analysis and drafting the manuscript were performed by Ragnhild Oesterhus. Advice on data analysis and interpretation, critical revision of manuscript, and approval of the final version were performed by Hogne Soennesyn, Dag Aarsland, Svein R. Kjosavik, Arvid Rongve, and Geir Selbaek.

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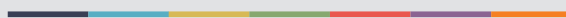
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