Use of acetylcholinesterase inhibitors: length of treatment, sex differences and comedication with focus on psychotropics, analgesics and heart rate related drugs

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LIST OF PAPERS

Paper 1
Efjestad AS, Molden E, Øksengård AR
Pharmacist-initiated management of antagonistic interactions between anticholinergic drugs and acetyl cholinesterase inhibitors in individuals with dementia.
JAGS, September 2013 Vol 63 no. 9; 1624-25.

Paper 2
Sverdrup Efjestad A, Ihle-Hansen H, Hjellvik V, Salvesen Blix H.
Comedication and treatment length in users of acetylcholinesterase inhibitors.
Dement Geriatr Cogn Disord Extra 2017; 7:30-40.

Paper 3
Drug use before and after initiating treatment with acetylcholinesterase inhibitors.

Paper 4
Sex differences in psychotropic and analgesic drug use before and after initiating treatment with acetylcholinesterase inhibitors.
PLoSOne 2021;16 (9):e0243804; DOI:10.1371/journal.pone.0243804

Paper 5
Efjestad AS, Ihle-Hansen H, Hjellvik V, Engedal K, Salvesen Blix H,
Use of drugs with risk of heart rate-related problems is common in Norwegian dementia patients treated with acetylcholinesterase inhibitors. A prevalence study based on the Norwegian Prescription Database.
SUMMARY

The goal of this thesis was to gain more knowledge about length of treatment, sex differences and comedication in patients treated with acetylcholinesterase inhibitors (AChEIs). The present work was mainly performed using data from the Norwegian Prescription Database.

**Paper 1 and 2** showed that a large proportion of the patients treated with AChEIs were co-medicated with anticholinergic agents that may limit or counteract the clinical effect. Study 1 showed that a pharmacist-geriatrician cooperation could be effective to reduce the Anticholinergic Drug Scale (ADS)-score in order to avoid this kind of irrational combination therapy in patients with dementia. Study 2 showed that co-prescribing with potentially unfavourable medications was common, and that patients being prescribed antipsychotics were more likely to stop AChEI treatment. In addition, patients with low ADS scores continued treatment longer.

**Paper 3** showed that the use of antidepressants and antipsychotics increased before and after initiation of AChEIs, and the results may indicate that behavioural symptoms occur in an early- or preclinical phase of Alzheimer’s disease (AD). The prescription pattern of analgesics with a low use of opioids may indicate an undertreatment of pain in people with AD.

In **paper 4**, female sex showed to have a significant influence on the prescriptions of psychotropics and analgesics in AD patients in a pre-dementia and dementia stage. The exception was for antipsychotics, which men used more than women. The prescription pattern showed a higher extent of polypharmacy of psychotropics and/or opioids in women than in men. The total prescription pattern of analgesics indicated an undertreatment of pain in pre-dementia and dementia stages, most pronounced in men.

In **paper 5**, we reported on the prevalence of prescriptions of drugs commonly prescribed for heart rate control, and drugs with a known risk of Torsades de Pointes (TdP), before and after initiating treatment with AChEIs. Further, we studied changes in use of combinations of drugs with a known risk of TdP and drugs with a known heart rate lowering effect, before and after initiating treatment with AChEIs. We found that a large proportion (~44%) of patients treated with AChEIs were prescribed drugs that could cause bradycardic and prolonged time from the start of the Q wave to the end of the T wave (QT interval). Up to 6% of the study population were prescribed both betablockers and citalopram/citalopram in addition to AChEIs, a
combination that increased over the follow-up period and was observed most frequently in women in the oldest age group of 81-88 years.

Taken together, results from the studies show that prescribers should in particular be aware of the potential drug-drug interactions and ADRs, which may cause discontinuation of AChEI treatment and accelerate cognitive decline, for example caused by drugs with anticholinergic properties and antipsychotics in general, except for short time use of antipsychotics indicated for the use of BPSD. An interdisciplinary collaboration and involvement of a clinical pharmacist is of importance, for instance with regard to better selecting drugs with minor anticholinergic effects. Inappropriate drugs with known ADRs should be avoided in patients in a predementia or dementia stage, especially in the oldest age groups, due to increased effect of psychotropics and other drugs in the elderly. In this respect, pain should be detected and treated as early as possible, to ensure that psychotropic medication is not prescribed for possible wrong indications. It is advisable to focus on women being more susceptible to ADRs of drugs than men, and the fact that polypharmacy is more frequently observed in women. Because of the cholinergic effects of AChEIs, co-prescribing of drugs with an effect of the heart rate, or with known prolongation of the QT interval should be monitored closely, to avoid further pharmacodynamic interactions.
Målet med denne avhandlingen var å få mer kunnskap om behandlingslengde, kjønnssforskjeller og komedisinering med fokus på psykotrope legemidler, analgetika og legemidler som påvirker hjerterytmen hos pasienter som ble behandlet med antikolinesteraser. Prosjektet som førte til avhandlingen ble i all hovedsak utført med data fra Reseptregisteret.

**Studie 1 og 2** viste at en stor andel av pasientene behandlet med antikolinesteraser samtidig fikk legemidler med antikolinegare egenskaper som kan begrense eller motvirke den kliniske effekten. Studie 1 viste at et samarbeid mellom lege og farmasøyt var effektivt for å redusere Antikolinerg Legemiddel Skala skår (ADS-skår) og for å unngå uhensiktsmessig legemiddelbehandling hos pasienter med Alzheimers demens (AD). Studie 2 viste at samtidig forskrivning med potensielt uhensiktsmessige legemidler var vanlig, og at pasienter som ble forskrevet antipsykotika hadde større sannsynlighet for å slutte med antikolinesterasen. I tillegg viste det seg at pasienter med lav ADS skår fortsatte behandlingen lenger.

**Studie 3** viste at økt bruk av antidepressiva og antipsykotika før og etter oppstart av antikolinesterase forekom, og at resultatene kan tyde på at atferdssymptomer oppstår i en tidlig- eller preklinisk fase av AD. Forskrivningsmønsteret av analgetika med lavt forbruk av opioider kan indikere en underbehandling av smerte hos pasienter med AD.

**I studie 4** viste det seg at kvinner med AD ble forskrevet mer psykotrope legemidler og analgetika i pre-demens- og demensstadium enn menn. Unntaket var for antipsykotika som menn brukte mer enn kvinner. Reseptmønsteret viste en høyere grad av polyfarmasi av psykotrope legemidler og/eller opioider hos kvinner enn hos menn. Det totale forskrivningsmønsteret av analgetika indikerte en underbehandling av smerte i pre-demens og demensstadium, mest uttalt hos menn.

**I studie 5** studerte vi prevalens av forskrivning av legemidler som ofte benyttes for hjertefrekvenskontroll, og legemidler med kjent risiko for Torsades de Pointes (TdP), fra fire år før og til to år etter initiering av behandling med antikolinesteraser. Videre studerte vi endringer i bruk av kombinasjon av legemidler med kjent risiko for TdP og legemidler med kjent hjertefrekvensreduserende effekt, før og etter initiering av behandling med antikolinesterase. Vi fant at en stor andel av pasientene (~44%) som ble behandlet med antikolinesteraser samtidig fikk legemidler som kan forårsake bradykardi eller forlenget tid fra starten av Q-takken til slutten av T-bølgen (QT intervall). Opptil 6% av
studiepopulasjonen fikk forskret både betablokkere og citalopram/escitalopram i tillegg til antikolinesterase, en kombinasjon som økte i løpet av oppfølgingsperioden og som ble observer hyppigst hos kvinner i aldersgruppen 81-88 år.

Samlet sett viser resultater fra studiene at forskrivere bør være spesielt oppmerksomme på potensielle legemiddelinteraksjoner og bivirkninger som kan forårsake seponering av behandling med antikolinesterase og bidra til kognitiv reduksjon, for eksempel forårsaket av legemidler med antikolinerge egenskaper og antipsykotika generelt, med unntak av korttidsbruk av antipsykotika indisert for bruk ved BPSD. Et tverrfaglig samarbeid og involvering av en klinisk farmasøyt er viktig for bedre ivaretakelse av pasienter, for eksempel med tanke på valg av legemidler med mindre antikolinerge effekter. Uhensiktsmessige legemidler med kjente bivirkninger bør unngås hos pasienter i et predemens- eller demensstadium, spesielt i de eldste aldersgruppene, på grunn av økt effekt av psykofarmaka og andre legemidler hos eldre. I denne forbindelse bør smerte oppdages og behandles så tidlig som mulig, for å sikre at psykotrope legemidler ikke foreskrives på feil grunnlag. Det anbefales å rette fokus mot det faktum at kvinner er mer utsatt for legemiddelbivirkninger enn menn, og at polyfarmasi forekommer hyppigere hos kvinner. På grunn av de kolinerge effektene av antikolinesteraser bør samtidig forskrivning av legemidler med effekt på hjertefrekvensen, eller med kjent forlengende effekt av QT intervallet overvåkes nøyde, for å unngå forsterkede farmakodynamiske interaksjoner.
ABBREVIATIONS

ACh    Acetylcholine
AChE   Acetylcholinesterase
AChEI  Acetylcholinesterase inhibitor
AD     Alzheimer’s dementia
ADL    Activities of daily living
ADR    Adverse drug reaction
ADS    Anticholinergic drug scale
Aβ     amyloid β
APOE4  Apolipoprotein E (Apolipoprotein E genotype e4 allele)
ATC    Anatomical Therapeutical Chemical
BBB    Blood-brain barrier
BPSD   Behavioural and Psychological Symptoms of Dementia
BuChE  Butyryl cholinesterase
BZD    Benzodiazepine
CI     Confidence interval
CNS    Central nervous system
COX-2  Cyclooxygenase-2
CVD    Cerebrovascular disease
CYP2D6 Cytochrome P450 2D6
CYP2C19 Cytochrome P450 2C19
CYP3A4 Cytochrome P450 3A4
DDD    Defined daily dose
DLB    Dementia with Lewy bodies
DSM    Diagnostic and Statistical Manual of Mental Disorders
ECG    Electrocardiogram
EMA    European Medicines Agency
EOAD   Early onset AD
FDA    Food and Drug Administration
FDG-PET Fluorodeoxyglucose-positron emission tomography
FTD    Frontotemporal dementia
GABA   Gamma-aminobutyric acid
ICD  International Classification of Diseases and Related Health Problems
LBD  Lewy Body Dementia
LD   Logopenic Dementia
LOAD Late onset AD
MCI  Mild cognitive impairment
MMSE Mini Mental Status Evaluation
NFT  Neurofibrillary tangles
NICE National Institute for Health and Care Excellence
NMDA N-methyl-D-aspartate
NorPD Norwegian Prescription Database
NNH  Number Needed to Harm
NNT  Number Needed to Treat
NorCog Norwegian Register of Persons assessed for Cognitive Symptoms
PCC  Person Centered Care
PD   Parkinson´s disease
PDD  Parkinson’s disease dementia
P-gp  P-glycoprotein
PM   Poor metabolizer
PPP  Psychotropic polypharmacy
PR   Prevalence ratio
p-tau Phosphorylated tau
qEEG Quantitative electroencephalography
QT interval Time between the Q-tag and the T-tag in an electrocardiogram
SAA  Serum Anticholinergic Activity
SCI  Subjective Cognitive Impairment
SSRI Selective Serotonin Receptor Inhibitor
TCA  Tricyclic Antidepressant Agent
TdP  Torsades de pointes
USD  Urinary Spasmolytic Drug
VaD  Vascular dementia
Vd   Volume of distribution
1 INTRODUCTION

This thesis concerns findings and discussions of length of treatment, sex differences and comedication with focus on psychotropics, analgesics and heart rate related drugs in patients treated with acetylcholinesterase inhibitors (AChEIs). As the main indication for use of AChEIs is to treat Alzheimer’s dementia (AD) in an early stage of the disease, the start of AChEI treatment could be considered as a diagnosis of AD. Thus, we will use “start of AChEI treatment” as an expression for a diagnosis of AD.

As a clinical pharmacist for several years at Bærum hospital, Medical Department, I was included in clinical work in the geriatric ward with evaluation of comedication, polypharmacy and drug interactions. The leaders at the geriatric ward at the Medical Department provided a supportive scientific and social environment, which inspired me to carry on with a master thesis in clinical pharmacy. Results from the master thesis were further developed and resulted in paper 1 of this doctoral thesis. This experience gave me insight into treatment options of AD, an interesting pharmacological and clinical field, which, unfortunately, only has symptomatic treatment options. Therefore, it is of the utmost importance to choose the right treatment as early as possible to preserve the remaining cognitive capacity as long as possible in this vulnerable patient group. This, combined with my general experience as a pharmacist working with pharmaceutical- and medical quality questions, was a good basis for the present study. Based on this experience, and in contact with the National Institute of Public Health, co-authors and collaborating colleagues, this research project was created. On this background, the thesis aims to increase the knowledge of prescribing of agents with an anticholinergic effect, prescription patterns of drugs commonly used in the treatment of Behavioural and Psychological Symptoms of dementia (BPSD), analgesics and drugs with an effect on the heart rate in a predementia phase and in AChEI treated patients, and sex differences and polypharmacy burden. In addition (not scientific), we wanted with this thesis to shed more light on the role of the pharmacist working in an interdisciplinary team, focusing on drug related problems to improve indications and contraindications of drug treatment of people with AD to avoid adverse effects, bad interactions and inappropriate medications. Further on, we wanted the work to illustrate how collaboration between clinical pharmacists, doctors and a statistician has helped to answer research questions connected to polypharmacy, comorbidity, age and gender differences in persons with dementia. The Norwegian Prescription Database (NorPD) was chosen as a unique source of information of prescription
patterns of different drugs used in the symptomatic treatment of AD, as it gives an opportunity to study prescriptions from a huge number of individuals over time.

In addition to background information on dementia, I will in the first part of the thesis give an overview of the commonly used strategies for symptomatic treatment of AD and BPSD. In addition, I will discuss the following subjects related to patients with AD; anticholinergic burden, prevalence of use of psychotropics, psychotropic polypharmacy, sex differences in drug use, age, factors affecting response to and treatment length of AChEIs and risk of heart rate related adverse effects.

1.1 Background

1.1.1 Indications for therapy with acetylcholinesterase inhibitors

AChEIs are indicated in patients with a mild to moderate degree of AD, and in addition, rivastigmine may be offered to patients with mild to moderate degree of Dementia with Lewy Bodies (DLB) and Parkinson’s disease dementia (PDD). These therapies should be initiated as soon as a dementia diagnosis is made (1). In addition, a meta-analysis shows that AChEIs maintain a stable pattern of improved cognitive function in patients with post stroke cognitive impairment and vascular dementia (VaD) without the increased risk of side effects (2), and some patients with VaD are therefore treated with AChEIs as well, outside indication.

1.1.2 Definition and diagnosis of dementia

According to International Classification of Diseases and Related Health Problems version 10 (ICD-10), which is the classification system used in Norway (3), dementia is a syndrome due to a disease of the brain, usually of a chronic or progressive nature, in which there is disturbance of multiple higher cortical functions, including memory, thinking, orientation, comprehension, calculation, learning capacity, language, and judgement. Consciousness is not affected. The condition must have a duration of at least 6 months (4). The impairments of cognitive function are commonly accompanied, and occasionally preceded by, deterioration in emotional control, social behaviour, or motivation. This syndrome occurs in AD, in cerebrovascular disease, and in other conditions primarily or secondarily affecting the brain (3).
In the ICD-research criteria, patients are further divided into three degrees of severity according to functioning in activities of daily living (ADL) (5). Mild degree of dementia affects the ability to cope in daily life. In moderate degree of dementia, the patient cannot cope in daily life without the help of others, and continuous supervision and care around the clock is required in serious degree of dementia (3).

A diagnosis of dementia syndrome is based on anamnesis of cognitive decline from the patient and a carer during at least six months, cognitive assessments to assess performance on various cognitive domains and measures of dependency in ADL function and change of behaviour. The diagnosis must fulfil standardized criteria. Most used are criteria according to ICD-10 and Diagnostic and Statistical Manual of Mental Disorders V (DSM V) (5, 6). To diagnose etiological diagnosis of dementia, a physical and psychiatric examination is necessary, and according to the official Norwegian guidelines a MR or CT of the brain and blood test are mandatory to exclude disorders that can mimic dementia, but also to come closer an etiologic dementia diagnosis. In cases where the diagnosis is still unclear after this initial examination, fluorodeoxyglucose-positron emission tomography (FDG-PET) and spinal fluid examination of concentration of amyloid β (Aβ) and antibody tau protein may be carried out (1).

For the DSM-V criteria of the dementia syndrome, “major neurocognitive disorder” is the term used for dementia, and the major difference compared to ICD-10 is that impairment in only one cognitive domain (that does not have to include memory) is enough to fulfil the criteria. The requirement of memory impairments in the ICD-10 criteria is probably a weakness, as patients with atypical presentations will not receive a dementia diagnosis in an early phase of the disease (7). The DSM-V further divides mild and major neurocognitive disorders as due either to probable or possible AD, incorporating also genetic mutations in the criteria (6, 7). Social cognition is introduced in the DSM-V criteria as well, as one of the core functional domains that can be affected by a neurocognitive disorder. This concept may be particularly significant in the evaluation of patients with non-ADs, such as Frontotemporal dementia (FTD) (8).

According to the Norwegian National Guideline on Dementia, the basic assessment of suspected dementia workup of persons with suspected symptoms of dementia should be conducted first in general practice. The general practitioner should perform a basic, but thorough examination, including interviews with the patients and relatives, a somatic
examination, blood tests, assessments of delirium, cognitive adverse drug reactions (ADRs), and cognitive function, performing basic cognitive tests, such as the Mini-Mental State Examination (MMSE) test, the clock-drawing test and assessment of BPSD (symptoms like depression are a common differential diagnosis of dementia) (1, 7). Extended assessment of suspected dementia is proposed to be carried out in the specialist health care. Patients should be referred to specialist health care in cases involving younger patients, patients with atypical symptoms or with symptoms difficult to assess, patients with unclear or unusual symptoms, or when there is a clinical suspicion that the symptoms may be due to a rare dementia. The extended cognitive battery may include cognitive tests listed in the test battery for the Norwegian Register of Persons assessed for Cognitive Symptoms (NorCog), as well as other cognitive tests that have not been conducted in the basic examination, in addition to a physical and neurological clinical examination including blood tests. The tests may be unspecific, and if the first phase of the extended examination does not result in a disease-specific dementia diagnosis, a second phase can include a broad neurophysiological examination, functional examinations cerebrospinal fluid analysis and FDG-PET. This is decided on an individual basis (1, 7).

1.1.3 General symptoms of dementia
Dementia is a clinical syndrome that, similarly to Mild cognitive impairment (MCI), has different etiological causes; however, unlike MCI, the causes of dementia lead in most cases to a progressive decline of cognition. Cognitive deficits in memory, language, orientation, judgement and thinking are common in dementia, but will vary depending on the wide range of possible etiological causes, where AD is the most common cause.

In addition to cognitive decline, approximately 90% of people with dementia develop at least one BPSD which represent a heterogeneous group of non-cognitive symptoms and behaviours occurring in persons with dementia, like depression, agitation, psychosis, apathy or irritability over the course of the disease, especially agitation and apathy. Besides, disrupted sleep is common (9, 10).
1.1.4 Classification and symptoms of different forms of dementia

AD is the most common cause of dementia, followed by vascular dementia (VaD) and Lewy body dementia (LBD) (11).

1.1.4.1 Alzheimer’s dementia (AD)

A recent Norwegian prevalence study from 2021 reported that 101,118 persons in Norway had dementia, and 57% of them were diagnosed with AD (12). Most patients with AD are older than 65 years old, but about 2.1% of all AD dementia cases are estimated to be below 65 years of age in Norway (12, 13). The risk of dementia in the age category of 30-65 years in Norway has shown to be 76.3 per 100,000 persons. AD represents 56.9% of the total cases of early onset of Alzheimer’s disease (EOAD), occurring before age 65 (13). AD is a progressive neurodegenerative disorder characterized by three clinical phases: a preclinical phase (Subjective cognitive impairment, SCI, which is not noticed by everyone), a prodromal phase (MCI), and finally the dementia phase (7).

Typical AD (also referred to as amnestic or limbic form) is characterized by the impairment of episodic memory, which is the first and major impairment, in association with other cognitive domains (often visuospatial and executive function) that leads to a loss of functional independence, and the disease course is gradually progressive (14). Language difficulties, emotional changes, apathy, social isolation, mild depressive symptoms, visuospatial problems, and difficulties with orientation in time and space are also common.

Patients with EOAD sometimes present with a non-memory phenotype. Approximately one third of patients with EOAD present atypically, of which apraxia/visuospatial dysfunction is the most common presenting symptom (15, 16). This phenomenon is less common, but still encountered in late-onset AD (LOAD, occurring after age 65) as well (16).

1.1.4.2 Vascular dementia (VaD)

VaD is a common term for dementia where the cause is either due to one or more cerebral infarctions, an injury or disease in the blood vessels of the brain, or a lack of blood supply and hence a lack of oxygen to the brain (3). The ICD-10 criteria for VaD include requirements for both dementia (requiring impaired memory function) and radiological findings of
cerebrovascular disease (CVD) with a relationship in time to the cognitive decline (5). However, CVD and AD are suggested to interact and increase cognitive decline synergistically, while a third possibility is that CVD and AD share a common neuropathological substrate and pathways (7). A mixed presentation of AD and CVD is very common and as high as 75% in autopsy studies of patients > 80 years of age (17).

1.1.4.3 Lewy Body Dementia (LBD): Dementia with Lewy Bodies (DLB) and Parkinson’s Disease with Dementia (PDD)

DLB and PDD are two of the diagnoses in the Lewy Body Dementia (LBD) spectrum of disorders that have in common parkinsonian symptoms and disturbances of cognition, behaviour, sleep and autonomic function (7). The clinical entities of DLB and PDD have overlapping features because both are characterized by progressive cognitive impairment, psychiatric (hallucination and delusion) and behavioural disturbances, and parkinsonian motor symptoms. DLB and PDD are associated with mutation in the gene alpha-synuclein protein, causing alpha synucleopathy and neuronal death (3, 18). The distinguishing feature between DLB and PDD is the timing of dementia onset: In DLB, cognitive impairment precedes, or often co-occurs with parkinsonian motor syndrome, whereas in PDD the motor syndrome precedes cognitive decline (14). PDD is characterized with dementia arising in the setting of well-established idiopathic Parkinson’s disease (PD) (after at least 1 year of motor symptoms). Earlier cognitive impairment relative to parkinsonism denotes DLB. The distinction between these syndromes continues to be an active research question (19). DLB has been diagnosed in 4% of people with dementia in Norway (12). In some other studies it is reported that DLB accounts for as many as a quarter of all diagnosed dementia cases (20). PD affects 1-3% of people over the age of 50 (18). In those with a disease duration of PD of more than 10 years, the prevalence of PDD is 75-90% (21).

1.1.4.4 Frontotemporal dementia (FTD)

FTD is the umbrella term for a group of heterogeneous clinical syndromes resulting from neurodegeneration predominantly within the frontal and anterior temporal lobes, insular cortex, and subcortical structures. Early changes in emotion and behaviour, language, and executive problems are the hallmark features of FTD. These presentations can overlap with
atypical parkinsonian disorders, progressive supranuclear palsy and amyotrophic lateral sclerosis (22). FTD is a common cause of early onset dementia in patients younger than 65, with a prevalence of about 10-15% in all patients with early onset dementia (3). It is typically diagnosed in middle age and has an average age of onset of 56, although it has been reported in patients as early as in their early twenties (14).

Population-based estimates of the prevalence of FTD varies widely among studies. FTD may account for approximately 5% of all dementia cases, which is possibly an inaccurate estimate due to selection or referral bias. FTD is reported to account for an average of 2.7% (range 0-9.1%) of all dementia cases among prevalence studies which included subjects 65 and older, compared to 10.2% (range 2.8-15.7%) in subjects aged less than 65 (22). The prevalence of FTD ranges from 4-15 pr 100 000 before age 65 years in European and US epidemiological studies (23).

We have two main clinical syndromes of FTD, a behavioural variant (bFTD), comprising about 55% of cases, and the language variant (sFTD), comprising about 45%. The language variant is separated in three subgroups with about equally frequent occurrence: primary progressive aphasia (PPA), semantic dementia (SD) (memory for meaning) and logopenic dementia (LD) (3, 23). The underlying pathology of LD is most often AD, and the atrophy usually involves left temporoparietal regions (7).

### 1.1.5 Prevalence of dementia

Morbidity and mortality due to chronic diseases like neurological and mental disorders increase in older adults. Dementia is strongly related to age, with a prevalence in western Europe varying from about 1-2% in the age group 65-69 years to about 25-35% in the age group 85+ (24). AD accounts for a greater proportion and severity of the disease in the higher age groups (25), resulting in about 2/3 of patients with AD being women (24). Worldwide the prevalence of dementia is estimated to increase from about 55 today to 140 million in 2050, and there are nearly 10 million new cases every year (26).

The number of persons suffering from dementia in Norway, about 101.000, is expected to increase to about 237.000 in 2050 (12). The standardized prevalence of dementia of individuals aged ≥70 in Norway is 14.6%. There is a steady increase in dementia prevalence across age groups with nearly a doubling every five years, from 5.6% in the youngest age
group of 70-74 years, to 48.1% in the oldest group of 90+ years (12). An increasing reporting of cases is seen due to the increased number of older people (24, 27).

Almost every fifth person will develop dementia during their lifetime, and about 2-5% of patients developing dementia will get the disease before the age of 65 years (28).

1.1.6 Costs of dementia care

In Norway, there are good estimates for the incidence of dementia in nursing homes and among service recipients living at home. Just over 80% of those who have a long-term place in a nursing home have dementia, and 40% of those who are over 70 and receive home services have dementia. By combining these figures, it was estimated that there were about 71,000 people with dementia among home care recipients and nursing home residents in 2015 (1). Estimates show that a person with dementia costs the Norwegian society an average of NOK 362,800 per year in 2013 NOK (29). The total health and care costs associated with dementia are approximately NOK 28 billion per year (1). In Norway, costs are not estimated for relatives' help. Ninety percent of people with dementia receive help from relatives. About half of the relatives in a sample were in income-generating work. Of them, between 20 and 50% stated that they lose working hours due to care and supervision of the patient, but less than 1% of the relatives stopped working to care for the patient (29).

1.1.7 Caregiver burden

The range of behavioural disturbances is an important risk factor for increasing caregiver burden and psychological distress. BPSD is a strong predictor for institutionalisation of patients with dementia (30). Family caregivers of people with dementia have been found to be significantly more stressed than non-dementia caregivers and to suffer more serious depressive symptoms and physical problems such as cardiovascular diseases, especially hypertension (31). An overall prevalence rates of 34% and 44%, respectively, of elevated depressive- and anxiety symptoms have been reported in family caregivers of people with dementia (32). Clinical characteristics of patients (including BPSD and overall health), level of services, and caregiver’s sex (women) appear to be the predictors of caregiver burden. Severity of BPSD in the patients are found to be most predictive of caregiver burden (31). Women typically provide more care, and are more likely to report burden than men (33).
Nonpharmacological interventions should continue to be used as initial treatments for BPSD where these are available, also taking into consideration patient and caregivers priorities (34).

1.1.8 Risk factors of dementia

Little is known about the cause of AD and no curative treatments are available. Growing evidence points to a multifactorial origin of disease, implicating age, genetics, inflammation, oxidative stress and lifestyle, among others. Elimination of the seven most important risk factors could possibly lead to a 30% reduction in dementia incidence (35). Increasing evidence supports that many lifestyle-related and vascular risk factors are found, including diabetes, hypertension, obesity, physical and mental inactivity, depression and alcohol consumption, smoking, low educational level, and inappropriate diet. Cognitive reserve is thought to be built through education and a social and active life. Hearing loss is recently included as a risk factor as well, derived from a new review and meta-analysis (36). These findings show both a huge potential of risk-factor reduction, and the need for other therapeutic strategies for the remaining 70% of causes (35).

Aging of the brain is found to be the strongest risk for development of dementia. In the studies that report association between older age and rapid cognitive decline, comorbid vascular disease was suggested as the cause (7). As the reserve capacity of the brain decreases with increasing age, the vulnerability to AD also increases (3).

In addition to age, apolipoprotein E genotype e4 allele (APOE4), and family history of dementia are nonmodifiable risk factors for dementia. APOE4 has several effects on AD and is the major genetic risk factor for AD. It interferes with Aβ clearance from the brain and is also processed into neurotoxic fragments. There are three different forms (alleles) of APOE: E2, E3 and E4. Most people have E3 and fewest E2 (3). Lifetime risk for AD is more than 50% for APOE4 homozygotes and 20-30% for APOE4 heterozygotes, compared with 11% for men and 14% for women overall, irrespective of APOE genotype (35). Less than 1% of all patients with AD have a dominant genetic form (mutation on chromosome nos. 1, 14 or 21) (37).

Multiple medical comorbid diseases are common in persons with dementia (38) and the most common pre-existing comorbidities, such as hypertension and cardiovascular disease, are at the same time risk factors of dementia (39). Reducing cardiovascular risk factors to decrease
the incidence of dementia applies to both sexes (40). Several reports in the literature suggest that cardiovascular risk factors predispose to AD and VaD. One association between a high level of cholesterol and diabetes, and dementia might be related to damage of the blood vessels of the brain with subcortical vascular dementia as a result (3). The associations of hypertension, increased cholesterol and obesity with AD are complex. Whereas hypertension, increased cholesterol, and obesity in midlife increase the risk for later onset of dementia, blood pressure levels, cholesterol and body mass index levels decrease progressively before disease onset. Hence, persons with dementia have lower blood pressure levels, cholesterol and body mass values than other persons (41). The increased risk for AD in smokers is especially relevant for individuals having APOE2 or APOE3 (not E4) (3).

Concerning depression and AD, one theory is that the hippocampus becomes vulnerable in serious depression, because a long lasting period of depression could activate an inflammatory process which in turn could destroy cells of the hippocampus (3).

There is an increased risk of developing dementia among those with MCI, with 10-15% converting to dementia per year compared with 1-2% of healthy controls. Persons with MCI have a level of cognitive impairment beyond what is expected for their age and educational level, but they do not fulfil the diagnostic criteria for dementia. Both modifiable and non-modifiable risk factors, such as comorbid diabetes mellitus, metabolic syndrome, low folate level, depression and neuropsychiatric symptoms, and increasing age have been found to predict MCI conversion to dementia (7).

Quantitative electroencephalography (qEEG) has shown to be helpful in identifying patients with subjective cognitive decline and MCI that have a high risk of converting to dementia over a 5-year period. In a recent study, more than 60% of the MCI patients converted to AD through a mean observation period of 7 years (42).

1.1.9 AD – pathology and neurochemistry

Histopathologically, AD is characterized by extracellular amyloid plaque deposition and intracellular neurofibrillary tangles (NFT) in the hippocampal and cortical regions of the brain. The extracellular amyloid plaques consist of accumulated, misfolded and aggregated Aβ. The intracellular NFT consists of phosphorylated tau protein (phosphor-tau, p-tau) which are distributed in a typical pattern across different brain regions (43-45). Research since the
discoveries of Aβ and tau pathology has provided detailed information about molecular pathogenetic events. Toxic plaques are the earliest manifestation of disease, a statement supported by evidence of Aβ up to 20 years prior to the onset of symptoms (46). The past 30 years of AD research have produced substantial evidence of the Aβ hypothesis of AD, postulating that accumulation of abnormally folded Aβ is the primary factor in triggering a cascade that causes tau pathology, resulting in neurotoxicity, impaired synaptic function and clinical symptoms. This cascade is related to neurodegenerative processes in patients’ brains, and gives evidence for complexity and multicausality of dementia (35, 47) and subsequent neurodegeneration (48).

In AD, damage in the brain influences the production and transmission of various neurotransmitters. These neurotransmitters are synthesized from amino acids and transmit signals across the synapse and neuromuscular junctions. Neurotransmitters with a known role in AD pathogenesis include acetylcholine (ACh), which is synthesized from serine; dopamine, from L-phenyl alanine/L-tyrosine; gamma-aminobutyric acid (GABA), from glutamate; serotonin, from L-tryptophane; histamine, from L-histidine; and N-methyl-D-aspartate (NMDA) from D-aspartic acid and arginine (49).

Cholinergic neurons, such as ACh-producing neurons, are mainly involved in the pathogenesis of AD. ACh is mainly synthesized from the nucleus basalis of Meynert, and damage of the nucleus basalis of Meynert will lead to loss of ACh (3). It is present in the neuromuscular junctions, brain (Figure 1), spinal cord, in the autonomous nervous system, such as the ganglia and postganglionic terminal buttons of the parasympathetic nervous system. ACh plays an important role in learning and memory as the cortex originates from the basal forebrain and also regulates cortical structures, cerebral blood dynamics, and the wake-sleep cycle. Although much research has been done on ACh in AD pathogenesis, the precise molecular links are not well understood (50). However, reduced cognition and change in behaviour may be a direct result of the loss of ACh (51). Acetylcholinesterase (AChE) rapidly inactivate ACh in the synaptic cleft (52) (Figure 2). In AD, M1 muscarinergic proteins have a reduced binding to G-proteins, and the number of presynaptic M2 muscarinergic receptors is reduced. Less ACh is available in the synaptic cleft (53). Thus, to stimulate cholinergic transmission, AChEIs have been developed as symptomatic treatment in patients with mild to moderate degree of AD. The effect of AChEIs in the brain is through the relative increase of ACh, a hypothesized mechanism for improvements in cognition (54).
Figure 1. Acetylcholine pathways in the brain

Figure 2. Illustration of a normal cholinergic synapse

Abbreviations in figure 2: acetylcholine (ACh), acetylcholinesterase (AChE)
1.2 Symptomatic treatment of AD

1.2.1 Treatment with acetylcholinesterase inhibitors (AChEIs)

The available drugs for symptomatic treatment of AD are predominantly AChEIs, however, the efficacy of these drugs is limited, and they are not able to inhibit progression of the disease (48). Three AChEIs are currently available for the symptomatic treatment of mild to moderately severe AD in Norway, i.e. donepezil, rivastigmine and galantamine (51). All three cause a general increase of ACh in all cells in the body using ACh as a transmitter substance. Donepezil is a reversible AChEI that is highly selective for AChE in the central nervous system (CNS). Unlike rivastigmine and galantamine, it has a long half-life, approximately 70 hours, which supports once-daily administration. Donepezil is largely metabolized by isoenzymes cytochrome P450 3A4 (CYP3A4) and cytochrome P450 2D6 (CYP2D6). Pharmacokinetic interactions are unlikely to occur with rivastigmine because its metabolism is mediated by esterases rather than by hepatic microsomal enzymes.

Rivastigmine inhibits both AChE and butyrlycholinesterase (BuChE) with equal potency. Galantamine is a selective reversible inhibitor of AChEI and binds allosterically to the α-subunit of the nicotinic ACh receptor as well, which leads to an additional therapeutic mechanism. Galantamine is metabolized mainly via CYP2D6 and CYP3A4 (55, 56) (Table 1). No differences in clinical effect of the various AChEIs have been observed in clinical trials (57).
Table 1 Properties of the three acetylcholinesterase inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Donepezil</th>
<th>Galantamine</th>
<th>Rivastigmine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mode of action</strong></td>
<td>Inhibits AChE</td>
<td>Inhibits AChE and binds allosterically to the α-subunit of the nicotinic ACh receptor</td>
<td>Inhibits AChE and BuChE</td>
</tr>
<tr>
<td><strong>Half-life</strong></td>
<td>50-80 hours</td>
<td>7-8 hours</td>
<td>0.6-2 hours</td>
</tr>
<tr>
<td><strong>Elimination</strong></td>
<td>CYP2D6 and CYP3A4</td>
<td>CYP2D6 and CYP3A4</td>
<td>By esterases, no hepatic elimination</td>
</tr>
<tr>
<td><strong>Pharmacokinetic drug interactions</strong></td>
<td>Potent drugs affecting CYP2D6 and CYP3A4</td>
<td>Potent drugs affecting CYP2D6 and CYP3A4</td>
<td>No pharmacokinetic interactions</td>
</tr>
<tr>
<td><strong>Pharmacodynamic drug interactions</strong></td>
<td>Caution with drugs which can enhance the cholinergic heart-effect of the AChEIs (beta blockers, digoxin/digitoloxin, verapamil, amiodarone).</td>
<td></td>
<td></td>
</tr>
</tbody>
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Abbreviations in the table: acetylcholinesterase (AChE), acetylcholine (ACh), acetylcholinesterase inhibitor (AChEI), buturylcholinesterase (BuChE), cytochrome P-4502D6 (CYP2D6), cytochrome P-4503A4 (CYP3A4).

The AChEIs have proved to have a symptomatic effect in patients with mild to moderate AD, and in DLB and PDD (57-59). Donepezil, rivastigmine and galantamine are approved for AD of mild to moderate degree in Norway, while rivastigmine in addition is approved for PDD. AChEIs (donepezil, galantamine, rivastigmine) have consistent, statistically significant effects on global cognitive abilities, global function and ADL, but the effects are moderate and ADRs, especially gastrointestinal, occur frequently. A positive effect on quality of life has not been shown, neither has time to hospitalization nor survival (1).

Dose-related cholinergic ADRs of AChEIs connected to the peripheral cholinergic effects, like diarrhoea, urinary incontinence, muscle cramps, weakness and vagotonic effects on the heart (i.e. bradycardia, prolonged QT-interval), and central effects like nausea, vomiting (could also be peripheral effects), insomnia, agitation and nightmares may occur (55, 60). Older adults (generally > 65 years of age) are at higher risk for drug-induced Torsades de pointes (TdP), which may be related to declining serum testosterone concentration in men and lower serum progesterone concentrations in women (61). Vagotonic effect on the heart is of particular concern in patients with sick sinus syndrome or other supraventricular cardiac conduction disturbances, or indeed in those for whom other agents with similar effects (e.g. β-
blockers or digoxin) are co-prescribed (60). In addition, agents with central activity towards brain muscarinergic receptors will have the ability to counteract the effect of AChEIs (62).

The evidence of use is based on four systematic review articles, and a systematic report forming the basis of the National Institute for Care and Health Excellence (NICE) guideline for treatment of dementia (evidence based recommendations for health and care in England) (57, 63-67). If improvement of symptoms is used as a measure of efficacy, the Number Needed to Treat, (NNT) is 5–7. If stabilization and reduction of deterioration are also included, NNT becomes 2–3 (51).

The effect of AChEIs in AD patients with MMSE <10 is only expected to be 0.7-1.1 points on the MMSE scale score ranging from 0-30 (68). However, patients with AD of moderate to severe degree of severity, having used AChEI during a longer period of time, have shown to have a small to moderate effect on cognition and ADL-function of AChEI over a 12 months period, compared with patients who discontinued the AChEI (1).

Concomitant treatment with both AChEI and memantine is not recommended. The evidence is based on a meta-analysis of the effect of AChEIs in AD in relation to severity (69), where individuals with an average MMSE score <10 were evaluated (70-73). The four studies show a consistent, small/moderate statistical effect on cognition. However, concerning the ADL function, the results were non-significant in three out of the four studies. At the present, there is no recommended treatment for MCI with AChEIs (1). Several single studies have found a modest improvement in cognition in MCI using AChEIs. In total, however, meta-analyses of good quality have not confirmed the results of single studies, and the side effects are more pronounced than the therapeutic effect (7). Therefore, AChEIs are not recommended for use in MCI; neither is memantine (74-76).

1.2.2 Treatment with memantine
Memantine is an antagonist at the NMDA glutamate receptors. Excessive exposure to the neurotransmitter glutamate, or overstimulation of its receptors, has been implicated in many neurodegenerative diseases, and NMDA glutamate receptors have been implicated in many neurodegenerative diseases and play an important role in brain function like memory formation and synaptic communication (77). Memantine selectively blocks the excessive
NMDA receptor activity by inhibiting the pathological overactivation, without disrupting the normal physiological activity, which is essential for neuronal function. Its action is believed to result in reduced neuronal cell death (56).

Memantine is a weak base and undergoes a primarily non-hepatic metabolism and is predominantly excreted unchanged by the kidneys. Urine pH has been shown to be a major determining factor for its excretion (78). Memantine is generally well tolerated, but has been associated with headache, dizziness, somnolence, dyspnoea, constipation and hypertension (56). Marked changes of urine pH, by combination of drugs such as ranitidine, results in toxic effects, especially in older adults, where a reduced renal function has been described. Memantine should not be administered alongside compounds acting upon the same receptor (NMDA) system such as amantadine, due to the risk of pharmacotoxic psychosis. With respect to drug–drug interactions it is important to consider that memantine presents a weak dopaminergic agonist with atropinic effects (78).

Memantine is used to treat the cognitive deficits of AD, and is licensed for moderate-to-severe dementia in AD. It has been found to have a small beneficial effect in moderate-to-severe AD (79), but no significant differences compared with placebo were found in mild AD (56). A Cochrane review comprising 3 randomized, controlled studies in patients with mild to moderate degree of dementia, found that memantine only has a marginal positive effect on cognition (about 1 point on a scale from 0-70) and on global function (0.13 points on a scale of 1-7) (1). Memantine, rather than an AChEI, could be offered to patients with severe degree of AD or severe mixed AD and VaD who are not already treated with an AChEI (1) . Memantine is considered to have at least as good effect as AChEIs in patients with MMSE-score <10 and is associated with less adverse effects. Concerning patients already treated with an AChEI, and in consultation with patient and relatives, a change from AChEI to memantine could be considered, depending on how the effects and side effects were experienced for the individual patient. The recommendations in the use of memantine are based on the evidence effects described in the NICE dementia guideline (66, 67), and two systematic review articles (79, 80).
1.2.3 Aducanumab and future target therapies

Since AD is a multifactorial disease, dual and multi-target inhibitors have been developed. Therapies targeting tau protein reduce and prevent its hyperphosphorylation and aggregation, and several drugs are under development (48). Because there have been many failed phase 3 trials that included patients with symptomatic AD, trials of disease-modifying therapies should be conducted much earlier, either during the preclinical or MCI phase of AD (81).

Several anti-amyloid agents are under investigation as well. The human monoclonal anti-amyloid antibody aducanumab was approved by US Food and Drug Administration in June 2021. This was the first potential disease-modifying substance to treat Alzheimer’s disease in a dementia and MCI stage. The drug selectively binds to Aβ fibrils and soluble oligomers (which is a molecule that consists of a few similar or identical repeating units) (82). By attaching to Aβ, aducanumab is expected to help clear the plaques away and delay the worsening of the disease. This theory will be further investigated in ongoing studies for long-term efficacy. The European Medicines Agency, EMA, recommended the refusal of the marketing authorization in December 2021 (EMA/750220/2021). EMA noted that although aducanumab reduces Aβ in the brain, the link between this effect and clinical improvement has not been established. In addition, EMA did not judge the drug to be sufficiently safe. The Common Alzheimer’s and Related Dementias Research Ontology (CADRO) has identified early-stage and late-stage clinical drug development targets for potential new disease-modifying therapies (81).

1.3 Factors affecting response to and treatment length of AChEI treatment

Knowledge about factors affecting treatment length in AChEI users is important to improve the understanding of the etiology of the cognitive decline and the patient’s overall prognosis. In addition, knowledge regarding comedications of psychotrophic drugs and opioids is of importance to improve and preserve cognitive health in the pre-dementia and dementia stage. Although the clinical effect of AChEIs on cognitive function is small to moderate, the individual variability in response is extensive (51). This variability may be due to several factors, like individual variability, the prescriber, concurrent use of other medications and switch to another AChEI.
Individual patient variability may be related to genetic heterogeneity of CYP-isoenzymes responsible for the metabolism of the AChEI.

The prescriber’s prescription habits are important, as polypharmacy will increase the likelihood of using at least one drug with anticholinergic properties (83-87). In this respect, prescription of drugs contraindicated with AChEIs is of particular importance (88).

Discontinuation of AChEIs or switch to another AChEI can be related to environment (hospitalizations/change of care), medications (ADRs to AChEIs, inappropriate concurrent use of anticholinergic agents) and patient factors like individual patient variability (cognitive decline, anxiety, weight loss) (88-92). Cognitive decline has been shown to be linked to switching (92), indicating that the decision to switch to another AChEI may be made for a potentially better therapeutic response. AD related hospitalization has been shown to be the strongest predictor of discontinuation. During a hospitalization for worsening of AD, the question of effectiveness of AChEIs often arises, and the risk-benefit balance is often reconsidered (92). Knowledge of comedication to AChEI treatment in persons with AD may therefore be of importance.

1.4 Anticholinergic burden and Anticholinergic Drug Scale (ADS) scores

Knowledge of concurrent use of AChEIs and agents with anticholinergic properties is important to avoid the unfortunate interaction between AChEIs and anticholinergic drugs. Use of anticholinergic drugs is associated with low MMSE score as an expression of increased severity of cognition and increased mortality in the elderly (93, 94).

Anticholinergic drugs act on the muscarinic receptors in the central and peripheral nervous system. There are five subtypes of muscarinic receptors, M1, M2, M3 M4 and M5 (95). Many commonly used drugs have primary or secondary anticholinergic properties as they act on these receptors, e.g., urologic spasmyotics, antihistamines, antidepressants and antipsychotics (83-87). Moreover, there is a vast number of agents expressing anticholinergic activity in vitro (96), which might be of relevance when administered together with other anticholinergics. Anticholinergic drug scale (ADS) score models have therefore been developed as assessment tools for evaluation of the overall anticholinergic burden in patients using drugs which could have anticholinergic effects (85, 96-98). The basis for the ADS score evaluation is a list of drugs and their anticholinergic scores (99) founded on previously published classifications.
and studies (62, 87, 96, 97). The reviews are largely based on in vitro testing of anticholinergic activity, in which the ability to displace muscarinic ligand (tritiated quinuclidinyi benzylate, 3H-QNB) to rat brain muscarinic receptors is compared with atropine as a reference (100). Based on the ability to displace 3H-QNB, the drugs are given an anticholinergic score from 0 to 3, where 0 is defined as ‘no anticholinergic activity’, 1 as ‘potentially anticholinergic’, 2 as ‘clinically significant anticholinergic’ and 3 as ‘strong anticholinergic’ activity. The method does not take into account the dose of the anticholinergic drug and of inter-individual variations in pharmacokinetics, including the degree of distribution to the CNS (101, 102). The receptor binding studies used to measure anticholinergic activity have some weaknesses in that they lack complete specificity for muscarinic receptor subtypes and do not measure CNS effects directly (101, 103). However, there is no single standardized tool for measuring anticholinergic burden, and several expert-based anticholinergic rating scales show that the rating of anticholinergic activity for medicines among the various rating scales may differ. The Anticholinergic Cognitive Burden Scale (ACB) scale by Boustani et al., which is based on a systematic literature review of medicines with known anticholinergic activity, has shown to be the most frequently validated expert based anticholinergic scale on adverse outcomes (104).

Older adults are generally more sensitive to alterations in mental function caused by anticholinergic agents than younger people, possibly because of an age-related reduction in cholinergic transmission. In addition, comorbidity and polypharmacy are common phenomenon in older adults, and this may increase the general risk of central anticholinergic side effects. Reduced phenotype of P-glycoprotein (P-gp), an efflux membrane transporter which mediate efflux of drugs across the blood-brain barrier (BBB), is a factor that may be of particular relevance for risk of side effects from centrally acting drugs (105). Physiologically age changes are common in the elderly, and there is evidence of an age-related increase in the BBB permeability (55, 106). Moreover, comorbidity, such as VaD, AD, and diabetes mellitus type II, might affect BBB permeability of centrally acting drugs like anticholinergic agents. Drug interactions with inhibitors of P-gp could increase brain delivery of P-gp substrates and provoke unwanted central adverse effects of anticholinergic agents as well (62).

An observational study from nursing home residents in Norway investigated whether a reduced ADS score improved cognitive function in a frail population of older adults (107). The intervention carried out in the study did lead to reduced ADS scores, but did not improve
cognitive function of the nursing homes residents, indicating that the ADS score model is not necessarily suitable as a direct anticholinergic measure.

An explanation for the fact that the results from different studies vary could be that anticholinergic drug scales simplify complex pharmacological mechanisms (95) like different definitions of anticholinergic drugs, as well as different study populations. It is unfortunate that most of the methods do not take dosage into account, as the risk of anticholinergic side effects is concentration dependent. However, the methods presuppose a simple linear effect mechanism that can probably not be applied directly to clinical conditions (108). Lack of linearity was apparent in an in-vitro study comparing different urinary spasmylytic drugs (USDs) (62). Another reason why the ADS scale is not necessarily an accurate measure of serum anticholinergic activity is the possible association between inherited CYP2D6 and cytochrome P450 2C19 (CYP2C19) phenotypes and anticholinergic measures (109). The metabolism of many anticholinergic drugs like antipsychotics, tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and several USDs is catalysed by the polymorphic enzymes CYP2D6 and CYP2C19. The clearance of substrates metabolized via CYP2D6 or CYP2C19 is undergoing an extensive interindividual variability because of genetic heterogeneity (110). Variant alleles encoding deficient CYP2D6 activities occur commonly in whites, with as much as 5-10% classified as CYP2D6 poor metabolizers (PMs). Variant alleles encoding deficient CYP2C19 metabolism (PMs) occur in the extent of 3-5% in whites, and as much as 15-20% in Asian populations. A study in nursing home patients in Norway indicated that older adults with CYP2D6/CYP2C19 PMs with a high anticholinergic drug burden were at increased risk of elevated serum anticholinergic activity (109).

However, considering the antagonizing effect of anticholinergic drugs on AChEIs, high anticholinergic burden may put patients with dementia at risk of worsening of dementia symptoms as a result of the reduced effectiveness of AChEIs, and an improved clinical outcome may be expected with reduced anticholinergic burden in prescribed drugs. Previous studies investigating cognitive function have shown a greater decline in the cognitive function of AD patients after taking anticholinergic drugs and AChEIs concurrently (111). A retrospective study which has taken dosage of drugs with anticholinergic activity into account showed that exposure of drugs with high anticholinergic burden negatively affected the treatment response to AChEIs (6% of the patients) leading to treatment modification, delirium and mortality (112).
Pharmacoepidemiological studies have reported that 20-50% of the patients treated with AChEIs were co-prescribed with anticholinergic agents (83-87). In studies of Carnahan et al. (86) and Boudreau et al. (84), an ADS score of 2 or more was respectively reported in 35% and 37% of the patients treated with AChEIs. These antagonistic interactions should be minimized in clinical practice to gain the maximum clinical benefit AChEIs, but there is limited knowledge about possible approaches to reduce the anticholinergic burden in patients with dementia.

Pharmacological approaches are often required for treatment of dementia conditions and BPSD (113). Incontinence is more prevalent in demented than in non-demented older people (83, 85). USDs are often used to treat incontinence, which could be caused by both the dementia syndrome and an adverse effect of AChEIs (83, 86). The mechanism of action of these agents is blocking of M3 receptors in the bladder, but USDs may also induce negative brain effects through antagonizing of central muscarinergic receptors. Factors of importance regarding the potential negative effect of USDs include degree of brain distribution (pharmacokinetics), and affinity toward brain muscarinergic receptors (pharmacodynamics) (62). In addition, pharmacokinetic issues like dosage will influence the degree of brain distribution. Generally, it is recommended to avoid muscarinergic USDs in patients with dementia, if possible (62). However, darifenacin is considered to have the lowest potential to cause cognitive side effects among the USDs, with an ADS score of one. The favorable profile of darifenacin compared to the other USDs (e.g. tolterodine) is probably due to a lower anticholinergic activity towards muscarinic brain receptors and a lower central nervous system (CNS) distribution (62). Lower distribution to the CNS of darifenacin probably reflects that darifenacin is a P-gp substrate, which is likely to limit its transport across the blood-brain barrier. Since the relative brain exposure of darifenacin might be increased in older patients and during concurrent use of P-gp inhibitors, it would be advisable to evaluate the potential development of adverse cognitive effects of darifenacin as well. Nevertheless, it is important to be particularly aware of cognitive side effects when muscarinergic USDs and other drugs with an anticholinergic activity are used in elderly people who suffer from dementia.

The prevalence of co-prescribing of anticholinergic drugs in the AChEI treated patients in Norway is unknown.
1.5 Behavioural and Psychological Symptoms of Dementia (BPSD)

The prevalence of BPSD among cognitive diseases depends on the etiology of the dementia disorder (114). Moreover, it is possible that symptoms of apathy, depression, anxiety and irritability can be early signs of cognitive impairment and dementia due to the patient’s insight into the condition. Other factors have shown to be associated with symptoms of BPSD as well, like female gender and older age, which are examples of factors associated with depression in people with cognitive decline (115). Norwegian studies of nursing homes have shown that four factors were the most stable one of BPSD; psychosis, agitation, affective symptoms and apathy (114, 116).

A systematic review aiming at determine the pattern of BPSD in the course of dementia with 59 included studies, showed considerable methodological heterogeneity (117), but despite this fact, there were considerable differences in the longitudinal courses of different BPSD. Apathy was the only symptom with high baseline prevalence, persistence and incidence during the course of dementia. The incidence of different symptoms from 13 studies reporting symptoms of BPSD were as follows: Affective: depression 10-73%, anxiety 12-38%, apathy 27-64%; Psychosis: delusions 5-84%, hallucinations 4-45%; Hyperactivity: irritability 10-69%, agitation 19-80%, wandering not reported; Elation:4-5%, Sleep problems: 8-31% (117) (review 1, Table 2).

Another systematic review reports different incidences of BPSD in dementia and highlights that BPSDs are major risk factors for an earlier placement of affected individuals in nursing homes and a potentially more severe course of dementia over time (118) (review 2, Table 2). The results from these systematic reviews are summarized in Table 2.
Table 2. Type related incidence of Behavioural and Psychological Symptoms of dementia from two systematic literature searches.

Van der Linde et al (117) (review 1) and Preuss et al (118) (review 2).

<table>
<thead>
<tr>
<th>Syndrome</th>
<th>Symptom</th>
<th>Incidence (%) of syndrome, systematic review 1</th>
<th>Incidence (%) of syndrome, systematic review 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychosis</td>
<td>Hallucinations, Delusions</td>
<td>4-45%, 5-84%</td>
<td>17-24, 33-40</td>
</tr>
<tr>
<td>Depression</td>
<td>Anxiety</td>
<td>10-73%</td>
<td>54-64</td>
</tr>
<tr>
<td>Apathy</td>
<td>Social withdrawal</td>
<td>27-64%</td>
<td>33-63, 21-88</td>
</tr>
<tr>
<td>Aggression</td>
<td>Resistance</td>
<td>24-34</td>
<td>27-65</td>
</tr>
<tr>
<td></td>
<td>Verbal</td>
<td>11-61</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Physical</td>
<td>0-46</td>
<td></td>
</tr>
<tr>
<td>Agitation</td>
<td>Walking aimlessly</td>
<td>19-80%</td>
<td>38-64</td>
</tr>
<tr>
<td></td>
<td>Pacing</td>
<td></td>
<td>0-50, 26-48</td>
</tr>
<tr>
<td></td>
<td>Restlessness</td>
<td>8-31%, 10-69%</td>
<td>22-27, 0-47</td>
</tr>
<tr>
<td></td>
<td>Sleep problems</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Irritability</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BPSD is also reported in FTD, especially in the behavioural type (bvFTD), the most frequent symptoms are reported to be apathy, irritability, disinhibition, wandering, social inappropriateness, agitation/aggression and depression.

In VaD, sleep disturbances and depression seem to be the most common symptoms. BPSDs are also frequent in LBD and sometimes very difficult to manage (114).

The extent of most of the BPSDs increases with the severity of the dementia, especially agitation and apathy (9, 10). Apathy and agitation are most common in a late stage, psychosis in the middle phase, while mood symptoms seem to have a stable incidence throughout the course of the dementia disease (Figure 3) (3).
BPSD can be treated. An overall plan for treatment with non-pharmacological interventions and with drugs should be devised. Drug treatment should not be oriented solely to the particular behavioural manifestation that is present (e.g., aggressiveness), but should rather be directed against the underlying cause, if possible, which may also be of somatic origin. Short-term psychosocial intervention may be the first choice of treatment if psychosocial interventions have been ineffective, the patient is suffering from intense delusions, or if a dangerous situation has arisen (119).

1.5.1 Definition of Behavioural and Psychological Symptoms of Dementia

BPSD is a term to describe the diversity of psychological reactions, psychiatric symptoms and episodes of behaviour that occur in people with dementia, regardless of the cause. The core clinical criteria for AD focus on the presence of memory disturbance or other cognitive symptoms that interfere with the ability to function at work or in usual daily activities. But patients often show a broad range of “non-cognitive” disturbances, more commonly known with the term BPSD, which include psychotic symptoms, mood symptoms, anxiety.
symptoms, apathy and agitation (3) and constitute a major component of the dementia syndrome irrespective of its subtype. These disturbances are as clinically relevant as cognitive symptoms as they strongly correlate with the degree of functional and cognitive impairment. It is estimated that BPSD affects up to 90% of all dementia subjects over the course of their disease (120), and is independently associated with poor outcomes, including distress among patients and caregivers, long-term hospitalization, misuse of medication, and increased health care costs. Although these symptoms can be present individually, it is more common that various psychopathological features co-occur simultaneously in the same patient. Thus, categorization of BPSD in clusters taking into account their natural course, prognosis, and treatment response may be useful in the clinical practice (121). As much as 50% of subjects with AD show at least four BPSDs simultaneously. In systematic reviews of studies that applied unbiased approaches to cluster BPSD, the following domains were identified: Affective (anxiety and depression), disinhibition/hyperactivity (aggression, impulsivity, motor hyperactivity), apathy and psychosis (hallucinations, delusions, paranoia). However, the debate about the definition of an appropriate clusterisation in dementia is still ongoing (122).

1.5.2 Potential causes of Behavioural and Psychological Symptoms of Dementia

Many factors have been found to be associated with the development of BPSD. Changes and neurodegeneration in the brain of persons with dementia in centres that control cognition and emotion can impact the ability to interact with others and their environment (123). The ability to withstand stress depends on i.e. personal characteristics, life history and life stage (124), and BPSD arises in an interplay between biological and personal factors.

Possible causes of BPSD, in addition to organic brain changes, might be psychosocial and environmental factors, poorly adapted physical environment, coping failure, anxiety and/or depression, hallucinations and/or delusions, premorbid personality and somatic disorders such as pain, urinary retention/infection, constipation, sleep disturbance; as well as hunger and thirst, effects/side effects of medicines, and delirium due to somatic disease or unwanted drug effect (1, 3).

A number of psychosocial factors, like lack of person centered care (PCC), and environmental factors, can aggravate BPSD. Examples of such factors are dissatisfaction and frustration with experience of failing health and function, reaction to lack of social support or
negative reaction and disrespectful treatment from the environment, communication difficulties that reduce the ability to express needs, and inability or ability to maintain autonomy (1). It is important to meet the basic psychological needs of persons with dementia to confirm their experience of value as human beings (3). The cognitive changes in dementia mean that a person may have problems understanding what is happening in the environment and in expressing needs and wishes. The Norwegian National Guideline on Dementia states that treatment and care should be based on PCC to ensure that people with dementia are able to hold on to their identity, and to receive support, experiencing that the days contain meaningful activities. Studies of the effect of PCC have not only given positive results, but this fact can be related to differences between the studies (1).

One biological cause is the metabolic hypothesis, suggesting that dysregulation of the hypothalamic-pituitary-adrenal «stress axis» leads to neurotransmitter imbalances, producing delusions (dopamine) and depressive manifestations (serotonin). Atrophy of the nucleus raphe dorsalis leading to serotonin deficiency may be a further cause of affective manifestations. Early atrophy of the paralimbic system, as seen in AD, can impair dopamine metabolism, leading to paranoid delusions, and thereby to aggressiveness; in contrast, the aggressiveness seen in FTD is more the result of disinhibitory phenomena. Affect lability in VaD can also cause aggressiveness (119). Pain is thought to be one of the most important causal factors of BPSD, and BPSD arising as a result of pain, such as agitation and aggression, can be extremely distressing for both the individual and their caregiver, and can lead to the inappropriate prescribing of antipsychotic medication instead of adequate pain treatment (125). However, commonly used assessment tools are neither valid nor reliable, and are difficult to use. To provide effective treatment, it is essential to identify when a treatment response is present. Relatively strong associations have been shown between pain and depression, as well as unspecified behavioural problems (126).

1.5.3 Treatment of Behavioural and Psychological Symptoms of Dementia

1.5.3.1 Non-pharmacological treatment

The efficacy of non-pharmacological treatments against behavioural disorders is well documented (119) as the first-line treatment due to the significant impact on global BPSD measures and lack of ADRs (127), and include a wide array of interventions including
behavioural, environmental, and caregiver support interventions (123). Systematic reviews show that the most promising treatment appear to be music therapy and some behavioural management techniques, particularly those involving caregiver-oriented and staff-oriented interventions (128). The interventions found to have a significant effect on ADL function should not be difficult to implement routinely for persons with dementia. The non-pharmacological interventions that were effective (exercise and dyadic interventions) have been shown to involve regular participation and reduced functional decline relative to the control group rather than leading to improvements in functional performance compared with the baseline, indicating a slowing of functional decline rather than prevention (129). A systematic review shows that physical activity probably has little or no effect on depression in people with dementia, but possibly provides somewhat better cognitive and daily functioning (130).

None of the psychosocial interventions targeting persons with dementia in nursing homes or living at home have shown a significant reduction in agitation and aggression compared to a control group receiving standard care, however, during training in dementia and understanding of BPSD, health and care personnel experienced a positive effect in the handling of challenging situations (120, 131).

**Person centered care**

Although the underlying brain disease causing dementia is not curable, many of the symptoms of dementia are manageable, therefore the course of dementia and its symptoms changes with good dementia care. PCC is important, meaning that people with dementia and their families need to have their medical, social, and supportive care needs assessed and re-assessed as they change over time (11). The context of PCC should include elements like valuing people with dementia and caregivers, individualized therapy, and seeing the perspective of the person with dementia. Individualized therapy could consist of activities like walking, motor skills training, balance training, and everyday activities (3). Memory therapy, occupational therapy, music therapy, and physical activities have all been found to be beneficial in multiple clinical trials (119).

**Activities and adult day care centre**

There is a need for continued prolonged intensive personal interactions with people with dementia (132). Social interaction in small groups with cognitive stimulation has been
documented (medium quality of evidence) to have a positive effect on cognitive function and quality of life in people with dementia (133). Healthcare professionals should ensure that persons with dementia are encouraged to exercise (129). Studies of physical activity indicate a positive effect on ADL function (134), however, no statistical difference has been shown between the intervention- and placebo group with regard to depression, anxiety, behavioural problems, life quality, or caregiver burden (133). There is little international research on the effect of using day activity offers for persons with dementia, however, research on the effect of social interaction in small groups with cognitive stimulation is considered unproblematic to transfer to recommendations for day activity offers (1).

**Physical environment**
Familiar surroundings, like living in small units, few people to relate to, easy access to outdoor areas and opportunity to take part in meaningful activities is recommended (3).

**Caregiver support**
The evidence is not conclusive as to whether some BPSD impact a caregiver’s well-being more than others (135), however, training of relatives will for many be important in dealing with dementia and any BPSD in particular. Special attention should be payed to caring for the relatives of the person with dementia, so that they can both be a resource for the person with dementia and have their own life and health taken care of (136). Day care centers for people with dementia can meet the needs of the person with dementia, and at the same time give support for family caregivers. A individualized program is considered to make day care centers more effective (137).

**1.5.3.2 Drugs in the treatment of Behavioural and Psychological Symptoms of Dementia**
Pharmacological approaches are often used in the treatment of BPSD (113), and patients with dementia are frequently treated with psychotropic drugs such as antidepressants, anxiolytics, antipsychotics, hypnotics and sedatives for BPSD as part of the dementia syndrome.

**Adverse drug reactions**
In addition to the side effects and considerable morbidity, especially in older adults (138), psychotropics are not particularly effective (78, 139).
Use of psychotropics in Mild Cognitive Impairment and dementia in people living at home and in nursing homes in Norway and other countries

Affective symptoms such as anxiety and depressive symptoms are more frequent in MCI than in mild dementia (140). Studies in Norway show that people with a diagnosis of dementia use more psychotropics than those without, despite the consensus that they should be treated with utmost caution and less psychotropic drugs (141). Due to multimorbidity and polypharmacy, the therapy of BPSD is difficult and needs continuous clinical observation of the patients. Psychotropics are often used in the treatment of BPSD (Table 4), and with a higher prevalence of use in nursing homes than in people living at home (142). Even in patients with mild dementia living at home, nearly 70% of the patients have been reported to use one or more psychotropic drug (143).

Evidence of effect of psychotropics in people with dementia

The modest effect of psychotropic drugs for BPSD could be due to the fact that these symptoms may have causes not related to mental disorders like depression, anxiety or psychosis. Prescription of psychotropic drugs to these patients with AD in a preclinical phase could therefore be based on a wrong diagnosis and indication. In more severe stages of dementia, psychotropic drugs are often initiated to treat behavioural symptoms. Apparently, psychotropic drugs are sometimes prescribed for BPSD due to lack of resources and time to implement non-pharmacological treatment approaches (144, 145).

Evidence of adverse drug reactions of psychotropics in people with dementia

Management of BPSD is difficult due to risk of serious adverse effects of psychotropics and due to the absence of credible alternatives (139, 146). Older persons in general and persons with AD are susceptible to adverse effects of psychotropic drugs and thus, these drugs should be used with caution. Psychotropic drugs are associated with increased risk of injurious falls, hip fractures, stroke, hospitalization and mortality, and should generally be avoided in older persons with dementia (147). Older adults with AD often suffer from multimorbidity and painful conditions, and pain may be an additional cause of symptoms like anxiety, depression and irritability (148).
**Recommendations for use of psychotropics in dementia**

Psychotrophic drugs are generally not recommended in AD according to the Norwegian National Guideline on Dementia, because of weak evidence of effect. According to NICE Guideline on Dementia, psychological interventions are recommended to be the first treatment option for persons with mild to moderate dementia having mild to moderate depression and/or anxiety. Antipsychotics should only be offered for persons with dementia who are at risk of harming themselves or experiencing agitation, hallucination or delusions causing severe distress (149). Interventions to promote social engagement is an important component to enable effective antipsychotic discontinuation (150, 151). Generally, there is no scientific basis for offering AChEIs, memantine, antidepressants (selective serotonin receptor inhibitors, SSRIs) in psychotic symptoms, aggression and / or agitation in dementia, primarily due to uncertainty about the effect. There is no general scientific basis for offering typical antipsychotics, which show no clear efficacy in BPSD (with the exception of haloperidol, which has shown a favourable response in cases of aggression (152)) as well as mood stabilizing drugs such as lithium, carbamazepine and valproate in psychotic symptoms, aggression and / or agitation in dementia. This is primarily due to uncertainty about effect /small effect and a serious side effect profile (1, 125).

However, some psychotropics are recommended in specific situations in the treatment of BPSD (1), and these will be described in the following sections.

**Treatment with antipsychotics**

**Mode of action**

It is appropriate to distinguish between first-generation agents with strong dopamine receptor 2 (D2) antagonism and atypical antipsychotics, also known as second-generation agents such as risperidone, olanzapine, clozapine, quetiapine, ziprasidone and aripiprazole (153), which also are potent serotonin receptor 2 (5-HT2) antagonists and have significantly less tendency to give motor and mental side effects (apathy and emotional inhibition) (37). There may be effects on muscarinergic, α-adrenergic, or histaminic receptors, depending on the specific drug, resulting in anticholinergic effects, orthostatic hypotension, and sedation as a result of blocking these receptors (154).
Adverse drug reactions

Atypical antipsychotics have several side effects that occur frequently (1, 155). Research literature on the effects and side effects of long-term use of atypical antipsychotics is deficient. There is also little research on how the severity of dementia and possible comorbid pathology influence the treatment outcome (9, 153, 156).

Strong anticholinergic effects of antipsychotics may counteract the effect of AChEIs. A QT interval (time between the start of the Q wave and the end of the T wave in the heart’s electrical cycle) prolongation and extrapyramidal side effects caused by pharmacodynamic interactions between AChEIs and antipsychotics may occur. Thus, a close monitoring of the effect and ADRs should be conducted, especially among persons with risk of QT interval prolongation (61). Electrocardiogram (ECG) should for these persons be added to the regular monitoring visits. Is further suggested to minimize the frequency, dose and treatment duration of antipsychotics.

Warnings have been issued for all antipsychotic drugs (both first and second generation) prescribed for patients with dementia. The US Food and Drug Administration (FDA) issued a warning in 2008 against the use of all types of antipsychotics, both typical and atypical, in elderly patients with dementia, due to reported serious side effects, including death, stroke, coronary heart disease and metabolic syndrome. The risk of mortality with antipsychotics is generally increased with higher doses, and seems to be highest for haloperidol and lowest for quetiapine. Compared with risperidone, users of haloperidol had an increased risk of mortality (hazard ratio 2.07, 95% confidence interval (CI) 1.89 to 2.26), and users of quetiapine a decreased risk (0.81, 0.75 to 0.88) (157). Use of quetiapine has not shown any benefit for treating agitation or psychosis in patients with dementia and parkinsonism (158).

The knowledge about side effects of treatment with atypical antipsychotics is uncertain as the follow-up time in the studies is generally short (10-12 weeks) and side effects are inconsistently reported in the studies, and, in addition, the incidence of side effects may be underreported. Knowledge about side effects with long-term use (i.e. over 10-12 weeks) is limited. According to the knowledge summaries of the Agency for Research and Quality (2011, 2016), the most commonly reported ADRs with the use of atypical antipsychotics (aripiprazole, olanzapine, risperidone, quetiapine) are somnolence, fatigue, abnormal gait, extrapyramidal symptoms, weight gain, urinary tract infection, cardiovascular events, stroke...
and death (159). With regard to the risk of death, it is reported that 1 in 100 patients, number needed to harm (NNH) = 100, who receive atypical antipsychotics, die over a treatment period of 10-12 weeks (high quality of evidence). Observational studies indicate that the risk of death is likely to be higher over a six-month period. In a retrospective case-control study including 90,786 patients with dementia (age over 65 years), patients receiving risperidone had an increased mortality risk of 3.7% (95% CI 2.2% -5.3%) over a 6-month period, compared to non-users, NNH = 27. Olanzapine had an increased mortality risk of 2.5% (95% CI 0.3% -4.7%), NNH = 40 and quetiapine 2.0% (95% CI 0.7% -3.3%), NNH = 50. Aripiprazole was not included in the study (Table 3) (159, 160).

Table 3 Adverse drug reactions of atypical antipsychotics; Maglione et al (159) and Maust et al (160).

<table>
<thead>
<tr>
<th>Atypical antipsychotic</th>
<th>NNH</th>
<th>Increased mortality risk over a 6 month period compared with non-users</th>
<th>Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>olanzapine</td>
<td>40</td>
<td>2.5%</td>
<td>Increased risk in patients&gt;80 years</td>
</tr>
<tr>
<td>risperidone</td>
<td>27</td>
<td>3.7%</td>
<td>3%, increased risk in patients&gt;80 years</td>
</tr>
<tr>
<td>quetiapine</td>
<td>50</td>
<td>2.0%</td>
<td>Increased risk in patients&gt;80 years</td>
</tr>
</tbody>
</table>

Long-term use of antipsychotics is frequently prescribed, but not recommended in people with dementia (144, 161). The traditional pharmacological management of BPSD with typical and atypical antipsychotics has significant morbidity, including extrapyramidal signs and symptoms, gait abnormalities, sedation, an increased risk of falls and fractures, increased incidence of delirium, cerebrovascular adverse events and death (30). The duration of antipsychotic drug treatment should be as short as possible, because of the high risk of side effects (162). Antipsychotics should therefore only be offered for people living with dementia who are either at risk of harming themselves or experiencing psychosis (1, 163).

Of the other reported side effects, the Agency for Healthcare Research and Quality (2011, 2016) found a statistically significant increased risk of: Cerebrovascular events, reported in 3 out of 100 patients, NNH = 34, for risperidone. Elderly patients (> 80 years) have a higher risk of experiencing cerebrovascular events as a side effect of antipsychotics than younger
patients. Other cardiovascular events (cardiovascular symptoms, edema and vasodilation) was reported in 2 out of 100 patients, NNH = 53, for risperidone, and 2 out of 100 patients for olanzapine, NNH = 48 (159).

Extrapyramidal symptoms were reported in 5 out of 100 patients, NNH = 20, for risperidone and 10 out of 100 patients, NNH = 10, for olanzapine. Somnolence was reported in 10 out of 100 patients, NNH = 10, for risperidone, in 12 out of 100 patients, NNH = 8, for olanzapine, in 11 out of 100 patients, NNH = 11, for quetiapine and in 6 out of 100 patients, NNH = 16, for aripiprazole. Fatigue was reported in 3 out of 100 patients, NNH = 34, for risperidone, olanzapine and quetiapine, and in 5 out of 100 patients, NNH = 22, for aripiprazole. Urinary tract infection / incontinence has been reported for olanzapine, quetiapine and risperidone, but not for aripiprazole. The quality of evidence in included studies is too low to draw conclusions about the degree of risk of urinary tract infections / incontinence (1, 159).

Another meta-analysis showed a significantly higher risks (p < 0.05 for all) for somnolence (OR = 2.95), extrapyramidal symptoms (1.74), cerebrovascular ADRs (2.50), urinary tract infection (1.35), edema (1.80), gait abnormality (3.35), and death (1.52), and a lower risk for agitation (164).

**Effects of antipsychotics**

Some reviews and clinical trials support the use of antipsychotics in BPSD (56). The current research basis shows that atypical antipsychotics have some effect against psychotic symptoms and agitation (125). The literature does not distinguish between agitation that is of an aggressive versus non-aggressive nature. However, clinical experience indicates that atypical antipsychotics are primarily effective in agitation of an aggressive nature.

Effects on psychotic symptoms and aggression have been shown for both risperidone and aripiprazole, but the quality of evidence is best for risperidone. Olanzapine has, according to research literature, an effect on total symptom burden and aggressive agitation, but not on psychotic symptoms. For quetiapine, the current research literature has shown such a small and uncertain effect on total BPSD symptom burden, psychotic symptoms and aggression that this drug is therefore not suggested in BPSD (165). However, results from a meta-analysis confirm that a single most effective and safe treatment option of atypical antipsychotics in the treatment of BPSD does not exist, and that clinicians should individualize the assessment of safety risks against expected benefits when prescribing these medications to patients with
dementia (166). A meta-analysis concluded that the effect disappeared in long time treatment. For most patients with AD, withdrawal of antipsychotics had no effect on functional and cognitive status (163). Antipsychotics may have some value in the treatment of more severe BPSD, but the benefit must be weighed against the side effects.

**Recommendations in Norway and other countries**

In Norway, only risperidone is approved for the indication psychotic symptoms and aggressive agitation, for short term treatment (up to six weeks) in moderate-to severe AD, VaD or mixed AD/VaD, unresponsive non-pharmacological approaches and where there is a risk of harm to self and others. Aripiprazole or olanzapine (outside the approved indication) are suggested as second options (1), as results from meta-analysis show these antipsychotics to ameliorate behavioural symptoms (153).

According to NICE Guideline on Dementia (149), the marketing authorization for risperidone only covers short-term treatment of persistent aggression in people with moderate to severe AD unresponsive to non-pharmacological approaches, and when there is a risk of harm to self or others. The marketing authorization of haloperidol only covers treatment of persistent aggression and psychotic symptoms in people with moderate to severe AD and VaD when non-pharmacological treatments have failed, and when there is a risk of harm to self or others. This is in accordance with approved indications in Norway.

**Treatment with antidepressants**

It is important to distinguish between treatment of depression to reduce depressive symptoms and to reduce symptoms of BPSD, especially anxiety. Many patients with MCI and dementia do not meet the requirements for mental illness, but have symptoms of e.g. anxiety, depression and psychosis. A greater heterogeneity for depression in dementia compared to depression without dementia might explain why antidepressants working in cognitively normal groups of people with depression do not seem to work with depression in dementia (167). It remains unclear if extrapolating data from similar populations with depression are relevant to patients with dementia with depressive symptoms (168). Antidepressants should not routinely be offered to manage mild to moderate depression in people with mild to moderate dementia, unless they are indicated for a pre-existing severe mental health problem.
No relevant research basis has been found for recommending a combination therapy of antidepressants in dementia (1).

Mode of action
SSRIs have a strong inhibitory effect on the reuptake and thus inactivation of serotonin in serotonergic synapses. Tricyclic antidepressant agents (TCAs) inhibit reuptake and thereby inactivation of synaptically released serotonin and norepinephrine. In addition, TCA has more or less anticholinergic and antihistaminergic effects, that do not seem to play any therapeutic role, but often cause troublesome side effects like falls and increased risk of delirium (37). The receptor antagonists mianserine and mirtazapine block inhibitory presynaptic alpha-2 receptors, especially on noradrenergic, but to some extent also on serotonergic synaptic terminals, resulting in increases in the release of norepinephrine, which among other things stimulates serotonergic neurons via alpha-1 receptors (37).

Adverse drug reactions
Escitalopram and citalopram have shown superiority over placebo for reducing agitation in patients with AD (169), however, the dose of citalopram was high (30 mg), and due to cardiac adverse effect the drug cannot be generally recommended in that dose (170). The combination with AChEIs may have additive negative effects since both escitalopram/citalopram and AChEI may result in prolonged QT interval (78). Citalopram has been shown to be the most commonly involved drug substance among the clinically relevant drug-drug interaction in hospitalized people with dementia, which may partly be due to the prolongation of the QT interval that is not seen among other SSRIs, except for escitalopram (171). ADRs have been little studied in patients with comorbid depression and dementia, but can be expected to be the same as in the elderly with depression without dementia. Most often they will include nausea, diarrhea, headaches, sweating, tremors, somnolence, insomnia, restlessness, and sexual side effects (1). In addition, SSRIs can cause serious side effects including gastrointestinal bleeding, hyponatremia, falls, and fractures (169). Nausea and diarrhea are common ADRs of both SSRIs and AChEIs and can contribute to discomfort and weight loss (172). It is recommended to avoid the use of antidepressant drugs with anticholinergic effects (such as TCAs) as their use may impair the patient's cognitive functioning. TCAs may cause cardiac arrhythmias and QT interval prolongation, orthostatic hypotension, sedation, elevated intraocular pressure, and extrapyramidal effects (173). The receptor antagonists mianserine and mirtazapine have light side effects like initial drowsiness and weight gain; side effects
which are sometimes used therapeutically; and occasionally headache, dizziness, tremor, nausea, constipation, and in rare cases, blood dyscrasias (37).

Evidence of effect in people with dementia
The first choice for the treatment of patients with mild and mild / moderate depression in mild cognitive impairment or dementia is environmental, psychosocial and / or psychotherapeutic measures. Use of antidepressant medications to ameliorate mood in dementia patients may have limited benefits and may be associated with adverse outcomes (174). However, withdrawal studies have found that some people with dementia and BPSD may benefit from antidepressants (175). SSRIs are recommended in several guidelines for co-morbid depression in patients with AD (139), although the evidence for this effect is limited (113). The evidence for treatment of mild to moderate depression in people with dementia is of variable quality and low evidence of efficacy (176). For people with mild to moderate dementia in combination with mild to moderate depression, psychological treatments and social activities should be preferred over antidepressants (1, 169). In severe depression, or depression not managed through nonpharmacological means, a trial of an antidepressant may be initiated (177). In moderate to severe depression, the effect of SSRIs is likely to be better because many of the patients have a depressive disorder in accordance with ICD-10 or the DSM-5 criteria, and these patients are suggested to be offered an SSRI in combination with environmental, psychosocial measures and / or psychotherapeutic treatment. According to Nelson et al, 2013, patients with a disease duration of more than 10 years and severe degree of depression may have a better effect of antidepressant drug treatment than patients with late-onset depression and a short disease duration (< 2 years) (1). No basis has been found for using one specific SSRI drug over another (1). When choosing a drug and dosage, the patient's age, comorbidity, drug interactions, and possibly the patient's previous experience with SSRIs should be taken into consideration. There is insufficient evidence to assess the long-term safety of antidepressant use for BPSD in persons with dementia (169).

Recommendations in Norway and other countries
According to the Norwegian National Guideline on Dementia, a SSRI drug should be offered as additional treatment to patients, but only when appropriate environmental psychological and/or psychotherapeutic measures have been attempted without achieving the desired effect (1). According to NICE-guidelines on dementia, antidepressants should not routinely be offered to manage mild to moderate depression in people living with mild to moderate
dementia, unless they are indicated for a pre-existing severe mental health problem (149). Due to the limited benefits and considerable risks, antidepressants should only be used if all other nonpharmacological interventions for BPSD are unsuccessful. The risks and benefits of different antidepressants should be carefully evaluated when these drugs are prescribed to older persons (178, 179).

_Treatment with benzodiazepines and z-hypnotics_

**Mode of action**
BZDs acts on specific receptors and increases the inhibitory effect of GABA in the CNS. An inhibitory effect on sleep centres may explain the hypnotic effect. Inhibition of the amygdala is thought to correspond to the anxiolytic effect. Chemically, z-hypnotics are different from the BZDs, but they bind to the BZD receptor complex and act in the same way via the GABA system. Sleep time is shortened. At therapeutic doses, zopiclone has a duration of effect almost equal to the normal sleep duration of one night. REM sleep and deep sleep are little affected, without the clinical significance of this being clarified.

**Adverse drug reactions**
There is a clear development of tolerance for the hypnotic effect (37). BZDs should generally be avoided in people over 65 years of age and in people with cognitive impairment / dementia under 65 years of age, due to the risk of serious side effects and risk of addiction (1). BZDs are associated with significant adverse effects, especially in older adults, and include daytime sleepiness ("hangover"), tolerance development, lethargy, fatigue, amnesia, impaired learning- and psychomotor skills, dizziness, vertigo, delirium, euphoria, paradoxical aggression and increased risk of falls and hip fractures, and respiratory suppression (56, 123, 180). The use of BZDs have been connected to the risk of development of AD, especially the short-acting agents (181), however, another possible explanation is that insomnia could be a prodromal symptom of AD (182).

**Evidence of effect in people with dementia**
The evidence for using BZDs in the treatment of BPSD is limited and their use in BPSD is poorly supported (56, 123). There is a limited number of controlled studies, and a significant heterogeneity between the studies (180).
Recommendations in Norway and other countries
Given the lack of evidence of supporting use of BZDs over placebo or other medications, use is not recommended outside of an acute behavioural crisis (123).

Treatment with analgesics

Mode of action
A common mechanism of action of opioid analgesics is that they bind to opioid receptors in the CNS and increase activity in some of these endogenous analgesic systems. The analgesic effect of paracetamol is the same as for NSAIDs, both via central (including weak cyclooxygenase-2 (COX-2) inhibition and stimulation of serotonergic pain inhibition) and peripheral mechanisms (including weak COX-2 inhibition in the CNS) (37).

Adverse drug reactions
Respiratory depression, sedation, delirium, hallucinations, dizziness and instability are possible adverse effects of opioids (37). However, good evidence indicates that under-treatment of pain is a greater risk factor for the development of delirium than the use of opioids (183). Risk of liver damage with prolonged use in large doses and risk of drug-related headache is connected to the use of paracetamol which has few side effects with short-term use and in therapeutic doses.

Evidence of effect in people with dementia
Pain is a very common manifestation in people with dementia and often neither diagnosed nor treated. Pain-related diagnoses has been shown to be associated with higher use of psychotropics in persons with dementia (184). More specific and better treatment of pain are thought to have a positive effect on mood (185). Numerous studies have shown that pain sensitivity remains largely intact with advanced dementia (186). In addition, the placebo component of analgesic treatment is disrupted in AD patients (187). Delirium, hearing and vision impairment, falls and injury, incontinence and pain may coexist with dementia (188), and in severe dementia it may be difficult to communicate symptoms like pain. Therefore, pain and discomfort may trigger behavioural disturbances such as aggression and agitation, and also depression (189). Associations have been found between pain and depression, and depression plays an important role in development of agitation (190). A clear association has
been reported between pain and increased antipsychotic use, which may be related to mistreatment of pain in persons with AD (189, 191). Persons with moderate to severe dementia may have impaired communication, and this can impact on their self-report of pain (189).

**Recommendations in Norway and other countries**

Persons who show BPSD or other symptoms of discomfort should be examined and possibly treated for pain. Pain assessment, as part of palliative care, should be carried out using structured tools to adapt pain relief as needed. Special attention is required to detect pain in persons with moderate / severe degree of dementia and communication difficulties. Assessment of pain should be based on both the patient's own reporting and observations of the patient's behaviour. There seems to be little relevant research documentation that deals with the assessment and treatment of pain in people with dementia. Treatment recommendation is based on current legislation, including regulations on quality in nursing and care services for the provision of services pursuant to Act of 19 November 1982 no. 66 on health services in municipalities and pursuant to Act of 13 December 1991 no. 81 on social services etc. (Lovdata.no) and on clinical experience (1). Paracetamol should always be considered the first-line therapy for pain. In case of moderate to severe pain, low and titrated dosages of an opioid are recommended, and transdermal buprenorphine may be an option (189). When prescribing opioids for treating pain in dementia, great consideration should be given to drug selection and dosing frequency (186). Particularly in older people with dementia, pharmacological treatment should be initiated with great caution. Competence in pain assessment should include pain in dementia (192). Starting dosage(s) should be low and titrated to response (189).

**Occurrence of use in people with dementia**

The analgesic drug use has been reported to increase among nursing home patients. From 2000 to 2011, analgesic drug prescription increased by 65% in Norwegian nursing home patients with and without dementia. In 2011, 48.4% of patients in nursing homes were prescribed paracetamol and 23.8% received opioids, a relative increase of 113 and 118%, respectively, compared with 2000. In 2011, patients with dementia received the same amount of analgesics compared with patients without dementia. Older women (>80 years) were more likely than men to be treated with analgesics, especially paracetamol, and one explanation may be that women are expected to have more pain-related diagnoses (193).
Studies have reported frequent use of opioids in patients with dementia (194). However, a possible under-treatment of opioids can be caused by persons with dementia underreporting pain as a symptom, in addition to the prescribers’ fear of adverse effects of opioids (186).

**Treatment with AChEIs**

AChEIs use for BPSD in AD may be beneficial (113, 195), but the evidence is inconsistent (56). Some studies have suggested that these medications have a modest effect in alleviating BPSD (9, 30, 123, 196). Although AChEIs may afford some benefit, their effect appears after several weeks. NICE recommends their use in BPSD only when non-pharmacological options and antipsychotics are either inappropriate or ineffective (56). AChEIs are usually initiated at the time of a diagnosis of AD, but we do not know if this may affect the prescription of psychotropic drugs.

**Treatment with memantine**

Growing evidence for memantine suggests that it may be beneficial in treating BPSD in AD, although there is doubt as to whether its benefits are clinically significant (56). Meta analysis has shown that BPSD does not show significant improvement with memantine (30, 197).

**Treatment with antiepileptics**

Carmabazepine has shown some effect in BPSD, but with significant ADRs (198). Other mood stabilizers like valproate have not shown to be effective in the treatment of BPSD (153). A Cochrane review concludes that valproate preparations probably are ineffective in treating agitation in people with dementia, and associated with high rate of ADRs (199).

**1.6 Prevalence of use of psychotropics in Behavioural and Psychological Symptoms in Dementia**

Long-term treatment with psychotropic drugs are frequently used among nursing home residents (162), and has also shown to be frequent among community-dwelling persons with AD (144). A study based on the NorPD showed that the concomitant use of psychotropic drugs with anti-dementia drugs was extensive, especially among women, with a total of
57.4% in men and 65.8% in women (200). However, a recent study shows that outpatients who have less advanced dementia need less psychotropic drugs than institutionalised dementia patients (142). Psychotropic drugs are commonly involved in treatment of BPSD in nursing homes in Norway. In one study, the proportion of patients in nursing homes using antipsychotics was about 18% and antidepressants about 37%, while opioid use was observed in about 34% of the patients. These numbers were reduced following a medication review (10, 145). Another study of nursing home patients showed that 41% used multiple psychotropic drugs (141). Different studies describe prevalence of use of psychotropics (10, 141-145, 147, 162, 200-212). An overview of several studies concerning prevalence of use of psychotropics is given in Table 4.

Table 4 Prevalence of use of psychotropics in different studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Prevalence of use of psychotropics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Callegari E, Benth JS, Selbek G, Grttnnerød Lic C, Bergh S. Does psychotropic drug prescription change in nursing home patients the first 6 months after admission? JAMDA 2021 (22)101-108 (Norway)</td>
<td>Antipsychotics: 13.5% on admission, 19% six months later. Sedatives/Hypnotics: 22.6% on admission, 30.3% six months later. Anxiolytics: 17.1% on admission, 21.4% six months later. Antidepressants: 31% on admission, 40.1% six months later.</td>
</tr>
<tr>
<td>Fog AF, Mdala I, Engedal K, Straand J. Variation between nursing homes in drug use and in drug-related problems. BMC Geriatrics 2020, 20:336 (Norway)</td>
<td>Antipsychotics: 3-50%, BZDs: 24-99%, antidepressants: 9-75%</td>
</tr>
<tr>
<td>Fog AF, Straand J, Engedal K, Blix HS. Drug use differs by care level. A cross sectional comparison between older people living at home or in a nursing home in Oslo, Norway. BMC Geriatrics 2019, 19:49 (1-9) (Norway)</td>
<td>Antipsychotics 4.0% living at home, 17.2% nursing home, anxiolytics 16.2% living at home, 48.4% nursing home, hypnotics/sedatives 28.6% living at home, 49.2% nursing home, antidepressants 11.2% living at home, 31.6% nursing home</td>
</tr>
<tr>
<td>Lornstad MT, Aaroen M, Benth S, Benth JS, Helvik A-S. Prevalence and persistent use of psychotropic drugs in older adults receiving domiciliary care at baseline. BMC Geriatrics. 2019, 19:119 (Norway)</td>
<td>Sedatives 21-23%, antipsychotics 4-7% (the majority of the participants used traditional antipsychotics), antidepressants 16-22%</td>
</tr>
<tr>
<td>Helvik A-S, Benth JS, Wu B, Engedal K, Selbek G. Persistent use of psychotropic drugs in nursing home residents in Norway BMC Geriatrics. 2017;17(52) (Norway)</td>
<td>Antidepressants: 32.7% at last follow-up. Among those who completed all assessments: Antipsychotics: 10.4%, antidepressants: 19.8%, anxiolytics 11.5%, sedatives: 9.4%</td>
</tr>
<tr>
<td>Maust DT, Langa KM, Blow FC, Kales HC. Psychotropic use and associated neuropsychiatric symptoms among patients with dementia in the United States. Int J Geriatr Psychiatry. 2017;32:164-74. (USA)</td>
<td>41.4% were prescribed a psychotropic medication, including 84.0% of nursing home residents and 28.6% of community-dwellers. 23.5% were prescribed an antidepressant.</td>
</tr>
<tr>
<td>Reference</td>
<td>Summary</td>
</tr>
<tr>
<td>--------------------------------------------------------------------------</td>
<td>-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Nyborg G, Brekke M, Straand J, Gjelstad S, Romøren M. Potentially inappropriate medication use in nursing homes: an observational study using the NORGEP-NH criteria. BMC Geriatrics 2017;17:220 (Norway)</td>
<td>Over 10 % of residents used antipsychotics, 30.9% used hypnotics, and 35.3% used antidepressants on a regular basis.</td>
</tr>
<tr>
<td>Oesterhus R, Aarsland D, Soensyn H, et al. Potential inappropriate medications and drug-drug interactions in home-dwelling people with mild dementia. Int J Geriatr Psychiatry. 2017;32:183-92. (Norway)</td>
<td>Even in these patients with mild dementia, nearly 70% of the patients were using one or more psychotropic drug.</td>
</tr>
<tr>
<td>Ravona-Springer R, Davidson M. Considerations in psychotropic treatments in dementia - can polypharmacy be avoided? Int J Neuropsychopharmacol. 2014:17:1107-17 (Review article)</td>
<td>Review article: Rikala et al 2011: 38% at least one psychotropic drug 31% BZDs, 12% antidepressants, 6% antipsychotics. Fick et al 2007: 80% of demented patients in the community were prescribed CNS active medications</td>
</tr>
<tr>
<td>Koopmans RT, Reinders R, van Vliet D, et al. Prevalence and correlates of psychotropic drug use in community-dwelling people with young onset dementia: the NeedYD-study. Int Psychogeriatr 2014;26:1983-89. (The Netherlands)</td>
<td>36.2% of patients used one drug, and Antidepressants (36.2%) and antipsychotic drugs (17.3%) were the most frequently prescribed psychotropic drugs</td>
</tr>
<tr>
<td>Selbak G, Kirkevold Ø, Engedal K. The course of psychiatric and behavioral symptoms and the use of psychotropic medication in patients with dementia in Norwegian nursing homes - a 12-month follow-up study. Am J Geriatr Psychiatry. 2008;16(7):528-36 (Norway)</td>
<td>Persistent use of antidepressants (79%), antipsychotics (75%), or any psychotropic drug (88%) was common.</td>
</tr>
</tbody>
</table>
1.7 Psychotropic polypharmacy

Psychotropic polypharmacy (PPP), the use of two or more psychotropic drugs concomitantly, is reported to be frequent in AD patients (213), especially in women (214). People with dementia use more psychotropics compared to the general population, despite the recommendations of a restrictive use of psychotropics in BPSD (141). Severe BPSD, especially affective symptoms and agitation, has been related to multi-use. Polypharmacy of psychotropics has shown to be more frequent in demented community dwelling people compared to non-demented old people (207). Polypharmacy is a well-known phenomenon in older adults, with increased risk of interactions (105, 215) and leads to an increase in the likelihood of high anticholinergic scores (83, 216). Given the polypharmacy often observed in older adults, the likelihood of being prescribed an anticholinergic drug is not negligible (92). The highly increased fall risk in elderly individuals with AD can be the result of interaction of several factors including polypharmacy and anticholinergic side effects reported with antipsychotics (78, 188).

Polypharmacy may be a result of multimorbidity, and the use of multiple psychotropic drugs might indicate that clinicians try to treat a symptom with one drug, and if the symptom persists, they add another drug, often with the same indication, without stopping or re-evaluating the treatment. This can be due to belief in the additive effect, or to the burden BPSD puts on patients and caregivers, resulting in a pressure from caregivers to prescribe (141). Increase in caregiver support and medical education, among others in avoiding inappropriate drug prescribing (217), may help decrease requests for medications (207).

Factors associated with PPP are reported to be high age (<75 years), female sex and prior psychiatric diagnosis (147). Previous studies on sex difference in the prevalence of BPSD have reported that women experience behavioural symptoms, especially depressive symptoms, anxiety and delusions, more frequently than men. This might explain why PPP is more common among women (147).

About 25% of patients with dementia living at home have been reported to be prescribed two or more psychotropic drugs (213). Combination of drugs with cardiac activity and AChEIs may explain harmful drug-drug interactions (78), likewise combinations of AChEIs with some psychotropic drugs. Different studies describe prevalence of psychotropic
polypharmacy (141, 143, 147, 204, 207, 208, 210, 211, 213, 218). An overview of studies concerning polypharmacy of psychotropics is given in Table 5.

### Table 5 Prevalence of use of psychotropic polypharmacy in different studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orsel K, Taipale H, Tolpanen A-M, Koponen M, Tanskanen A, Tiilhonen J</td>
<td>The use of ≥ 2 psychotropic drugs increased from 5.9% five years before to 18.3% four years after AD diagnosis.</td>
</tr>
<tr>
<td>Nyborg G, Brekke M, Straand J, Gjelstad S, Romøren M.</td>
<td>Three or more psychotropics were used concomitantly by 14.5% of residents on a regular basis.</td>
</tr>
<tr>
<td>Nørgaard A, Jensen-Dahm C, Gasse C, Hansen ES, Waldemar G.</td>
<td>Psychotropic polypharmacy was found in 2.8% of the patients.</td>
</tr>
<tr>
<td>Oesterhus R, Aarsland D, Soensyns H, Rongve A, Selbaek G, Kjosavik SR</td>
<td>Psychotropic polypharmacy was found in 2.8% of the patients.</td>
</tr>
<tr>
<td>Gulla C, Selbaek G, Flo E, Kjome R, Kirkevold O, Husebø B.</td>
<td>41% exposed to multi-psychotropic drug prescriptions</td>
</tr>
<tr>
<td>Ravona-Springer R, Davidson M.</td>
<td>Rikala et al 2011: 28% of subjects used at least two psychotropics. Bartlett et al: at least two psychotropics associated with persistent use</td>
</tr>
<tr>
<td>Koopmans RTCM, Reinders R, van Vliet D, Verkey FRJ, de Vugt ME, Bor H</td>
<td>12.2% used two different drugs.</td>
</tr>
<tr>
<td>Selbek G, Kirkevold O, Engedal K.</td>
<td>Approximately 75% receive one or more psychotropic drugs.</td>
</tr>
<tr>
<td>Giron MST, Forsell Y, Bernstein C, Thorslund M, Winblad B, Fastbom J</td>
<td>Psychotropic drug use ranged from 0-5 with 7.6% using three or more</td>
</tr>
</tbody>
</table>

We have sparse information regarding sex differences in polypharmacy burden in a predementia and dementia phase of AD patients in Norway.
1.8 Implications of sex, age and heart rate related drugs

1.8.1 Sex differences in use of psychotropics, analgesics and cardiovascular drugs

ADRs are more common in women than in men, attributed to factors such as overdosing as a result of pharmacokinetic and pharmacodynamic differences between the sexes and women taking more medications than men (219, 220). Women and men differ in body size and composition, metabolism, elimination, oral absorption, which can also be compounded by age. In women, hydrophilic drugs have smaller volume of distribution (Vd) which is the theoretical volume in which the total amount of drug would need to be uniformly distributed in order to produce the desired blood concentration of a drug. Lipophilic drugs have higher Vd in women. Lower body surface in women, differences in kidney function, drug resorption and metabolism by hepatic enzymes and excretion compared to men, will cause significant differences in pharmacokinetics (221). Renal clearance may be about 10% less in women than in men, and this will impact drugs subject to elimination by renal clearance mechanisms, with risk of increased toxicity, especially in elderly women who present other changes in their physiology which render them at greater risk (222). Therefore, pharmacokinetic differences may predispose women to more dose-related adverse effects (220).

Women with dementia more often concurrently use drugs known to impair cognition (223) compared to men, with a higher risk of ADRs and death (224). Female sex has been shown to be associated with a higher likelihood of inappropriate drug use (225). Besides, dependency-producing properties of anxiolytics are more pronounced in women than in men (226). Further, women have an increased risk of polypharmacy (227), are more likely to have functional and cognitive disabilities due to aging and to live alone, known to be associated with depressed mood and over-utilization of psychotropic drugs (226). The increased risk may be driven by combinations with BZDs (224). Studies have shown that psychotropic drugs are used more common in hospitalised elderly women than in men (226). However, antipsychotic drug use has been reported to be higher among men with AD, and antidepressant drug use higher among women with AD (228, 229). Psychotropic drugs and opioids are most commonly involved in all types of drug related problems in elderly people in nursing homes in Norway (145), and female sex has been associated with multi-use (141). Women have a much higher prevalence of many pain disorders than men, and sex differences in the use of analgesics probably mirror the higher prevalence of chronic pain in women (230). In
Norway, older women living at home are reported to use more opioids and paracetamol than men (142), and female sex has been associated with an increased risk of drug related problems with opioids involved in nursing homes (145).

Women will in general suffer from cardiovascular disease 6-10 years later than men do, among others explained by women having longer life expectancy and thereby different development of blood pressure (231). The QT interval has been reported to be longer in women, and female sex is reported to be associated with higher risk of drug induced ventricular arrhythmias (232) and a greater response to drugs that prolong the QT interval (233).

Sex aspects are generally not included in drug product monographs and in treatment guidelines, even in areas where sex differences are obvious such as for ischaemic heart disease (221, 234). The literature is sparse regarding sex differences in medication use in individuals with dementia (214). Knowledge of sex differences might assist clinicians in selecting the most efficacious interventions in cases with suspected or confirmed dementia (235).

Little is known about the sex-differences of prescription of psychotropics, analgesics and drugs with the effect on the heart rate in Norway during the years before and after the AD diagnosis.

1.8.2 Age differences in use of psychotropics, analgesics and cardiovascular drugs

The burden of age-related comorbidities, such as dementia, cardiovascular diseases, hypertension, diabetes mellitus and renal impairment, increases in the elderly, resulting in twice as high medication use compared with middle-aged adults (78, 236). Older adults are more vulnerable to ADRs due to the aging process, including changes in drug metabolism, and increased co-morbidities and polypharmacy (237). In old age, muscle mass and total body water are reduced, affecting pharmacokinetics of hydrophilic drugs with a smaller volume of distribution. Body fat increases from 20% to 40% with age, resulting in larger volume of distribution of lipophilic drugs (78). In older adults, the distribution of drugs into the CNS tissue might be affected considering that the BBB becomes more porous in the elderly, resulting in increased drug availability to the CNS. In addition, age-related decrease in
apparent liver blood flow has been reported. However, the most significant change with adult aging is the reduction in renal drug clearance with a decline in the glomerular filtration rate (236).

Psychotropic medications are frequently used to treat mental health disorders which are common in the population of older adults. This use pattern is complicated by an increase in the effect of psychotropics in older adults due to age-related changes in pharmacokinetic and pharmacodynamic parameters (238). AD patients present an increased risk of ADRs and drug-drug interaction due to several factors such as age, age of disease onset and the presence of polypharmacy. Anxiolytics, BZDs, and antidepressants might interact with other concomitant used drugs through both pharmacokinetic and pharmacodynamic mechanisms. The impaired neurotransmission in AD patients may increase CNS drug activity or sensitivity, and these disease-related CNS alterations may cause sensitisation to the effects of psychotropic drugs. Altered sensitivity to drugs such as psychotropic and cardiovascular drugs predisposes older persons to ADRs (239), in particular, AD patients (78).

A large percentage of older people have complex arrhythmias, and prolongation of the QT interval is related to age-associated degenerative change in the conduction system (240). The most common risk factor for drug-induced Torsades de Pointes (TdP) has been shown to be age over 65 years (241).

1.8.3 Risk of heart rate related adverse effects

Although the target organ for AChEIs is the brain, the heart is also rich in cholinesterases, thus cholinergic effects of AChEIs may adversely affect cardiac function, especially in older patients, implying risks of arrhythmias, prolonged QT interval and TdP (240). Aging affects the cardiovascular system in many ways, such as decreased compliance of blood vessels through arterial thickening and stiffening, left ventricular thickening and later diastolic filling. In addition, symptomatic sinus bradycardia occurs almost only after the age of 65, and the prevalence of sinus bradycardia is less than 5% for both men and women older than 65 years, while the prevalence of first-degree AV block in healthy older men is about 3-4% (242). Overall, a large percentage of older adults have conduction disorders or arrhythmias (242). Prolongation of the QT interval is related to age-associated degenerative change in the conduction system (240). A higher risk of hospitalization related to the use of cardiovascular
medications has been observed in the oldest population, for example in the use of antiarrhythmics and beta-blocking agents (237).

Of the AChEIs, only donepezil is classified with a known risk of QT-prolongation and TdP (243), still, the current knowledge on this topic is limited, and no population-based epidemiological studies have examined the comparative risk with use of the different AChEIs (244). Effects on the heart is a class effect of the AChEIs (60) and associated with bradycardia, one mechanism is through the blockage of cholinesterase connected to the vagal nerve which can cause atrioventricular (AV), or sinoatrial block (244). Use of AChEIs has been associated with more than two-fold risk of hospitalization due to bradycardia among older patients. In addition, those receiving concurrent therapy with negative chronotropic drugs such as betablockers, digoxin, and verapamil had an increased risk as well (245).

According to a US study among veterans with AD, patients taking betablockers, with a history of falls and of myocardial infarction, heart failure, or hypertension have been reported to be at the greatest risk for a decrease in heart rate after starting to use AChEIs (246). As betablockers and cardiotropic calcium blockers are among drugs which may increase heart related problems like bradycardia and hypotension, and because bradycardia in older people is associated with syncope, arrhythmias and falls, it is important to identify high-risk patients (246).

The most serious ADR of digoxin are life-threatening cardiac disorders, and bradycardia is an early warning sign (247). Through its heart rate lowering effect, digoxin can cause TdP. The risk increases with co-administration of heart rate lowering drugs and drugs that can prolong the QT interval, such as AChEIs (247). Among the commonly used agents for treatment of BPSD are escitalopram/citalopram and to some extent haloperidol, which have a known risk of QT interval prolongation and TdP, like donepezil (243).

Both conventional and atypical antipsychotics can cause prolonged QT interval, with the overall effect depending on a variety of risk factors (248). Prescriptions of drugs like betablockers, digoxin and verapamil can be considered as a proxy for heart disease, and patients with dementia suffering from pre-existing cardiac disease like heart rate disturbances are reported to have higher risk of antipsychotic-induced arrhythmias and sudden cardiac death, related to prolongation of the QT interval (234). QT-prolongation remains an imperfect, though well-established marker of risk for TdP. A careful analysis of QT risk
factors when prescribing psychotropics is the most important risk-reducing intervention (249). The current knowledge in Norway on co-prescribing of AChEIs and drugs with an effect on the heart is poor.

In summary, the literature review shows that information on prevalences of concurrent use of AChEIs and agents with anticholinergic properties in Norway is missing in AD patients, as well as knowledge of prevalences of use of psychotropic drugs, of polypharmacy burden and of analgesics in users of AChEIs before and after initiating treatment with AChEIs, and extent of psychotropic polypharmacy. The possible impact of sex differences and age in these respects is unknown, like co-prescribing of AChEIs and drugs with an effect on the heart rate.
1.9 Aims of the thesis
The overall aim was to gain more knowledge about prescription patterns of drugs that have the potential to interact with AChEIs. This thesis aims to increase the knowledge of prescription patterns of agents with an anticholinergic effect, of drugs commonly used in the treatment of BPSD, analgesics, and drugs with an effect on the heart rate, in a predementia phase and in AChEI treated patients. In addition, impact of sex differences and age, polypharmacy burden of psychotropics, analgesics, and heart-rate related drugs before and after initiating AChEIs were studied. This was done by examining drug prescription in AChEI users and in persons of the general population. Data was retrieved from the NorPD.

Specifically, the aims were as follows in the five sub studies which were conducted:

1. To examine the effect on total ADS-scores of a pharmacist-geriatrician co-operation management of unfavourable concomitant use of AChEIs and drugs with anticholinergic effects.

2. To analyze the incident use of AChEI and concomitant use of drugs with anticholinergic properties.

3. To study the use of different drugs commonly prescribed for BPSD in persistent users of AChEIs before and after AChEI initiation.

4. To examine the sex differences on prevalence, pattern and trends in the prescription of psychotropics and analgesics in users of AChEIs, before and after AChEI initiation.

5. To study changes, from four years before to two years after initiating treatment with AChEIs, of: i) the prevalence of use of drugs commonly prescribed for heart rate control, and drugs with a known risk of TdP commonly prescribed for treatment of BPSD, ii) the prevalence of combinations of drugs with a known risk of TdP, and drugs with a known heart rate lowering effect, iii) the differences in prescription patterns of i) and ii) by age and sex.
2 Material and methods

2.1 Use of data from pharmacoepidemiological studies and description of the Norwegian Prescription Database

In modern epidemiology, epidemiological studies with inclusion of all persons in a population followed for decades are important. Pharmacoepidemiology is a field evaluating drug use and effects in populations, and covers identification and quantifications of ADRs, drug use pattern, and identification of whether drugs developed for one indication might be used for another (250).

The main strengths with pharmacoepidemiological studies are that data already exists and valuable time has passed, that data have been collected independently and the complete study population minimizes selection bias. The large sample size in studies based on prescription databases allows precise estimates to be made. On the other hand, important limitations are that necessary information may be unavailable, and that missing data are difficult to handle because the data collection procedures are not designed for specific research studies (251, 252).

The health registers are used for health analysis, health statistics, improving the quality of healthcare, research, administration and emergency preparedness. The registries used in Norway are regulated according to the Act relating to Personal Health Data Registries. The registries with personally identifiable information that are not based on consent are established after evaluation by the Norwegian government. Some of the national health registries do not contain personally identifiable data. The registries in Norway are managed by different institutions, and the NorPD is managed by the National Institute of Public Health and is one of the mandatory national health registries in Norway which were established to maintain national functions. This database covers, since 2004, information from all prescriptions dispensed at Norwegian pharmacies to individual patients. Drugs dispensed to patients in hospitals and long-term institutions (including nursing homes) are not included in the NorPD, so when a patient moves to a nursing home, we are not able to follow the patient’s drug use any longer. However, in 2022 the NorPD will be extended with a new drug register, and the intention is to get nursing home and hospital data included. It is possible to follow all individuals having purchased drugs through their personal unique identifying number (253).
Data registered in the NorPD include sex, age, year of death (when relevant) and information on drugs dispensed.

### 2.2 Study group and general population

In **sub study 1** we recorded drug use of 22 in-hospital and 28 out-clinic patients in a prospective manner (**paper 1**). For **sub study 2 to 5**, drug use data was collected from the NorPD (**paper 2-5**).

We assumed that dispensed drugs represented consumed drugs. The drugs were classified according to the Anatomical Therapeutic Chemical (ATC) classification system (254). For each dispensed prescription, the following data for analyses in our studies were obtained: the date of dispensing, medicinal product name and formulation, ATC-code, defined daily doses (DDDs) and the number of tablets/capsules/plasters (allowing us to calculate treatment periods), and the prescriber’s specialty.

For **sub study 3-5**, the use of each studied drug in the study population was compared to the use in the general population. See later on for further explanation.

### 2.3 Clinical pharmacy as a method of preventing drug related problems

Clinical pharmacy was used as a method in **paper 1** to identify and prevent drug related problems defined as an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes (255). A high rate of drug related hospital admissions and drug related problems have been reported in the geriatric ward. The high number of drug related problems have been detected by clinical pharmacists working in a systematic way in an interdisciplinary team with a limited amount of time (256). Drug related problems can contribute to increased morbidity and mortality, and many studies have shown that clinical pharmacists can contribute to identification and prevention of drug related problems (255). One study reporting the impact of a clinical pharmacist in a geriatric team in Norway highlights that drugs with anticholinergic activity were to a great extent withdrawn, due to the unfavourable effects, and in particular with regard to cognitive function (257).
2.4 Project design

**Sub study 1** was a simple intervention study with no control group. It had a prospective design (see later about the intervention). In the retrospective studies published in paper 2 to 5, we had access to individual data from the NorPD for all persons being dispensed at least one prescription of AChEIs (ATC-code N06DA) in the period 01.01.2004 – 31.12.2012 (**paper 2**) and 01.01.2004 – 31.12.2016 (**paper 3-5**) (Table 6). In addition, for every ATC-code, we had access to the yearly total number of users in the population by sex and one year age groups (up to and including 89 years).

**Table 6. Project design of study 2-5**

<table>
<thead>
<tr>
<th>Paper</th>
<th>Data period</th>
<th>Start of AChEI</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-5</td>
<td>2004-2016</td>
<td>2008-2013</td>
<td>37-88</td>
</tr>
</tbody>
</table>

2.5 Study populations of sub studies 2-5

The Norwegian National Guideline on Dementia recommends patients with AD of mild degree mixed with VaD to be offered symptomatic treatment with AChEI (1). AD has been diagnosed in 57% of patient with dementia in a recent very large Norwegian study, and LBD in only 4% (12). As most of the patients using AChEIs according to indication having AD, we have used time of start with AChEI as a surrogate measure of a diagnosis of AD in this thesis.

Incident use was defined as being prescribed an AChEI drug after more than 365 successive days with no AChEI prescriptions. The incident users being prescribed AChEI treatment for less than eight months are called “quitters”, the remaining are referred to as “persistent users”, for details, see 2.5.2 Statistical considerations.

Some patients were repeated “incident users” (having several AChEI-free periods of more than 365 days). For each patient we started follow-up at the date of the prescription initiating the longest period with subsequent prescriptions less than 365 days apart (index date). The ‘longest period’ means the period with the largest number of prescriptions.

According to recommendations made by the Norwegian Directorate of Health, suggested time intervals for controls after starting treatment with AChEI are at minimum 14-28 days, 4-6 months and thereafter according to the patient’s needs. At the first control (after 14-28 days), drug compliance and side effects as well as ECG results are usually checked, while later
controls also include effect evaluation (1). We did not have information about how many patients underwent evaluation of treatment after the different treatment periods, due to lack of clinical data. We chose 8 months (240 days) as a cut-off to leave lag time for physician evaluation visits.

In sub study 1, we examined drug use in 50 patients (22 inpatients and 28 outpatients) initiating or undergoing treatment with AChEIs, who were prospectively recruited from June to December 2011 at Bærum Hospital, Gjettum, Norway. Intervention by a pharmacist guided the geriatricians to reduce the anticholinergic burden in the AChEI-treated patients exposed to an ADS score of 2 or more. Assessment of anticholinergic burden was performed using the ADS score model.

In sub study 2, we examined drug use of persons aged 65-80 years, who were persistent users of AChEI (see Table 1). We examined patients who started treatment between 1.1.2005 (the earliest possible index date) and 31.12.2011 to ensure inclusion of new users and with one year follow-up. Treatment length was estimated as the time from index date until the drug dispensed in the last prescription of the longest period was supposed consumed.

In sub study 3-5, we included persistent AChEI users aged 88 years or younger (see Table 7). The age limit of 88 was set to make a comparison with the general population for which data with one year age resolution was available up to and including 89 years. The included patients were alive two years after the year of AChEI treatment initiation and were registered in the NorPD the second year after AChEI initiation (not yet in nursing home). They were followed from 4 years (1460 days) before initiation to 2 years (729 days) after initiation of AChEI in the period of 2008-2013. The six-year interval was from 2004-2009 for those starting first (1.1. 2008) and from 2010 to 2015 for those starting latest (31.12.2013). The earliest possible index date was 1.1.2008 and the latest index date was 31.12.2013. The reason for this is that we needed information about prescriptions 4 years before and 2 years after index date.

Concerning subgroups, the study populations included in sub study 3 and 4 were stratified into four subgroups according to age at initiation. Due to the definition of early onset of dementia, the young onset group included persons 37-64 years old. The last three groups were selected to reach equal age spans (65-72, 73-80 and 81-88 years old). In sub study 5, the study population was stratified into two subgroups according to age at initiation of AChEI: 37-age
79 and 80-88 years old. This cut off point was chosen because older adults above the age of 80 are more vulnerable due to the aging process and increased co-morbidities.

The general population was stratified into the same subgroups as the respective sub studies (table 7).

**Table 7. Number of individuals in the general population in the different subgroups**

<table>
<thead>
<tr>
<th>Paper</th>
<th>Age</th>
<th>Subgroups</th>
<th>General population</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-4</td>
<td>37-88</td>
<td>37-64</td>
<td>1 828 796</td>
</tr>
<tr>
<td></td>
<td></td>
<td>65-72</td>
<td>324 288</td>
</tr>
<tr>
<td></td>
<td></td>
<td>73-80</td>
<td>216 488</td>
</tr>
<tr>
<td></td>
<td></td>
<td>81-88</td>
<td>147 924</td>
</tr>
<tr>
<td>5</td>
<td>37-88</td>
<td>37-79</td>
<td>2 345 312</td>
</tr>
<tr>
<td></td>
<td></td>
<td>80-88</td>
<td>172 184</td>
</tr>
</tbody>
</table>

### 2.6 Ethical considerations and data protection issues

**Study 1**
The research protocol of sub study 1 was evaluated by the regional committee for medical and health research ethics, REC South-East. The project was not considered mandatory for approval by REC, according to letter from REC South-East with reference 2011/685 D. The project was considered to be a quality assurance project. The project protocol was submitted to and approved by the Data protection officer and the management at Bærum hospital. After the study procedure had been explained to the patients, written consent to participate was provided. Consent to participate was provided by next of kin if the patient was unable to consent. The pharmacist signed a declaration of confidentiality which was used in Bærum hospital and had access to the electronic medical record system and to the patients' curve documents. The responsible doctor noted the results of the drug review in the patient's medical record. The pharmacist documented and handled the deidentified necessary information according to current rules.

**Study 2-5**
All the pharmacies in Norway register prescriptions electronically, and the information is sent in monthly reports to the NorPD. The patient’s personal ID number and the prescriber’s ID number are replaced by a unique pseudonym by Statistics Norway. This makes it possible to
link drug use to individuals without knowing their identity. Personal information is not disclosed from the NorPD. The database is governed by the national regulation of 17 October 2003 about the collection and processing of health data in the Norwegian Prescription Database. The NorPD generated pseudonymous files for research purposes, as regulated by Norwegian Personal Health Data Filing Act (253), hence there was no demand of additional approval by the ethics committee as documented in the Norwegian Health Research Act. The data holder of NorPD, the Norwegian Institute of Public health, has approved a full Data Protection Impact Assessment (DPIA) of the project.

2.7 Statistics

2.7.1 Statistical methods
In sub study 1, a Wilcoxon signed-rank test was used to statistically evaluate the effect of pharmacist interventions on ADS scores.

In sub study 2-5, Period prevalence, age adjusted prevalences, means, medians, percentages, 95% CIs and treatment periods were presented when appropriate. R version 3.1.0 (258) was used for descriptive statistics. Treatment periods were calculated based on number of tablets/capsules and dose intervals. The CIs were computed using the ‘binom.confint’ function in R with method=”wilson”. In sub study 2, the R-function prop.trend.test was used to test for associations between comedication at the start of treatment and treatment length. In sub study 3-5, drug use in the study population was compared with the use in a general population, for details, see 2.5.2 Statistical considerations. Age adjusted prevalences were computed for the general population, using the ‘ageadjust.direct’ function in R. Age-adjusted prevalence ratios (PRs) were calculated by dividing the prevalence in the AChEI users by the age- and gender adjusted prevalence in the general population.

2.7.2 Statistical considerations concerning sub study 2-5
The patients being prescribed AChEi treatment for less than 8 months were called quitters, the remaining were referred to as persistent users (Figure 4). Incident use was defined as being prescribed an AChEI drug after more than 365 successive days with no AChEI prescriptions.
The following algorithm was applied to define persistent use (8 months treatment): A user was defined as persistent if any of the following was true: (a) a new prescription was given between day 210 and day 240 after initiation (index date), (b) drugs for at least 210 days’ consumption were prescribed during the first 210 days from initiation, or (c) the last prescription before day 210 lasted to day 210. A stricter definition (either drug for at least 240 days prescribed during the first 240 days or the last prescription before day 240 lasting to day 240) resulted in fewer persistent users. However, 29% of those who were defined as nonpersistent by the strict definition were prescribed AChEI drugs after the 240-day limit (“false quitters”), compared to 16% using the first definition; thus, the first definition was chosen to reduce the number of “false quitters”.

Figure 4. Illustration of incident and persistent use. Circles are prescriptions. A is not an incident user since the first prescription comes less than 365 days after 01.01.2004. B is an incident user with AChEI initiation 01.01.2007. C and D have two new-user periods, where the last one has most prescriptions, and AChEI initiation is at 01.01.2007. D fulfills the criterion for persistent use, but is not included in the study population since AChEI initiation is before 01.01.2008. E is a persistent user with AChEI initiation 01.01.2008. F has three new-user periods, where the last one has most prescriptions but does not fulfill the criterion for persistent use. Hence F is not a persistent user. Thus, all except A are incident users, but only E is a persistent user that fulfills the criteria for inclusion in the study population.

Sub study 2
We wanted to analyze to which extent incident users became persistent users (≥ 8 months treatment), and to study whether there was a relationship between comedication in the first period after initiation of AChEI treatment and duration of treatment in persistent users. To make the length of the comedication period independent of the length of treatment, we
examined comedication during the first six months after initiation of AChEI treatment. The length of treatment was studied after at least 8 months of therapy.

Users that were younger than 65 years or older than 80 years at start of follow-up were excluded. There are few patients who are diagnosed with dementia <65 years old, but there are many who are diagnosed with mild dementia after the age of 80 years, and most of them will not be nursing-home residents. Many of these patients will become nursing-home residents during the follow-up period, whereupon many of the residents will stop the AChEI treatment.

Out of the 13,609 incident users (period 2005-2011), only 3,284 persistent users were included (Figure 5). We excluded the 4,070 users with a limited use of less than 8 months, since potential response to treatment should then have been evaluated. We also included data on comedication for this group. One could discuss if we missed valuable information and half of our results by excluding this group of 4,070 users. However, it would have been difficult to evaluate whether end of AChEI treatment was due to a normal low response of the AChEIs, or due to anticholinergic effect of concomitantly prescribed drugs, therefore, we decided to exclude this group.

The remaining 6,255 that we excluded in the co-medication analysis were excluded because we wanted to examine the relationship between co-medication and treatment length (time from start to voluntary end), and therefore we must know the treatment length. Then it seemed natural to exclude those who died shortly after the last prescription and those who most likely continue to use AChEIs after the last registered prescription (institutionalized or end of follow-up).
Figure 5. Flow chart Paper 2. Time for study period, all users of AChEIs, new users of AChEIs, persistent users, quitters and subgroup for concomitant treatment.

Sub study 3-5
In sub study 3-5, based on data from the NorPD in the period of 2004-2016, the study population consisted of 11,764 persistent AChEI users aged 37-88 years who initiated treatment between January 1, 2008, and December 31, 2013. They were followed from 4 years (1,460 days) before initiation to 2 years (729 days) after initiation and stratified into different age groups (Figure 6).
Figure 6. Flow chart sub study 3-5. Time for study period, all users of AChEIs, new users of AChEIs, persistent users, quitters and subgroup for concomitant treatment.

The use of e.g. antidepressants in the study population the first year after initiation of AChEI was compared to the use in the general population as follows: For each of the years 2008-2013, the age- and gender adjusted prevalence of antidepressant use in the general population was computed, using the age- and sex distribution of those initiating AChEI the actual year as reference. The over-all age- and sex adjusted prevalence in the general population was thereafter estimated as \[ \frac{\sum_{y=2008}^{2013} u_y}{\sum_{y=2008}^{2013} N_y} \] where \( u_y \) and \( N_y \) are the age-adjusted number of antidepressant users and the population in year \( y \), respectively. As an example, the antidepressant use the first year after initiation for a man initiating AChEI in 2008 at an age of 81 was compared to the antidepressant use of the 81-year-old male general population in
2008. His antidepressant use the second year after initiation (2009, at age 82) was compared to the antidepressant use of the 82-year-old male general population in 2009.

In the study population, we are able to follow the same individual over a six-year interval. This is not possible in the general population. When comparing the antidepressant use in AChEI initiators X years before/after initiation with the general population, the dispensing years and the age in the general population was shifted X years. Thus, antidepressant use in the 81–88-year age group four years before initiation (which was in 2004-2009, as initiation was in 2008-2013) was compared to use in the 77–84-year-old persons (as the age group was 4 years younger than the 81-88 group- four years before, i.e. 77-84 years olds) in 2004-2009 in the general population. Antidepressant use in the same age group the second year after initiation was compared to use in the 82–89-year-old in 2009-2014 in the general population. Age-adjusted prevalence ratios (PRs) for each sex were calculated by dividing the prevalence in the AChEI users by the age- adjusted prevalence in the general population.
3 Results

Paper 1
Pharmacist-initiated management of antagonistic interactions between anticholinergic drugs and acetylcholinesterase inhibitors

The aim of this study was to examine the effects of a pharmacist-geriatrician co-operation on management of the unfavourable, antagonistic interactions between AChEIs and drugs with anticholinergic properties.

A total of 50 patients, comprising 22 inpatients and 28 outpatients initiating or undergoing treatment with AChEIs, were prospectively recruited from June to December 2011 at Bærum Hospital, Gjettum, Norway. Intervention by a pharmacist guided the geriatricians to implement a reduction in anticholinergic burden in the AChEI-treated patients exposed to an ADS score of 2 or more. The results from this study showed that about 50% of the patients that used or were about to start treatment with AChEIs also concurrently used drugs reported to express anticholinergic activity. Assessment of anticholinergic burden was performed using the ADS score model founded on previously published classifications (96, 97) (0 = no anticholinergic activity, 1 = potentially anticholinergic, 2 = clinically significant anticholinergic and 3 = strong anticholinergic activity). For more than a quarter of the patients the total ADS score was 2 or more. Within the included population of this study, inpatients had a higher ADS score compared to the outpatients (table 8). This difference is consistent with the inpatient group using the highest number of drugs, with a median of 8.0 vs. 4.5 in the outpatient group. In general, it is therefore important to limit the drug use as much as possible in patients treated with AChEIs. Four out of the 6 patients receiving a drug with an ADS score of 2 or 3 were prescribed a USD.
Table 8. Characteristics of the patients and anticholinergic drug scale (ADS) scores before and after pharmacist-guided interventions among patients with ADS score ≥ 2

<table>
<thead>
<tr>
<th>Variable</th>
<th>Inpatients (n=22)</th>
<th>Outpatients (n=28)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>82 (66-92)</td>
<td>80 (61-94)</td>
</tr>
<tr>
<td>Female gender, n (%)</td>
<td>13 (59 %)</td>
<td>17 (60 %)</td>
</tr>
<tr>
<td>Number of regular drugs, median (range)</td>
<td>8 (1-14)</td>
<td>4.5 (0-10)</td>
</tr>
<tr>
<td>Number of drugs on demand, median (range)</td>
<td>1 (0-5)</td>
<td>0 (0-1)</td>
</tr>
<tr>
<td>ADS score, median (range)</td>
<td>1 (0-7)</td>
<td>0 (0-3)</td>
</tr>
<tr>
<td>Drugs with ADS score 3, n</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Drugs with ADS score 2, n</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Drugs with ADS score 1, n</td>
<td>23</td>
<td>10</td>
</tr>
<tr>
<td>Number of patients with ADS score ≥ 2</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>Score before intervention, median (range)</td>
<td>2 (2-3)</td>
<td>3 (2-7)</td>
</tr>
<tr>
<td>Score after intervention, median (range)</td>
<td>0.5 (0-1)</td>
<td>1 (0-1)</td>
</tr>
</tbody>
</table>

Concurrent use of AChEIs and anticholinergic drugs showed to be a relevant problem in outpatients as well as inpatients in this study. Whether this action improved the responsiveness to AChEI treatment in these patients was not evaluated. However, high ADS scores have been shown to be associated with negative clinical outcomes in several studies such as cognitive dysfunction and increased mortality among older adults (53, 93, 94, 260-263). Therefore, one would expect that the clinical outcome would be improved in this population following reduction of the anticholinergic burden.

In conclusion, the study showed that about 50% of the patients treated with AChEIs were co-medicated with anticholinergic agents that may limit or counteract the clinical effect. The study also showed that a pharmacist-geriatrician co-operation could be effective to avoid this kind of irrational combination therapy in patients with dementia.
Comedication and treatment length in users of acetylcholinesterase inhibitors

This was a retrospective study applying drug use data from the NorPD aiming at analyzing the incidence of AChEI use and comedication with drugs with anticholinergic properties and other potential unfavourable effects.

We registered co-prescribed drugs with anticholinergic properties, and included the following group of drugs, according to the ATC-system: 1) USDs (ATC group G04BD) have substances with anticholinergic properties and may be initiated due to incontinence being prevalent in patients with dementia. 2) antiparkinsonian drugs (N04) are well-known to have anticholinergic effect, and 3) psychotropic drugs were selected; Anxiolytics (N05B), hypnotics/sedatives (N05C), antipsychotics (N05A), antidepressants (N06A) and 4) analgesics (N02). The ADS score model was used as a measure of anticholinergic activity which was founded on previously published classifications (96, 97) (0 = no anticholinergic activity, 1 = potentially anticholinergic, 2 = clinically significant anticholinergic and 3 = strong anticholinergic activity). Patients being prescribed AChEI treatment for < 8 months were called quitters (n= 4,070), the remaining referred to as persistent users (n=3,284). The persistent users registered in the NorPD were followed in the period from 2008 to 2013.

Concerning overall anticholinergic burden, most of the anticholinergic drugs were considered to have a clinically significant or strong anticholinergic effect; 438 (13.3%) of the patients had at least one drug with an ADS score ≥ 2, and 513 users (15.6%) had a total ADS score ≥ 2.

Patients with high ADS score were more frequently discontinuing treatment early. A significantly higher proportion of those with < 1 year treatment than of those with > 3 years treatment had at least one drug with ADS ≥ 2 (16.1% vs 10.9%) and a total ADS score ≥ 2 (18.4% vs 12.9%). Co-prescribing of antipsychotics was strongly associated with early discontinuation of AChEI treatment. While 15.3% of those with treatment length of AChEI of < 1 year were co-medicated with antipsychotics, only 6.2% of those with > 3 years treatment were. A high proportion of co-prescription was observed for sedatives/hypnotics (31.6%) and antidepressants (28.4%). For antidepressants and anxiolytics/hypnotics and sedatives there was also a significant shorter treatment length with higher degree of co-medication, whereas for urologic spasmyotics, analgesics, and antiparkinsonian drugs treatment length was not associated with co-medication the first 6 months. The most frequently used antidepressant (N06A) was escitalopram (taken by 41% of those who used antidepressants), followed by
mirtazapine (16%), citalopram (14%), and mianserin (14%). Only 8% of the antidepressant users in the study population were administered a TCA (N06AA, nonselective monoamine reuptake inhibitors, with anticholinergic effect).

Persistent users and quitters did not differ in age and gender, but a higher proportion of persistent users had their treatment initiated by a specialist in geriatrics (16.4% [95% CI 15.7–17.2] vs. 14.2% [13.2–15.3]). Possible differences in prescribing could be attributed to the prescriber (specialists in geriatrics or not). An explanation could be that geriatricians possibly have more focus on polypharmacy in elderly people, resulting in total lower ADS score.

In conclusion, increased use of antidepressants and antipsychotics was observed both before and after initiation of AChEIs and may indicate that behavioural symptoms occur in a preclinical or early phase of AD. Co-prescribing of antipsychotics was strongly associated with early discontinuation of AChEI treatment. The prescription pattern of analgesics with a low use of opioids may indicate an undertreatment of pain in people with dementia.

**Paper 3**

**Drug use before and after initiating treatment with acetylcholinesterase inhibitors**

This was a retrospective study applying drug use data from the NorPD aiming at study the prevalence of use of different drugs commonly prescribed for BPSD in persistent users of AChEIs before and after AChEI initiation and to compare with the use in the general population. In total 11,764 users of AChEIs registered in the NorPD were followed in the period from 2008 to 2013. They were stratified into four age groups, 37-64, 65-72, 73-80 and 81-88 years old. Patients being prescribed AChEI treatment for <8 months were called quitters, the remaining referred to as persistent users. In addition, we compared with drug use in the general population (N ~ 2.5 million), using data from a web-based tool provided by the NorPD. For example, antidepressants use in the age group 81-88 years 4 years before initiation was compared to use in the age group 77-84 years in 2004-2009 in the general population.

We followed the 11,764 patient’s use of the following drugs four years before and two years after AChEI initiation in the period 2004-2016: Antidepressants (ATC group N06A excluding amitriptyline N06AA09 commonly prescribed for neuropathic pain), antipsychotics (N05A
excluding prochlorperazine N05AB04 commonly prescribed for vertigo), and analgesics (weak analgesic and opioids N02), which are frequently used among patients with dementia, but have anticholinergic activity or other known adverse effects, interactions and precautions. The drugs were classified according to the ATC-system.

The prevalence of the use of antidepressants strongly increased in the study population over the 6-year interval from 13.5% in the fourth year before initiation to 30.2% in the second year after initiation. In the general population, the prevalence was quite unchanged in all the age groups and increased from 10.3% to 11.1%. The highest prevalence of use of antidepressants was observed for AChEI users in the lower age groups. The prevalence of use of antidepressants the year before AChEI initiation was twice the prevalence in the age-adjusted general population and continued to rise in the first two years after initiation of AChEI.

The prevalence of use of antipsychotics the year before AChEI initiation was twice the prevalence in the age-adjusted general population and continued to rise in the first two years after initiation of AChEI. The prevalence of the use of antipsychotics 2 years before AChEI initiation was similar to that in the general population; 3.2%, but increased strongly in the year prior to the prescription of AChEIs to 6.0%, and continued to increase in the 2 years after initiation to 9.3% in the second year. The highest prevalence was observed in the younger age groups.

In the study population, the prevalence of use of weaker analgesics was similar to that in the general population until one year before AChEI initiation, where the prevalence in the study population increased more rapidly. Opioid use was generally lower than in the general population and was not influenced by AChEI initiation.

In conclusion, increased use of antidepressants and antipsychotics before and after initiation of AChEIs may indicate that behavioral symptoms occur in a preclinical or early phase of AD. The prescription pattern of analgesics with a low use of opioids may indicate an undertreatment of pain in people with dementia.
Sex differences in use of psychotropics and analgesics before and after initiating treatment with acetylcholinesterase inhibitors

This was a retrospective study applying drug use data from the NorPD aiming at exploring the impact of gender on prevalence, patterns and trends in the prescription of psychotropics and analgesics in users of AChEIs, before and after AChEI initiation and to compare with the use in the general population.

Prescriptions of antidepressants (ATC group N06A, excluding amitriptyline (N06AA09), commonly prescribed for neuropathic pain), antipsychotics (N05A), (excluding prochlorperazine (N05AB04), commonly prescribed for vertigo), analgesics including opioids (N02A and N02B), benzodiazepines (N05BA and N05CD), and z-hypnotics (N05CF) were studied in persistent AChEI users, in a follow-up period from four years before to two years after AChEI initiation in men and women. The drugs were classified according to the ATC-system.

In total, 11,764 persistent users of AChEIs registered in the NorPD were followed in the period from 2008 to 2013. They were stratified into 4 age groups, 37-64, 65-72, 73-80 and 81-88 years old. Patients being prescribed AChEI treatment for <8 months were called quitters, the remaining referred to as persistent users. In addition, for comparison we included individuals from the general population (including the study population). For example, antidepressants use in the age group 81-88 years 4 years before initiation was compared to use in the age group 77-84 years in 2004-2009 in the general population.

We observed a marked increase in the use of antidepressants, antipsychotics and weaker analgesics of both sexes among AChEI users the last two years prior to AChEI initiation, and the use of these drugs continued to rise the first two years after initiation. The increase was as follows during the six-year interval: The use of antidepressants in women increased from 16.2% (95% CI: 15.4%-17.1%) the fourth year before initiation to 34.1% (33.0%-35.2%) the second year after. The corresponding increase in men was from 8.8% (95% CI: 8.0%-9.6%) to 23.7% (22.5%-25.0%). The use of antipsychotics in women increased from 3.0% (95% CI: 2.7%-3.4%) the fourth year before initiation to 9.0% (95% CI 8.3%-9.6%) the second year after. The corresponding increase in men was from 2.2% (95% CI: 1.8%-2.7%) to 9.8% (8.9%-10.7%). The use of weaker analgesics increased in both sexes in AChEI users the last
two years prior to AChEI initiation, and the use of these drugs continued to rise the first two years after initiation. However, a decreasing prevalence in the use of BZDs and Z-hypnotics following AChEI initiation in women was observed.

Women of the study population had a higher prevalence of use of the studied drug classes compared to the general population except for opioids and Z-hypnotics, and a higher prevalence of use of the studied drug classes except for antipsychotics. The prevalence of opioids was lowest in the lowest age group in both sexes. The highest prevalence rates of antidepressants and antipsychotics were observed in the lower age group in both sexes.

The proportion of women in the study population with use of one drug group increased from 27.1% (95% CI 26.1%-28.1%) four years before AChEI initiation to 35.9% (34.8%-37.0%) the first year after. The corresponding increase in the general population was from 25.5% to 26.0%. The proportion of women with two drug groups increased from 10.3% (9.6%-11.0%) to 17.0 (16.1%-17.8%) in the study population and from 10.7% to 10.8% in the general population. The proportion of men in the study population with use of one drug group increased from 19.7% (18.6%-20.9%) to 30.1% (28.7%-31.5%). The corresponding increase in the general population was from 19.3% to 20.2%. The proportion of men with two drug groups increased from 5.3% (4.7%-6.0%) to 10.8% (9.9%-11.8%) in the study population, whereas it was stable at 5.7% in the general population.

In conclusion, female gender showed to have a significant influence on the prescriptions of psychotropics and analgesics (more use compared to men) in AD patients in a pre-dementia and dementia stage. The exception is for antipsychotics, which men used more than women. The prescription pattern showed a higher extent of polypharmacy of psychotropics and/or opioids in women than in men. The total prescription pattern of analgesics could indicate an undertreatment of pain in pre-dementia and dementia stages, most pronounced in men.
**Paper 5**

Use of drugs with risk of heart rate related problems is common in Norwegian dementia patients treated with acetylcholinesterase inhibitors. A prevalence study based on the Norwegian Prescription Database.

This was a retrospective study applying drug use data from the NorPD, aiming at studying the use of drugs commonly prescribed for heart rate control, drugs with a known risk of TdP and drugs used to treat BPSD, before and after initiating treatment with AChEIs. Another aim was to study changes in use of combination of drugs with a known risk of TdP and drugs with a known heart rate lowering effect, before and after initiating treatment with AChEIs in men and women.

A total of 11,764 users of AChEIs registered in the NorPD were followed in the period from 2008 to 2013. They were stratified into two age groups, 37-80 and 81-88 years old. Patients being prescribed AChEI treatment for <8 months were called quitters, the remaining referred to as persistent users. A comparison was made to drug use in the general population. As an example, betablocker use in the 81-to-88-year age group four years before initiation was compared to use in the 77–84-year-old persons in 2004-2009 in the general population and betablocker use in the same age group the second year after initiation was compared to use in the 82–89-year-old in 2009-2014 in the general population.

Prevalence of haloperidol (ATC code N05AD01), citalopram (N06AB10) + escitalopram (N06AB04), verapamil (C08DA01), betablockers (C07) and digitoxin/digoxin (C01A) was studied in the 4 years before and the 2 years after initiation of AChEIs.

In addition, we studied prevalence of concomitant use of betablockers + citalopram or escitalopram, and of verapamil + citalopram or escitalopram in the 4 years before and the 2 years after initiation of AChEIs. Citalopram or escitalopram was selected as a drug with known risk of TdP, commonly used in the treatment of BPSD. The drugs were classified according to the ATC-system.

In the general population of the 37–88-year age group, the prevalence for verapamil decreased from 1.7% to 1.4% in men and from 1.9% to 1.7% in women; for betablockers it increased from 29.4% to 34.6% in men and from 26.1% to 30.9% in women; for
**digoxin/digitoxin** it decreased from 3.4% to 3.3% in men and increased from 2.5% to 2.8% in women. For **haloperidol** and **citalopram/escitalopram**, no specific sex differences were observed during the study period.

In the study population, a small number of patients were prescribed **haloperidol** (~1.5% the 2nd year after AChEI initiation), **digoxin/digitoxin** (~3%) and verapamil (~1.3%), while a substantial proportion were prescribed **betablockers** (~28%) and **citalopram/escitalopram** (~17%). Up to 6% of the study population were prescribed both betablockers and citalopram/citalopram in addition to AChEIs, a combination that increased over the follow-up period and was observed most frequently in women in the oldest age group.

A large proportion (~44%) of patients treated with AChEIs were prescribed drugs commonly used in the treatment of BPSD that could cause bradycardic and prolonged QT interval. Thus, action should be taken to reduce combination of drugs with risk of bradycardia and prolonged QT interval. Medication review on a regular basis could be an option as an important risk-reducing intervention.

In users of AChEIs, a high prevalence of use of betablockers and of citalopram/escitalopram was found. The prevalence of use of haloperidol and citalopram/escitalopram was higher in the study population compared to the general population. The prevalence of use of verapamil was low in the general population and even lower in the study population and use of the digitalis drugs was flattening out in the study population following introduction of AChEIs.

The proportion of the study population with concomitant use of betablockers and citalopram/escitalopram was higher in women than in men. The use in men in the study population overall increased from 1.0% (95% CI: 0.8%-1.7%) the fourth year before initiation via 3.1 (2.6%-3.7%) the first year before to 4.0% (3.4%-4.6%) the second year after. The use in women in the study population overall increased from 2.1% (95% CI: 1.8%-2.4%) the fourth year before initiation to 4.7% (4.3%-5.2%) the first year before, thereafter, flattened out to 4.9% (4.4%-5.4%) the second year after.

In conclusion, a large proportion (~44%) of patients treated with AChEIs were prescribed drugs that could cause bradycardic and prolonged the QT interval. Thus, action should be taken to reduce combination of drugs with risk of bradycardia and prolonged QT interval. Medication review on a regular basis could be an option as an important risk-reducing intervention.
4 Discussion

The incidence of dementia in Norway is around 10,000 persons every year, including 6,000 with suspected AD (3, 264). The number of incidents AChEI users over the 7 year period (paper 2) was 13,609 persons.

Data from Statistics Norway shows that the general population in these years includes 540,776 persons. According to a systematic review and meta-analysis, the incidence of AD in the community setting in individuals age 60+ was 34.1 per thousand inhabitants (264). Based on these data, which have some statistical heterogeneity, we can estimate that the approximate number of dementia cases in our population in the given period was 18,440. This means that about 2/3 of persons with AD in the age group of 65-80 years start with AChEI treatment, indicating that drug treatment with AChEIs for slowing down decline in cognition is lower than recommended. As the incidence of dementia due to AD increases with increasing age, a large number of patients with dementia are diagnosed after the age of 80 years, however, many of these individuals live in nursing homes (142). In addition, the incidence of AD in our study population is expected to be higher than in the reported meta-analysis, due to our age limit of 65 years old. The possible underuse of AChEIs in people living at home should be addressed, and could be explained by late diagnosis, a high proportion of mixed dementia, or low confidence in the therapeutic effect.

Based on findings from sub study 1 and 2, a high proportion of co-medication was observed among AChEI users, and the AChEI treatment was discontinued early in patients being prescribed antipsychotics and in patients with a high ADS score, compared to other AChEI users. The explanation for this finding is probably related to lack of effect or occurrence of unpleasant side-effects or a combination of both. High anticholinergic burden has been significantly associated with higher mortality among persons with dementia, and this could explain why the treating physician discontinued the treatment with AChEI early in patients with a high ADS score (265). In addition, reduction of anticholinergic burden in older persons with dementia has shown to reduce BPSD and caregiver burden (266). Further, use of drugs with high anticholinergic burden has shown to have a negative effect on AChEI treatment (112, 267). We do not know the exact reason for why the treating physicians discontinued the AChEI treatment early in patients with a high ADS scores, but as geriatricians compared to general practitioners more often discontinued the AChEI treatment early, we suggest that the reason for early withdrawal is related to a holistic clinical
judgement that includes judgement of effect size (or poor effect), occurrence of ADRs, and the possible negative effects of polypharmacy. In other words that discontinuation of AChEI therapy may be related to concomitant and inappropriate drug use. Increasing polypharmacy leads to an increased likelihood of high anticholinergic scores, which is shown in some studies (83, 216), and polypharmacy results in increased risk of interactions (106). The many combination therapies observed demonstrate the need of regular monitoring of clinical response and potential side effects and interactions, especially in the initial phase of AChEI treatment. If necessary to use, agents with no or low ADS scores should be selected to maintain the already limited effect of the AChEIs.

4.1 Use of psychotropic drugs and analgetics in various stages of AD (AChEI treatment)

Sub study 3 showed that the study group receiving AChEIs differed from the general population with regard to concomitant use of antidepressants, antipsychotics and analgesics. Many older adults experience changes in brain activity with memory decline as part of the normal aging process, and these symptoms may be difficult to distinguish from early signs of dementia (269). The prevalence of use of antidepressants and antipsychotics the year before AChEI initiation was twice the prevalence in the age-adjusted general population and continued to rise in the first two years after initiation of AChEI. The prescription pattern of analgesics showed a low use of opioids compared to the general population. Further, within the group of AChEI user the prescription of the various psychotropic drugs differed during the six years we followed the patients. Antidepressants were more often used early in the course of AD, whereas antipsychotics were initiated later on. The increase in the use of antidepressants started at least 4 years before initiation of AChEI. The increased prescription of antidepressants before diagnosing AD and initiation of AChEI treatment indicates that depressive symptoms and anxiety (worrying) may be early signs of dementia due to AD, which is not unexpected as many people with AD in an MCI stage have insight in their own situation with declining cognitive and ADL abilities. Affective symptoms such as anxiety and depressive symptoms are more frequent in MCI than mild dementia (140). Anxiety has been reported to be highly prevalent in people with dementia (269). Thus, we believe that evaluation of depressive and other BPSD symptoms in people with cognitive dysfunction (MCI stage) should be prioritized to avoid the unfortunate use of psychotropic drugs and
misinterpretation of affective symptoms that could be early symptoms of AD that should lead to a comprehensive diagnostic assessment instead of prescription of antidepressants. Studies suggest that many cases of AD go unrecognized and undiagnosed for years after symptom onset (268, 270), and that the proportion of people with undetected dementia living in the community varies between 50-90% (271-273). There are many benefits of a timely diagnosis of AD. Early diagnosis allows for advanced-care planning, improves prognosis by slowing or delaying cognitive decline due to AD at a point in the disease where the interventions may be effective, like lifestyle and medical interventions, and it may delay nursing home admissions (274), and the family and professional caregivers learn how to support the person with a dementia disorder.

The first choice for the treatment of patients with mild and mild/moderate depression in mild cognitive impairment or dementia is environmental, psychosocial and or psychotherapeutic measures. Use of antidepressant medications to treat affective symptoms in dementia may have limited benefits and may be associated with adverse outcomes (174). However, some withdrawal studies find that some people with dementia and BPSD may benefit from antidepressants (175). Side effects have been little studied in patients with depression and dementia, but can be expected to be the same as in older adults with depression without dementia. ADRs of SSRIs include nausea, diarrhea, headaches, sweating, tremors, somnolence, insomnia and restlessness (1) or more serious side effects including gastrointestinal bleeding, hyponatremia, falls, and fractures (169). It is recommended to avoid the use of antidepressant drugs with anticholinergic effects (such as TCAs) as their use may impair the patient's cognitive functioning. TCAs may cause cardiac arrhythmias and QT interval prolongation, orthostatic hypotension, sedation, elevated intraocular pressure, and extrapyramidal effects (173).

The prevalence of use of antipsychotics increased strongly in the last year before AChEI initiation, and a possible explanation is that BPSD increases in intensity during the course of the dementia illness, resulting in the introduction of more psychotropics. The increasing prescription pattern in the use of antidepressants, antipsychotics and weaker analgesics in both sexes during the study period probably mirrors that BPSD, sleep disturbances and pain increase in intensity or in symptomatology with increasing severity of AD, without achieving the desired effect of the initially initiated drug treatment. It may also indicate that the diagnosis of AD is given late in the course of AD, as psychotic symptoms such as delusion
occur in most cases in a moderate stage of dementia (Figure 5) (117, 118). This is also supported by the fact that antipsychotics in Norway are approved for the indication psychotic symptoms and aggressive agitation, for short term treatment (up to 6 weeks) in moderate- to severe AD, VaD or mixed AD/VaD, in situations where the patients are unresponsive to non-pharmacological approaches, and where there is a risk of harm to self and others (1).

Antipsychotics may have some value in the treatment of more severe BPSD, however, due to the risk of serious ADRs, the benefits must be weighed against the side effects like strong anticholinergic effects, QT interval prolongation and extrapyramidal side effects, causing increased risk of death, stroke, coronary heart disease and metabolic syndrome.

Pain is a very common manifestation in people with dementia and often neither diagnosed nor treated. In our sub study 3, the prevalence of use of weak analgesics increased strongly in the last year before AChEI initiation, but opioid use was generally lower than in the general population and was not influenced by AChEI initiation. The prevalence of pain in people with dementia is high and reported to range between 47-68%. Due to cognitive difficulties, people with AD have difficulties with reporting pain and therefore pain may go untreated (125). As pain may contribute to BPSD, treatment is important, and paracetamol should be the first treatment option, while opioids should be used with caution (125). However, good evidence indicates that under-treatment of pain is a greater risk factor for the development of delirium than the use of opioids (183). Risk of liver damage with prolonged use in large doses and risk of drug-related headache is connected to the use of paracetamol, which has few side effects with short-term use and in therapeutic doses. Respiratory depression, sedation, delirium, hallucinations, delirium, dizziness and instability are possible adverse effects of opioids (37). Pain-related diagnosis has been shown to be associated with higher use of psychotropics in persons with dementia (184). The prescription pattern of analgesics with a low use of opioids may indicate an undertreatment of pain in people with AD.

4.2 Use of drugs that could influence on heart rate

Sub study 5 showed that a high prevalence of use of betablockers and of citalopram/escitalopram was found. The prevalence of use of haloperidol and citalopram/escitalopram was higher in the study population compared to the general population. The prevalence of use of verapamil was low in the general population and even lower in the study population, and use of the digitalis drugs flattened out in the study.
population following introduction of AChEIs. The proportion of the study population with concomitant use of betablockers and citalopram/escitalopram was higher in women than in men. In summary, with regard to potential adverse reactions on the heart, even the low prevalence of use of haloperidol is concerning. The high prevalence of use of betablockers may give rise to bradycardia and disorders of AV conduction, and induce vertigo and falls, as well as interactions with other drugs with an effect on the heart. Due to the high prevalence of use of citalopram/escitalopram, especially in women, a substantial proportion of the patients are at risk of developing pharmacodynamic interactions, a risk which increases when combined with AChEIs and betablockers. Cardiovascular side effects should be monitored, and an ECG performed at checkup, specifically important in patients already taking bradycardic drugs. One explanation might be that prescribers are not fully aware of the possible pharmacodynamic interactions of heart-rate related drugs and AChEIs.

4.3 Sex differences
Sub study 4 showed that use of antidepressants, antipsychotics and weaker analgesics increased in both sexes during the follow-up period. More female patients compared to men were prescribed psychotropics and analgesics in a pre-dementia and dementia stage, except for antipsychotics that men used more compared to women. Men with dementia are often more physically aggressive compared to women, which may result in more use of antipsychotics in men (228, 229).

Female sex showed to have a significant influence on psychotropic prescribing. The prescription pattern showed a higher extent of polypharmacy of psychotropics and/or opioids in women than in men. PPP has been reported to be frequent in AD patients (213), especially in women (214). Women with pre-dementia and dementia stages of AD showed a prescription pattern with more polypharmacy of psychotropics and opioids than men, except for antipsychotics. The higher use of psychotropics in women in the study population indicates that women with AD experience BPSD more frequently than men, as shown in other studies (229). Due to more polypharmacy and higher prevalence of use of psychotropics in women with AD than in men, except for antipsychotics, women with AD have a higher risk of interactions and ADRs.
Sub study 4 showed a high prescription pattern of BZDs for women, in particular in the higher age groups, which is a concern. BZDs should generally be avoided in people over 65 years of age and in people with cognitive impairment/dementia under 65 years of age. This is due to the risk of serious side effects and risk of addiction (1) like drowsiness, fatigue, impaired motor coordination, dizziness, vertigo, increased risk of falls and hip fractures, and they are associated with cognitive decline, and respiratory suppression (56, 123, 180). However, a decreasing prevalence was observed in the use of BZDs and Z-hypnotics in women and in Z-hypnotics in men, which may reflect a precaution to reduce the extent of co-medication in people with an AD diagnosis, especially in women.

Women have a higher prevalence of many pain disorders than men, and sex differences in the use of analgesics probably mirror the higher prevalence of chronic pain in women (230). The total prescription pattern of analgesics could indicate an undertreatment of pain in pre-dementia and dementia stages, most pronounced in men. Pain in dementia should be monitored separately for women and men.

Sub study 5 showed that the prevalence of use of concomitant use of betablockers and citalopram/escitalopram declined in men following initiation of AChEIs, while increased in women. This could reflect that women get cardiovascular disease later than men do, and that treatment with betablockers and citalopram /escitalopram was considered to be important.

4.4 Age differences

In sub study 3, we observed an increasing trend within each age group of opioids and of paracetamol. This increased use by age indicates that pain-related diagnoses are more frequent in the older age group. However, the total prescription pattern of analgesics indicates an undertreatment of pain related disorders.

The highest prevalence of use of antidepressants was observed in the lower age groups of the study population. In the youngest age group, the prevalence of use of antidepressants was about twice as high in the study population. The prevalence of use of antidepressants strongly increased in all the age groups of the study population during the 6-year interval. The high use of antidepressants observed in the older age groups of the study population with AD compared to the general population may be inappropriate; but could also indicate that other
treatment strategies have either failed or not been offered. This is worrisome in light of potential severe adverse effects antidepressants may induce.

In the youngest age group, the prevalence of use of antipsychotics was higher than in the general population all six years, while antipsychotic use 4 years before initiating AChEIs in the oldest age group was only about half the prevalence of the general population. This age difference indicates that aggression was most pronounced in the youngest age groups from 4 years before the introduction of AChEIs. However, the prevalence of use of antipsychotics increased from two years before introduction of AChEIs and continued to rise in all the studied age groups during the study period, with risks of ADRs, interactions and increased morbidity. The highly increased fall risks especially in elderly individual with AD can be the result of interactions of several factors including polypharmacy and anticholinergic side effects commonly reported with antipsychotics (78, 188).

Sub study 4 showed that the use of BZDs and Z-hypnotics was increasing with age. Anxiety has been reported to be highly prevalent in people with dementia, and our results indicate that anxiety is more common in the higher age groups. This use of BZDs may be inappropriate due to elderly patients being more vulnerable to the ADRs of BZDs.

In sub study 5, the prevalence of use of combinations of betablockers and AChEIs in the study population, especially the higher age group of 81-88 years olds, is a concern, due to increased risks of interactions and ADRs by age.

In conclusion, patients with AD present an increased risk of ADRs and drug-drug interaction ADRs due to several factors such as age, age of disease onset and the presence of polypharmacy. This use pattern is complicated by an increase in the effect of psychotropics in older adults due to age-related changes in pharmacokinetic and pharmacodynamic parameters (238). The high use of antipsychotics, antidepressants and BZDs in the higher age groups is therefore a concern, as well as the high use of drugs with an effect of the heart rate. Sex needs to be taken into consideration in clinical practice in treatment of pre-dementia and dementia conditions, to improve patient outcomes.
4.5 Methodological strengths and limitations

Data from the NorPD gives us a unique opportunity to study drug use patterns, highlighting changes over time in selected drug groups. The large sample size and the long study period is a strength of the study. A limitation is that patients in institutions are not included in the NorPD and therefore not included in the present study, hence the patients with the most severe symptoms of AD are probably not included in our study. However, the AChEIs are only indicated for mild and moderate degree of dementia, which indicates that most patients treated with AChEIs are home-dwelling.

The NorPD does not include data on the use of over-the-counter drugs and herbal drugs, which may lead to an underestimation of weak analgesics in our study, as paracetamol in small pack sizes are available as over-the-counter drugs.

As we used data from the NorPD and not clinical data, we do not know the indications for the studied drugs; like BPSD, depression, congestive heart failure and atrial fibrillation. AChEIs are mainly prescribed for treatment of AD, however, we did not have information with regard to clinical rationale for prescriptions and indications. Variables like dementia diagnosis or the indication for psychotropic drug use would have helped estimate to what extent patients were treated with approved indications. Purchased drugs were used as a surrogate for consumed drugs and may cause overestimation. However, medicine adherence in AChEI users was expected to be good, as caregivers usually are responsible for drug management in patients with dementia.

We do not know the duration of symptoms before the diagnosis, and generally, the described increases in prevalence of use of psychotropic drugs might have been started more than four years before AChEI initiation. We also assume younger people seek medical attention earlier than older people, however, early onset dementia is not always suspected and probably rather interpreted as depression.

We did not study dosage differences between men and women, which could be of relevance due to pharmacokinetic differences between the sexes.

Concerning prevalence of PPP and opioids, we only record ATC classes and not number of substances. Each of the registered drug groups of antidepressants, antipsychotics, opioids and
BZDs may consist of more than one prescribed substance, and this fact probably leads to an underestimation of prevalence of polypharmacy.

We have used the time of patients starting with AChEI as a surrogate measure of a diagnosis of AD. However, this may cause an overestimation, as patients with LBD are treated with AChEIs as well. However, this group is small compared to the AD group.

Concerning drugs with anticholinergic activity, the ADS score model is not necessarily suitable as a direct anticholinergic measure, as the ADS scores simplify complex pharmacological mechanisms. The method does not take into account the dose of the anticholinergic drug and of inter-individual variations in pharmacokinetics, including the degree of distribution to the CNS (101, 102), and possible association between anticholinergic measures of inherited CYP2D6/2C19 phenotypes, mainly of psychotropics.

In sub study 2 we did not include patients above 80 years old, and in sub study 3-5, we only included persistent AChEI users aged 88 years or younger to be able to make a comparison with the general population for which data with one year age resolution was available up to and including 89 years. These age limits mean that we did not include all relevant patients in the high age group.

Concerning sub studies 3-5, medicine use was quantified up to 4 years prior to AChEI initiation, and as only one-year wash-out was used to define initiation, the study population included 494 patients who used AChEIs 2-4 years prior to index date. However, the majority of these (61%) had < 4 prescriptions in this period, and we have included the 494 in the analysis. Only persistent users were included, and people who were still alive at two years post-initiation.

In sub study 5, people who developed a cardiovascular issue or had a cardiovascular event (potentially due to co-prescribing of medicines associated with cardiovascular problems) might have discontinued AChEIs before they fulfilled the persistence criteria, or have been more likely to die the two first years after AChEI initiation. This could lead to bias in who is included in the study (e.g., people with lower rates of use of the medicines of interest being excluded). There have been no changes in guidelines related to the drugs being studied since 2013. Hence the therapy valid at that time is still valid today.
Our results should be interpreted with these methodological aspects in mind.

4.6 Conclusions and future directions

**Paper 1 and 2** showed that a large proportion of the patients treated with AChEIs were co-medicated with anticholinergic agents that may limit or counteract the clinical effect. Study 1 showed that a pharmacist-geriatrician cooperation could be effective to reduce the ADS-score in order to avoid this kind of irrational combination therapy in patients with dementia. Study 2 showed that co-prescribing with potentially unfavourable medications was common, and that a high ADS score was associated with early discontinuation of treatment.

In **Paper 3**, we showed that the use of antidepressants and antipsychotics increased before and after initiation of AChEIs, and the results may indicate that behavioural symptoms occur in an early- or preclinical phase of AD. The prescription pattern of analgesics with a low use of opioids may indicate an undertreatment of pain in people with AD.

In **paper 4**, female sex showed to have a significant influence on the prescriptions of psychotropics and analgesics in AD patients in a pre-dementia and dementia stage. The exception was for antipsychotics, which men used more than women. The prescription pattern showed a higher extent of polypharmacy of psychotropics and/or opioids in women than in men. Increased use of psychotropics in AD patients compared to the general population and the high extent of polypharmacy of psychotropics observed is in accordance with findings from other studies. The total prescription pattern of analgesics could indicate an undertreatment of pain in pre-dementia and dementia stages, most pronounced in men.

**Paper 5** showed that even the low prevalence of use of haloperidol is concerning, with regard to potential ADRs on the heart. The high prevalence of use of betablockers observed may give rise to bradycardia and disorders of AV conduction, and induce vertigo and falls, as well as interactions with other drugs with an effect on the heart. Due to the high prevalence of use of citalopram/escitalopram, especially in women, a substantial proportion of the patients are at risk of developing pharmacodynamics interactions, a risk which increases when combined with AChEIs and betablockers.
Taken together, paper 1-5 show that prescribers in particular should be aware of the potential drug-drug interactions and ADRs, which may cause discontinuation of AChEI treatment and accelerate cognitive decline, for example caused by drugs with anticholinergic properties and antipsychotics in general, except for short time use of antipsychotics indicated for the use of BPSD. Because of the cholinergic effects of AChEIs, co-prescribing of drugs with an effect of the heart rate or with known effect on QT-prolongation should be monitored closely, to avoid further pharmacodynamic interactions. Inappropriate drugs with known ADRs should be avoided in patients in a predementia or dementia stage, especially in the oldest age groups, due to increased effect of psychotropics and other drugs in the elderly. In this respect, pain should be detected and treated as early as possible, to ensure that psychotropic medication is not prescribed for possible wrong indications. Concerning sex-differences, it is advisable to focus on women being more susceptible to ADRs of drugs than men, and the fact that polypharmacy is more frequently observed in women.

A timely diagnosis of AD potentially offers the opportunity of early intervention to obtain correct treatment to control symptoms and avoid medications that may worsen symptoms. By giving the correct diagnosis early, doctors can avoid mistreatment of the group that does not develop dementia, and take earlier action, such as non-pharmacological and pharmacological interventions based on recommendations like the Norwegian National Guideline on Dementia.

Health professionals working in the primary care must be aware of the risks connected to drugs used in patients in a predementia- and dementia stage of AD. Prescribers should focus on concomitant use of AChEIs, and drugs commonly used for the treatment of BPSD, drugs with an effect on the heart rate, polypharmacy, and treatment aspects related to sex differences, age, and pain related disorders.

In summary, our studies add important knowledge to current symptomatic pharmacologic treatment of AD and of commonly used co-medications in the years before and after the dementia diagnosis. Recommendations based on our findings may be a useful tool in future directions for symptomatic treatment of AD in a preclinical and clinical stage, in order to improve patient clinical outcome as well as patient’s safety, and to increase the confidence in the therapeutic effect.
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Several drugs have anticholinergic properties, and pharmacoepidemiological studies have reported that many individuals treated with AchEIs are coprescribed anticholinergic agents. The objective of the present study was to examine the effect of a pharmacist–geriatrician cooperation on management of these unfavorable, antagonistic interactions.

METHODS

Fifty inpatients or outpatients initiating or undergoing treatment with AchEIs were prospectively recruited from June to December 2011 at Baerum Hospital, Gjettum, Norway. The regional ethics committee, the data protection officer, and the hospital investigational review board approved the study. Assessment of anticholinergic burden was performed using the anticholinergic drug scale (ADS) score model founded on previously published classifications. (0 = no anticholinergic activity, 1 = potentially anticholinergic, 2 = clinically significant anticholinergic activity, and 3 = strong anticholinergic activity). In cases in which the total ADS score was two or more, the study pharmacist (ASE) alerted the respective geriatricians about the antagonistic interactions, including suggestions to reduce the anticholinergic burden. A Wilcoxon signed-rank test was used to statistically evaluate the effect of pharmacist interventions on ADS scores.

PHARMACIST-INITIATED MANAGEMENT OF ANTAGONISTIC INTERACTIONS BETWEEN ANTICHOLINERGIC DRUGS AND ACETYL CHOLINESTERASE INHIBITORS IN INDIVIDUALS WITH DEMENTIA

To the Editor: To stimulate cholinergic transmission in the brain, acetyl cholinesterase inhibitors (AchEIs; donepezil, rivastigmine, galantamine) have been developed as symptomatic treatment in individuals with Alzheimer’s dementia (AD). Concurrently used drugs with primary or secondary anticholinergic properties can antagonize the cholinergic stimulation of AchEIs.

Table 1. Participant Characteristics and Anticholinergic Drug Scale (ADS) Scores Before and After Pharmacist-Guided Interventions in Individuals with and ADS Score ≥2

<table>
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<th>Variable</th>
<th>Inpatients, n = 22</th>
<th>Outpatients, n = 28</th>
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<tr>
<td>Age, median (range)</td>
<td>82 (66–92)</td>
<td>80 (61–94)</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>13 (59)</td>
<td>17 (60)</td>
</tr>
<tr>
<td>Number of regular drugs, median (range)</td>
<td>8 (1–14)</td>
<td>4.5 (0–10)</td>
</tr>
<tr>
<td>Number of drugs on demand, median (range)</td>
<td>1 (0–5)</td>
<td>0 (0–1)</td>
</tr>
<tr>
<td>ADS score, median (range)</td>
<td>1 (0–7)</td>
<td>0 (0–3)</td>
</tr>
<tr>
<td>Drugs with ADS score 3, n</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Hydromazine</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Tolterodine</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Tramipramine</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Drugs with ADS score 2, n</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Solifenacin</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Drugs with ADS score 1, n(^{a})</td>
<td>23</td>
<td>10</td>
</tr>
<tr>
<td>Citalopram</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Escitalopram</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Furosemide</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Ipratropium bromide</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Number of patients with ADS score ≥2</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>Score before intervention, median (range)</td>
<td>2 (2–3)</td>
<td>3 (2–7)</td>
</tr>
<tr>
<td>Score after intervention, median (range)</td>
<td>0.5 (0–1)</td>
<td>1 (0–1)</td>
</tr>
</tbody>
</table>

\(^{a}\)Score 1 agents used by single patients not mentioned.
RESULTS
Twenty-four of 50 individuals were concurrently using drugs reported to have anticholinergic activity. Table 1 provides an overview of population characteristics, drug use, and ADS scores before and after pharmacist-guided interventions in individuals with an ADS score of 2 or greater. Ten of 28 outpatients (35.7%) and four of 22 inpatients (18.2%) had a score of 2 or greater. In individuals with an overall score of 2 or greater, the median ADS score was significantly reduced, from 2.5 to 1.0 (P = .009), after pharmacist intervention.

DISCUSSION
Pharmacist-initiated interventions on anticholinergic medications led to a substantial and significant reduction in anticholinergic burden in AchEI-treated individuals with an ADS score of two or greater. Whether this action improved the responsiveness to AchEI treatment in these individuals was not evaluated, but several studies have shown high ADS scores to be associated with negative clinical outcomes in terms of mild cognitive dysfunction, low Mini-Mental State Examination score, and greater mortality in elderly adults.6,8–10 Therefore, one would expect that the clinical outcome would be better in this population after reduction of the anticholinergic burden, but randomized clinical trials should be performed to elucidate this hypothesis.

REFERENCES

VALIDATION OF A FRAILTY INDEX FROM THE OLDER PERSONS AND INFORMAL CAREGIVERS SURVEY MINIMUM DATA SET

To the Editor: Frailty refers to a state of vulnerability to adverse health outcomes.1 Although clinically assessing a breadth of health complexities is a robust method of measuring frailty,1 such a detailed assessment is timely and cost prohibitive in large studies. For this reason, a growing body of literature has begun to apply a frailty index (FI) based on the concept of deficit accumulation.2–4 Deficits in health may include a range of symptoms, morbidities, or functional limitations.6 Because such deficits can be easily extracted from survey data, a study was designed to compare construct validity of a FI derived from a minimal data set with that derived from a clinical assessment, the reference standard.

METHODS
Data were derived from the Easycare Two-Step Older Persons Screenign Study.7 Individuals aged 70 and older were randomly sampled from six primary care practices in Nijmegen, the Netherlands, to test a new frailty identification tool. All participants underwent a clinical assessment and were asked to complete The Older Persons and Informal Caregivers Survey Minimum Data Set (TOPICS-MDS) as part of a national initiative to create a minimum data set on older persons’ health. Details on this initiative are available elsewhere.8 TOPICS-MDS collected information on morbidity status, functional limitations using a modified version of the Katz activities of daily living (ADL)
Comedication and Treatment Length in Users of Acetylcholinesterase Inhibitors

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Keywords
Acetylcholinesterase inhibitors · Alzheimer disease and medical treatment · Pharmacoepidemiology of dementia · Pharmacotherapy for behavioral and psychological symptoms of dementia

Abstract
Background/Aims: Reduced clinical effect on cognitive decline in dementia by acetylcholinesterase inhibitors (AChEIs) may be due to concurrent use of drugs with anticholinergic properties. The aim was to analyze the incidence of AChEI use and comedication with drugs with anticholinergic properties and other potential unfavorable effects. Methods: A prospective study applying drug use data from the Norwegian Prescription Database. Anticholinergic Drug Scale (ADS) scores were used as a measure of overall anticholinergic burden. Results: Patients with high ADS scores were more frequently discontinuing treatment early. Coprescribing of antipsychotics was strongly associated with early discontinuation of AChEI treatment. Conclusion: Coprescribing with potentially unfavorable medications was common. A high ADS score was associated with early discontinuation of treatment.

Introduction
Reduced cognition and change in behavior in Alzheimer disease (AD) may be a direct result of the loss of acetylcholine [1]. Thus, to stimulate cholinergic transmission, acetylcholine esterase inhibitors (AChEIs) are used in patients with AD. About 70,000 people...
suffered from dementia in Norway in 2010 [2], worldwide 47.5 million people (2015), and there are 7.7 million new cases every year [3].

Donepezil, rivastigmine, and galantamine are currently available in Norway for the symptomatic treatment of mild to moderately severe AD. Although the clinical effect of AChEIs on cognitive function is generally limited, the individual variability in response is extensive. This variability has to some extent been explained by the prescriber, which could reflect prescription of drugs which are contraindicated in combination with AChEIs, or by individual patient variability [4]. Moreover, discontinuation of AChEIs or switch to another AChEI can be related to environment (hospitalizations/change of care), medications (adverse drug reactions to AChEIs and inappropriate concurrent use of anticholinergic agents), and patient factors (cognitive decline, anxiety, and weight loss) [5–8]. Rapid cognitive decline has been shown to be linked to switching [8], indicating that the decision to switch to another AChEI may be made for a potentially better therapeutic response. A drug holiday may be undertaken to assess the real benefit of AChEI use. AD-related hospitalization has been shown to be the strongest predictor of discontinuation [8].

Patients with dementia are frequently treated with psychotropic drugs such as antidepressants, anxiolytics, antipsychotics, and hypnotics/sedatives for behavioral and psychological symptoms of dementia (BPSD) as part of the dementia syndrome. Management of these symptoms is difficult due to the risk of serious adverse effects and due to the absence of credible alternatives [9, 10]. The use of psychotropic drugs may result in considerable morbidity, especially in the elderly who are more susceptible to both effects and adverse effects of drugs [11, 12]. Polypharmacy is a well-known phenomenon in older adults, with increased risk of interactions [13].

Reduced clinical effect of AChEIs may be due to concurrent use of interacting drugs with anticholinergic properties [1, 14–16]. The prevalence of coprescribing of anticholinergic drugs in the AChEI-treated patients in Norway is unknown. Many commonly used drugs have primary or secondary anticholinergic activity, e.g., drugs for urinary frequency and incontinence (urologic spasmolytics), antihistamines, antidepressants, and antipsychotics [1, 12, 14–17]. Moreover, there is a vast number of agents expressing anticholinergic activity in vitro [18]. These could possibly interact and have a synergistic effect when administered together with other anticholinergics. Anticholinergic Drug Scale (ADS) score models have therefore been developed as assessment tools for the evaluation of the overall anticholinergic burden in patients [17–20] and comprise agents from several drug classes. Total ADS scores have been shown to be associated with cognitive dysfunction [21], resulting in low Mini-Mental State Examination scores [20, 22] and increased mortality in older patients [22, 23]. Moreover, cognitive impairment has been found to be associated with polypharmacy [13] and increased mortality in the elderly [22].

The aim of the study was to analyze the incidence of prescribed AChEI treatment in Norway, to which extent incident users became persistent users (≥8 months treatment), to which extent persistent AChEI users differed from nonpersistent AChEI users in regard to age, sex, and prescriber, and to which extent comedication (with focus on drugs with anticholinergic properties) was associated with treatment length in persistent AChEI users.

Materials and Methods

Data

Drug use data were collected from the Norwegian Prescription Database (NorPD). This database covers the total population and, since 2004, information from all prescriptions dispensed at Norwegian pharmacies to individual patients has been included in the database.
It is possible to follow all individuals who have purchased medicines through their personal unique identification number [24]. Drugs dispensed to patients in institutions are not included in the NorPD, so when a patient moves to a nursing home, we are not able to follow the patient’s drug use any more.

Data registered in the NorPD include sex, age, year of death (when relevant), and information on drugs dispensed. In this study, we assumed that dispensed drugs represented consumed drugs. The drugs were classified according to the Anatomical Therapeutic Chemical classification system, version 2015 [25]. For each dispensed prescription, the following data were obtained: the date of dispensing, medicinal product name and formulation, Anatomical Therapeutic Chemical code, defined daily doses and the number of tablets/capsules/plasters (allowing us to calculate treatment periods), and the prescriber’s specialty. Specialists in general medicine or geriatric medicine are the specialists who in practice initiate antidementia treatment in Norway and were considered specialists in the care of patients with dementia; all other physicians were considered nonspecialists.

**Users and Incident Users of Antidementia Drugs**

Users of AChEIs registered in the NorPD in the period from 2005 to 2011 were eligible for inclusion in the study (Fig. 1). Persons using solely the antidementia drug memantine were not eligible. Incident use was defined as being prescribed an AChEI drug after >365 successive days with no AChEI prescriptions. Some patients were repeated incident users (having several AChEI-free periods of >365 days). For each patient, we started follow-up at the date initiating the longest period with subsequent prescriptions <365 days apart (index date). The “longest period” means the period with the largest number of prescriptions. Treatment length was estimated as the time from the index date until the drug dispensed in the last prescription of the longest period was supposed to be consumed. The earliest possible index date was January 1, 2005. To allow for at least 1 year of follow-up, we only included patients with an index date before January 1, 2012. Users that were younger than 65 years or older than 80 years at the start of follow-up were excluded. For repeated incident users, only the treatment periods starting when the individual was between 65 and 80 years

**Fig. 1.** Flow chart. Time for study period, all users of acetylcholinesterase inhibitors (AChEIs), new users of AChEIs, persistent users, quitters and subgroup for concomitant treatment.
were considered. The 80-year limit was set because older patients with dementia are likely to become nursing home residents during the follow-up period, whereupon many of the residents will stop the AChEI treatment. For nursing home residents, medication is not registered in the NorPD. The lower limit of 65 years was chosen due to the definition of “elderly” [26].

Persistent Users and Quitters

New guidelines for dementia treatment are under revision in Norway, but currently, both specialists in geriatric medicine and general medicine can initiate and evaluate clinical effects of AChEIs treatment. Potential response to treatment should be evaluated 3–6 months after initiation including measures of cognitive, global, functional or behavioral symptoms. Furthermore, possible adverse drug effects should be assessed. We chose 8 months (240 days) as a cutoff to leave a lagtime for physician evaluation visits. The patients being prescribed AChEI treatment for <8 months are called quitters, the remaining are referred to as persistent users.

A user was defined as persistent if any of the following was true: (a) a new prescription was given between day 210 and day 240 after initiation (index date), (b) drugs for at least 210 days’ consumption were prescribed during the first 210 days from initiation, or (c) the last prescription before day 210 lasted to day 210. A stricter definition (either drug for at least 240 days prescribed during the first 240 days or the last prescription before day 240 lasting to day 240) resulted in fewer persistent users. However, 29% of those who were defined as nonpersistent by the strict definition were prescribed AChEI drugs after the 240-day limit (“false quitters”), compared to 16% using the first definition; thus, the first definition was chosen to reduce the number of “false quitters.”

Treatment, Coprescribing and Anticholinergic Scores

To investigate the association between coprescribing and treatment length, we defined a subgroup of persistent users for whom we could assume that we actually knew the treatment length, and for whom the end of treatment was not due to conditions leading to death shortly thereafter. It is reasonable to assume that many patients will be institutionalized during follow-up. However, for these patients, we cannot know whether they continue using AChEIs in the institution since drugs distributed in institutions are not registered in the NorPD. Since the majority of AChEI users also used other drugs, disappearance from the NorPD altogether would be a strong indication of institutionalization (or emigration) rather than the end of AChEI treatment. For this analysis, we therefore excluded users who: (1) were not registered in the NorPD after the last AChEI prescription (probably institutionalized or emigrated), (2) had the last prescription in 2012 (might have continued after 2012), (3) started treatment in 2011 (short follow-up) or (4) died the same year or the year after the last prescription (probably nondeliberate end of treatment). For this group, coprescribing was defined as being prescribed another medication (see selected drug groups below) during the first 6 months after initiation. AChEI users with different treatment duration were compared, and the 6-month coprescription window was chosen to make the length of the coprescription window independent of treatment duration. The 6-month period for comedication was chosen independently of the 8-month cutoff limit used to define persistent users.

We registered coprescribed drugs with anticholinergic properties. Urologic spasmyotics (G04BD) have substances with anticholinergic properties and may be initiated due to incontinence prevalent in patients with dementia. However, incontinence is also a common adverse effect of AChEIs [15]. Dementia in Parkinson disease is common and rivastigmine is licensed for cognitive impairment in Parkinson disease, hence antiparkinson drugs (N04) were selected. Anxiolytics (N05B), hypnotics/sedatives (N05C), antipsychotics (N05A), antide-
pressants (N06A), and analgesics (N02) are frequently used in older age, but have anticholinergic activities or other known adverse effects in patients with dementia.

To compare the prevalence of the drugs listed above in AChEI users with the prevalence in the general population, we computed the age-adjusted 6-month prevalence ratio (PR_A6) by dividing the prevalence in the AChEI users by the age-adjusted prevalence in all 65- to 80-year-olds in Norway (including the AChEI users) in the 6-month period July to December 2007, with the AChEI users as standard population.

The ADS score for each AChEI user was calculated. The basis for the ADS score evaluation is a list of drugs and their anticholinergic scores [27] founded on previously published classifications and studies [16, 18, 19, 28]. The ADS score is from 0 to 3, where 0 is defined as “no anticholinergic activity,” 1 as “potentially anticholinergic,” 2 as “clinically significantly anticholinergic,” and 3 as “strong anticholinergic activity.” The ADS score for each AChEI user was calculated as the sum of the ADS scores for each different drug prescribed during the 6-month coprescription window.

Statistical Analysis
R version 3.1.0 [29] was applied for descriptive statistics; period prevalence, means, medians, percentages and 95% confidence intervals (CIs) are presented when appropriate. The R-function prop.trend.test was used to test for associations between comedication at the start of treatment and treatment length. Treatment periods were calculated based on number of tablets/capsules and dose intervals.

Ethics
The NorPD generated anonymous files for research purposes, as regulated by Norwegian law for health registers [24], hence there was no demand of additional approval by the ethics committee.

Results
17,321 persons aged 65–80 years were registered users of AChEIs in the 7-year period from January 1, 2005 throughout 2011, and 13,609 of these were incident users; 13,056 (96%) initiated treatment once, while 534 (3.9%) and 19 (0.1%) started treatment 2 and 3 times during the period, respectively, i.e., they had 1 or 2 intervals of at least 1-year duration without any AChEI prescriptions. For 324 patients (59%) of those with >1 treatment period, the second or third treatment period was the longest.

The mean age of the 13,609 incident users at first prescription was 75.1 years (interquartile range 73–78), and 7,961 (58.5%) were women. The most frequently used AChEI was donepezil, followed by rivastigmine and galantamine. The prescription patterns have changed over the years; i.e., annual incidence rates have decreased for donepezil and galantamine and increased for rivastigmine. Moreover, the use of memantine has increased, and combined use of AChEIs and memantine increased from 4.2% in 2004 to 8.6% in 2012 in prevalent users of all ages.

Around one-third of the incident users (4,070) were prescribed AChEIs for <8 months and were considered to be quitters (Fig. 1). Persistent users and quitters did not differ in age and gender, but a higher proportion of persistent users had their treatment initiated by a specialist in geriatrics (16.4% [95% CI 15.7–17.2] vs. 14.2% [13.2–15.3]).

Unfavorable Drug Combinations – Concomitant Coprescription
In the subgroup of persistent AChEI users with known treatment length (3,284 persons) (Fig. 1), a high proportion of coprescription was observed, being the highest for sedatives/
Table 1. Comedication during the first 6 months of treatment with acetylcholinesterase inhibitors (AChEIs) according to treatment duration (percentages with 95% confidence intervals)

<table>
<thead>
<tr>
<th>Coprescribed drug class (ATC group)</th>
<th>n</th>
<th>PR_A6</th>
<th>Users according to treatment duration, % (95% CI)</th>
<th>p (trend)</th>
<th>% users (95% CI) (total n = 3,284)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>&lt;1 year (n = 901) 1–2 years (n = 1,164) 2–3 years (n = 622) &gt;3 years (n = 597)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urologic spasmolytics (G04BD)</td>
<td>189</td>
<td>1.9</td>
<td>5.8 (4.4–7.5) 6.3 (5.0–7.8) 4.7 (3.3–6.6) 5.9 (4.2–8.0)</td>
<td>0.69</td>
<td>5.8 (5.0–6.6)</td>
</tr>
<tr>
<td>Analgesics (N02)</td>
<td>691</td>
<td>1.1</td>
<td>20.5 (18.0–23.3) 22.3 (20.0–24.8) 20.1 (17.1–23.4) 20.3 (17.2–23.7)</td>
<td>0.67</td>
<td>21.0 (19.7–22.5)</td>
</tr>
<tr>
<td>Antiparkinson drugs (N04)</td>
<td>167</td>
<td>3.7</td>
<td>5.9 (4.5–7.6) 4.6 (3.6–6.0) 4.5 (3.1–6.4) 5.4 (3.8–7.5)</td>
<td>0.57</td>
<td>5.1 (4.4–5.9)</td>
</tr>
<tr>
<td>Antipsychotics (N05A)</td>
<td>319</td>
<td>2.8</td>
<td>15.3 (13.1–17.8) 8.9 (7.4–10.7) 6.4 (4.8–8.6) 6.2 (4.5–8.4)</td>
<td>0.001</td>
<td>9.7 (8.7–10.8)</td>
</tr>
<tr>
<td>Anxiolytics/hypnotics and sedatives</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(N05B+N05C)</td>
<td>1,037</td>
<td>1.2</td>
<td>34.4 (31.4–37.6) 31.7 (29.1–34.4) 30.7 (27.2–34.4) 28.0 (24.5–31.7)</td>
<td>0.01</td>
<td>31.6 (30.0–33.2)</td>
</tr>
<tr>
<td>Antidepressants (N06A)</td>
<td>933</td>
<td>2.9</td>
<td>31.1 (28.1–34.2) 28.4 (25.9–31.1) 26.2 (22.9–29.8) 26.6 (23.2–30.3)</td>
<td>0.03</td>
<td>28.4 (26.9–30.0)</td>
</tr>
<tr>
<td>Sum ADS score &gt;2</td>
<td>513</td>
<td>1.9</td>
<td>18.4 (16.0–21.1) 15.8 (13.8–18.0) 13.8 (11.3–16.8) 12.9 (10.4–15.8)</td>
<td>0.002</td>
<td>15.6 (14.4–16.9)</td>
</tr>
<tr>
<td>At least 1 drug with ADS score ≥2</td>
<td>438</td>
<td>1.9</td>
<td>16.1 (13.8–18.6) 13.8 (12.0–15.9) 10.8 (8.6–13.5) 10.9 (8.6–13.6)</td>
<td>0.001</td>
<td>13.3 (12.2–14.5)</td>
</tr>
</tbody>
</table>

For all AChEI users, the number of patients being coprescribed the various drug types (N) and the prevalence ratio compared to the general population (PR_A6) are given. p (trend) is the p value for the observed values under the null hypothesis of no trend. ATC, Anatomical Therapeutic Chemical classification system; PR_A6, age-adjusted 6-month prevalence ratio (prevalence in AChEI users divided by the age-adjusted prevalence in all 65- to 80-year-olds in Norway); CI, confidence interval; ADS, Anticholinergic Drug Scale.
hypo-otics (31.6%) and antidepressants (28.4%) (Table 1). The most frequently used antidepressant (N06A) was escitalopram (taken by 41% of those who used antidepressants), followed by mirtazapine (16%), citalopram (14%), and mianserin (14%). Only 8% of the antidepressant users in the study population were administered a tricyclic antidepressant (N06AA, nonselective monoamine reuptake inhibitors, with anticholinergic effect). Analgesics and antipsychotics were used by 21 and 10%, and antiparkinson drugs and urologic spasmolytics by 5 and 6%, respectively. Concerning overall anticholinergic burden, 13.3% of the patients (438 users) had at least 1 drug with an ADS score ≥2, and 15.6% (513 users) had a total ADS score ≥2.

Compared to the general population, the age-adjusted prevalence in this population was about 4 times as high for antiparkinson drugs (PR A6 = 3.7), 3 times as high for antidepressants and antipsychotics (PR A6 = 2.9 and 2.8, respectively), and twice as high for urologic spasmolytics (PR A6 = 1.9). For anxiolytics, hypnotics/sedatives and analgesics, the prevalence was similar in the study population as for the general population (PR A6 = 1.2, 1.2, and 1.1, respectively).

There was a strong association between comedication with antipsychotics during the first 6 months of treatment and duration of treatment (Table 1). While 15.3% of those with a treatment length <1 year were comedicated with antipsychotics, only 6.2% of those with >3 years of treatment were. A significantly higher proportion of those with <1 year of treatment than of those with >3 years of treatment had at least 1 drug with an ADS score ≥2 (16.1 vs. 10.9%) and a total ADS score ≥2 (18.4 vs. 12.9%). For antidepressants and anxiolytics/hypnotics and sedatives, there was also a significant trend towards shorter treatment with a higher degree of comedication, whereas for urologic spasmolytics, analgesics, and antiparkinson drugs, treatment length was not associated with comedication during the first 6 months.

The persistent users with <1 year of treatment were comparable to the 4,070 quitters with regard to comedication. More quitters used antiparkinson drugs (8.6% [7.8–9.5%] vs. 5.9% [4.5–7.6%]) and fewer quitters used antidepressants (26.7% [25.3–28.0%] vs. 31.1% [28.1–34.2%]). For the other drug classes and the ADS scores in Table 1, the confidence intervals overlapped.

Discussion

17,321 users of AChEIs were registered in the period, including 13,609 new users. Among those with known treatment length, the highest proportions of comedication were observed for sedatives/hypnotics and antidepressants. There was a strong association between comedication with antipsychotics during the first 6 months of treatment and duration of treatment. Patients with a high ADS score more frequently discontinued treatment than those with a lower ADS score. Concerning overall anticholinergic burden, most of the anticholinergic drugs used were considered to have a clinically significant or strong anticholinergic effect.

The incidence of dementia in Norway is around 10,000 persons every year, including 6,000 with suspected AD [30]. The number of incident AChEI users over the 7-year period was 13,609 persons, indicating that drug treatment for slowing down decline in cognition is uncommon. This may be due to late diagnosis, a high proportion of mixed dementia or low confidence in the therapeutic effect. Pharmacoepidemiological studies have reported that 10–50% of patients treated with AChEIs are prescribed anticholinergic agents [14–17]; in our study, the result was about 15%. The discrepancy between the studies may be due to different definitions of anticholinergic drugs, as well as different study populations and prescription patterns.
Improved clinical outcome may be expected with reduced anticholinergic burden in prescribed drugs. The highest proportions of comedication were observed for anxiolytics, hypnotics/sedatives, and antidepressants. This is consistent with other studies reporting that pharmacological approaches are often required for treatment of BPSD [31]. BPSD and insomnia may be part of the dementia syndrome, and insomnia is also an adverse effect of AChEIs. However, the use of anxiolytics, hypnotics/sedatives, and analgesics was similar in the study population as for the general population. Pain-related diagnosis has been shown to be associated with higher use of psychotropics in persons with dementia [32]. Pain-related conditions might be inappropriately treated with psychotropics, and more specific and better treatment of pain is thought to have a positive effect on mood [33].

The high proportion of comedication with antidepressants (N06A) indicates that depression is a major symptom in the dementia syndrome, and that many of the antidepressants are well tolerated. Selective serotonin reuptake inhibitors are recommended in several guidelines for comorbid depression in patients with AD [9], although evidence is limited [31]. Escitalopram and citalopram have shown superiority over placebo for reducing agitation in patients with AD, but the combination may have additive negative effects since both escitalopram/citalopram and AChEIs may result in a prolonged QT interval (time between the start of the Q wave and the end of the T wave in the heart’s electrical cycle) [34]. Nausea and diarrhea are common adverse effects of both serotonin reuptake inhibitors and AChEIs and can contribute to discomfort and weight loss [35].

Urologic spasmolytics are often used to treat incontinence, which could be caused by both the dementia syndrome and an adverse effect of AChEIs [14, 15]. Notably, the ADS scores of urologic spasmolytic agents range from 1 (darifenacin) to 3 (tolterodine and fesoterodine). Darifenacin, a P-glycoprotein substrate with a low central anticholinergic effect, has the supposedly lowest risk of interaction with AChEIs. In our study, only 11% of the urologic spasmolytic users were prescribed darifenacin. However, due to drug interactions with inhibitors of P-glycoprotein and individual variability in brain permeability, urologic spasmolytics as well as other drugs with any central anticholinergic effect, regardless of the dose, are not recommended to people with dementia [28].

Long-term use of antipsychotics is frequently prescribed, but not recommended in people with dementia [36, 37]. The high consumption of antipsychotics in patients with AD observed in this study may reflect the difficulties in implementing guidelines to clinical practice and a lack of feasible alternatives. Antipsychotics are probably prescribed for BPSD symptoms in the initial treatment period. AChEI use for BPSD in AD may be beneficial [31, 38], but the evidence is inconsistent [39]. Strong anticholinergic effects of antipsychotics may counteract the effect of AChEIs, and a QT interval prolongation and extrapyramidal side effects caused by pharmacodynamic interactions between AChEIs and antipsychotics may explain why so many patients using antipsychotics ended AChEI treatment after <1 year.

Nonmotor symptoms like dementia are rather common in patients with Parkinson disease, and AChEIs, especially rivastigmine, are recommended to slow the decline in cognition and activities of daily living. However, progression of motor symptoms with worsening of the tremor is frequently reported as side effects, and might limit the use [40]. In our study, only 5% were prescribed both AChEIs and antiparkinson drugs.

A higher proportion of persistent users than quitters had their treatment initiated by a specialist in geriatrics, which could be explained by geriatricians possibly having more focus on polypharmacy in elderly people than specialists in general medicine, resulting in a total lower ADS score.

The study has some limitations. The NorPD does not contain individual information on prescriptions made in institutions such as hospitals and nursing homes. Therefore, the total number of patients in Norway using AChEIs is higher than reported in this study. The age limit
of 80 years was set because many of the older patients would have become nursing home residents during the follow-up period, but we will lose some patients with this limit. The NorPD does not include data on the use of over-the-counter drugs and herbal drugs. This may lead to an underestimation of weak pain killers in our study as paracetamol in small pack sizes are available as over-the-counter drugs. Around one-third of the patients discontinued treatment of AChEIs before 8 months and was not included in the study regarding comedication (Fig. 1). In addition, we did not have information regarding all dementia diagnoses, neither in clinical presentation nor etiology nor about comorbidities. Therefore, it is difficult to compare the AChEI use to the prevalence of dementia. Regarding the strong association between antipsychotic use and treatment length, we do not know whether early quitters stopped treatment because they had more mental deterioration with a higher use of antipsychotics, or because of higher anticholinergic burden causing a limited response to AChEI therapy. Purchased drugs were used as a surrogate for consumed drugs and may cause overestimation. However, adherence is expected to be good, as caregivers usually are responsible for drug intakes in patients with dementia.

In conclusion, a high proportion of comedication was observed in AChEI users, and patients being prescribed antipsychotics were more likely to stop AChEI treatment. In addition, patients with low ADS scores continued treatment for a longer period of time. Our findings indicate that continuation of AChEI therapy may be related to concomitant and inappropriate drug use. The many combination therapies observed demonstrate the need for regular monitoring of clinical response and potential side effects and interactions, especially in the initial phase of AChEI treatment. If necessary, agents with no or low ADS scores should be selected, as illustrated by the use of urologic spasmolytics. Future studies on comorbidity could give more information on combination therapies and strategies to maintain the already limited effect of the AChEIs.

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References


Drug Use before and after Initiating Treatment with Acetylcholinesterase Inhibitors

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Keywords
Pharmacoepidemiology of dementia · Behavioral and psychological symptoms of dementia · Pharmacotherapy

Abstract

\textbf{Background/Aims:} The aim was to study the prevalence of use of different drugs prescribed for behavioral and psychological symptoms of dementia in persistent users of acetylcholinesterase inhibitors (AChEIs) before and after AChEI initiation, and to compare with the use in the general population. \textbf{Methods:} Use of antidepressants, antipsychotics, and analgesics in the 4 years before and 2 years after AChEI initiation was studied based on data from the Norwegian Prescription Database 2004–2016. \textbf{Results:} The prevalence of use of antidepressants and antipsychotics the year before AChEI initiation was twice the prevalence in the age-adjusted general population and continued to rise in the first 2 years after initiation of AChEIs. The prevalence of weak analgesics and antipsychotics increased strongly in the last year before AChEI initiation. The increase in the use of antidepressants started at least 4 years before initiation of AChEIs. Opioid use was generally lower than in the general population and was not influenced by AChEI initiation. \textbf{Conclusion:} Increased use of antidepressants and antipsychotics was observed both before and after initiation of AChEIs and may indicate that behavioral symptoms occur in a preclinical or early phase of Alzheimer’s disease. The prescription pattern of analgesics with a low use of opioids may indicate an undertreatment of pain in people with dementia.
Introduction

Morbidity and mortality due to chronic diseases like neurological and mental disorders increase in older people. More than half of all dementia cases are generally assumed to be caused by Alzheimer’s disease (AD), and an increased reporting of cases is seen due to the increased number of older people [1, 2]. Almost every fifth person will develop dementia during their lifetime [3], and the number is suggested to double in 30 years. Dementia is strongly related to age, with a prevalence in western Europe varying from about 1–2% in the age group 65–69 years to about 25–35% in the age group 85+ [2]. According to the national Norwegian guidelines it is recommended to start treatment with acetylcholinesterase inhibitors (AChEIs) as soon as possible when the diagnosis of dementia due to AD is made, and the initiation of these drugs can therefore be a surrogate marker of the time of the AD diagnosis [4].

Three AChEIs are registered in Norway for symptomatic treatment of AD of mild to moderate degree; donepezil, rivastigmine, and galantamine. All three cause a general increase of acetylcholine (ACh) in all cells in the body using ACh as a transmitter substance. This gives rise to cholinergic side effects, which is of special importance in the presence of drug interactions [5], and therefore general caution must be taken to reduce the risk of adverse effects. Knowledge of comedication to AChEI treatment in people with AD may therefore be of importance.

Almost 90% of patients with AD will experience behavioral and psychological symptoms of dementia (BPSD) like depression, agitation, psychosis, apathy, or irritability during the course of dementia, and the extent increases with the severity of the dementia, especially agitation and apathy [6, 7]. Moreover, it is possible that symptoms of apathy, depression, anxiety, and irritability can be early signs of cognitive impairment and dementia. Prescription of psychotropic drugs to these patients with AD in a preclinical phase could therefore be based on a wrong diagnosis and indication. In more severe stages of dementia, psychotropic drugs are often initiated to treat behavioral symptoms. However, these drugs are not particularly effective and may result in considerable side effects, especially in older people more susceptible for adverse effects of drugs [8, 9]. Due to multimorbidity and polypharmacy, the treatment of BPSD is difficult and needs continuous clinical observation of the patients. Focused intervention to promote social engagement is an important component to enable effective antipsychotic discontinuation [10, 11]. The modest effect of psychotropic drugs for BPSD could be due to the fact that these symptoms may have causes not related to depression, anxiety, or psychosis. Pain and discomfort may also trigger change of behavior. Psychotropic drugs are commonly involved in the treatment of BPSD in nursing homes in Norway [7, 12]. We followed patients’ use of antidepressants, antipsychotics, and analgesics, which are frequently used among patients with dementia but have anticholinergic activity or other known adverse effects, interactions, and precautions [9].

AChEIs are usually initiated at the time of a diagnosis of AD, but we do not know whether this may change the prescription of psychotropic drugs. Since the first subtle signs of AD may be behavioral symptoms, psychotropic drugs would probably be prescribed. Thus, the aim was to study the pattern of drug use before and after initiation of treatment with AChEIs and compare with drug use in the general population.

Materials and Methods

Data

Drug use data were collected from the Norwegian Prescription Database (NorPD). This database covers the total population of Norway and, since 2004, information from all prescriptions dispensed at Norwegian pharmacies to individual patients are included in the
database, as well as prescriptions following treatment in inpatient clinics and discharge from hospital. It is possible to follow all individuals who purchased drugs through their national personal unique identifying number [13]. However, drugs dispensed to patients in institutions are not included in the NorPD, making us unable to follow the patients’ drug use in nursing homes.

Data registered in the NorPD included sex, age, year of death (when relevant), and information on prescribed drugs dispensed. In this study, dispensed drugs represented consumed drugs. The drugs were classified according to the Anatomical Therapeutic Chemical (ATC) classification system version 2018 [14]. For each dispensed prescription we obtained the date of dispensing, medicinal product name and formulation, ATC code, number of defined daily doses, and the number of tablets/capsules/plasters (allowing us to calculate treatment periods).

We had access to individual data from the NorPD for all persons being dispensed at least one prescription of AChEIs (ATC code N06DA) in the period January 1, 2004, to December 31, 2016. In addition, for every ATC code, we had access to the yearly total number of users in the population by gender and 1-year age groups (up to and including 89 years).

Study Population

The study population consisted of all persistent (see below) AChEI users who initiated AChEI treatment between January 1, 2008, and December 31, 2013, at an age of 88 years or younger, who were alive 2 years after the year of AChEI treatment initiation, and who were registered in the NorPD the second year after AChEI initiation (not yet in a nursing home). The age limit of 88 years was set to make a comparison with the general population possible (number of users per 1-year age group in the general population was only available up to and including 89 years). The study population was stratified into four subgroups according to age at initiation. The first group, aged 37–64 years, was selected to study the presenile group (defined as onset of dementia before the age of 65). The last three groups were selected to get equal age spans (65–72, 73–80, and 81–88 years of age).

Use of Drugs before and after Initiation of AChEIs

We studied the prescriptions for the last 4 years (365-day periods) before and the first 2 years after AChEI initiation for the following drug groups: antidepressants (N06A excluding amitriptyline N06AA09, commonly prescribed for neuropathic pain), antipsychotics (N05A excluding prochlorperazine N05AB04, commonly prescribed for vertigo), and weak analgesics and opioids (ATC group N02). The day of AChEI initiation was counted as the first day of the first year (365-day period) after initiation.

Incident and Persistent Use of AChEIs

Incident use was defined as being prescribed an AChEI drug after 365 successive days with no AChEI prescriptions. According to Norwegian guidelines for dementia treatment, the treatment should be evaluated 3–6 months after initiation, and we considered users who continued treatment 8 months after initiation as persistent. Thus, an incident user was defined as persistent if any of the following was true: (i) a new prescription was given between day 210 and day 240 after initiation, (ii) drugs for at least 210 days’ consumption were prescribed during the first 210 days from initiation, or (iii) the last prescription before day 210 lasted to day 210. We assumed a consumption of one tablet per day for donepezil and galantamine and two tablets per day for rivastigmine. An illustration of incident and persistent use is given in Figure 1.
Comparison with Drug Use in the General Population

The use of, for example, antidepressants in the study population in the first year after initiation of AChEI was compared to the use in the general population (including the study population) as follows: for each of the years 2008–2013, the age- and gender-adjusted prevalence of antidepressant use in the general population was computed, using the age and gender distribution of those initiating AChEI in the actual year as reference. The overall age- and gender-adjusted prevalence in the general population was then estimated as the average of the six 1-year prevalences. When comparing antidepressant use in AChEI initiators X years before/after initiation with the general population, the dispensing years and the age in the general population was shifted X years. For example, antidepressant use in the age group 81–88 years 4 years before initiation was compared to use in the age group 77–84 years in 2004–2009 in the general population, and antidepressant use in the same age group the second year after initiation was compared to use in the age group 82–89 years in 2009–2014 in the general population. Age-adjusted prevalence ratios (PRs) were calculated by dividing the prevalence in the AChEI users by the age- and gender-adjusted prevalence in the general population.

Statistical Analysis

R version 3.4.3 [15] was applied for descriptive statistics; proportions with 95% confidence intervals (CIs) were computed for the study population. The 95% CIs were computed using the “binom.confint” function in R with the “wilson” method. Age-adjusted prevalence was computed for the general population using the “ageadjust.direct” function in R. The 95% CIs for the general population were very narrow and hence not shown.

Results

The study population consisted of 11,764 persistent AChEI users aged 37–88 years who initiated treatment between January 1, 2008, and December 31, 2013. The percentage of women in the four age groups was 56, 56, 61, and 68%, respectively, and 63% in the full study population. They were followed from 4 years (1,460 days) before initiation to 2 years (729 days) after initiation.
The proportions of the study population and the general population receiving at least one prescription of antidepressants, antipsychotics, weak analgesics, and opioids in the 4 years before initiation of AChEI and the 2 years after initiation are shown in Figures 2–5, respectively.

The prevalence of the use of antidepressants (ATC group N06A) strongly increased in the study population over the 6-year interval from 13.5% (95% CI: 12.9–14.1%) in the fourth year before initiation to 30.2% (29.4–31.1%) in the second year after initiation. In the general population, the prevalence was quite unchanged in all age groups and increased from 10.3% to 11.1% in the age group 37–88 years (PR increased from 1.3 to 2.7) (Fig. 2). The highest prevalence was observed for AChEI users in the lower age groups. The prevalence still increased in the 2 years following AChEI introduction. As many as 87 and 82% of those who were prescribed antidepressants the year before initiation of AChEI therapy were prescribed antidepressants the first and second year after, respectively.

In the total study population, the prevalence of the use of antipsychotics (ATC group N05A) 2 years before AChEI initiation was similar to that in the general population; 3.2% (2.9–3.5) (Fig. 3), but it increased strongly in the year prior to the prescription of AChEIs to 6.0%, and continued to increase in the 2 years after initiation to 9.3% (8.8–9.8) in the second year. The highest prevalence was observed in the younger age groups. The prevalence still increased in the 2 years following AChEI introduction. In addition, as many as 67 and 58% of those who were prescribed antipsychotics the year before initiation of AChEI therapy were prescribed antipsychotics the first and second year after, respectively.
The prevalence of the use of opioids (ATC group N02A) increased slightly with age, but was lower in the study population than in the general population, mostly in the oldest age group (Fig. 4). In the total study population, the prevalence was quite unchanged during the study period; 17.1% four years prior to AChEI prescription and 17.2% two years after (95% CI: 16.5–17.9). In the general population, the corresponding percentages were 19.0%, increasing to 20.4% (PR decreasing from 0.90 to 0.84). Of those who were prescribed opioids the year before initiation of AChEI therapy, 42 and 43% were prescribed opioids the first and second year after, respectively.

In the study population, the prevalence of the use of weaker analgesics (ATC group N02B; other analgesics and antipyretics), mainly consisting of paracetamol, was similar to that in the general population (Fig. 5) until 1 year before AChEI initiation, where the prevalence in the study population increased more rapidly. In the general population, the age-adjusted prevalence increased from 11.7 to 20.0% during the study period. Corresponding percentages in the study population were 11.5% (95% CI: 10.9–12.1) and 26.0%, and the PR increased from 0.98 to 1.30. The pattern was similar in the different age groups, with the lowest prevalence in the age group 37—64 years. As many as 63 and 59% of those who were prescribed drugs in ATC group N02B (other analgesics and antipyretics) the year prior to initiation of AChEI therapy were prescribed these drugs the first and second year after, respectively.
Discussion/Conclusion

We found a marked increase in the use of antidepressants, antipsychotics, and analgesics (except for opioids) in AChEI users in the years prior to AChEI initiation, and the prevalence continued to rise in the first 2 years after initiation. The majority of those who used antidepressants the year before initiation continued after initiation. Opioid use was not influenced by AChEI initiation. Some studies have been addressing the effect of AChEIs on BPSD [6]. Our study indicates that the use of AChEIs does not reduce BPSD, as the proportion of psychotropic drug users seems to increase after initiation of treatment with AChEIs.

Antidepressants prescribed in the years before the initiation of AChEIs could indicate that depression is a preclinical or an early symptom in AD and could be a psychological response to the ongoing cognitive decline [16]. However, symptoms such as social withdrawal, problem at the workplace, apathy, reduced ability to concentrate, and forgetfulness as part of the dementia syndrome could have been misjudged as depression. Use of antidepressant medications for mood in dementia may have limited benefits but is associated with adverse outcomes [17]. However, some withdrawal studies find that some people with dementia and BPSD may benefit from antidepressants [18]. According to the Norwegian guidelines, a selective serotonin reuptake inhibitor drug should be offered as additional treatment to patients, but only when appropriate environmental psychological and/or psychotherapeutic measures have been attempted without achieving the desired effect [4]. There is insufficient evidence on the long-term safety of antidepressant use for BPSD in people with dementia [19]. Due to the limited benefits and considerable risks, antidepress-
sants should be used only if all other nonpharmacological interventions for neuropsychiatric symptoms are unsuccessful. For people living with mild to moderate dementia in combination with mild to moderate depression, psychological treatments and social activities should be preferred over antidepressants [4, 19]. The risks and benefits of different antidepressants should be carefully evaluated when these drugs are prescribed to older people [20, 21].

The prevalence of the use of antipsychotics increased in the study population after initiating AChEI therapy, with risks of adverse effects, interactions, and increased morbidity. The duration of antipsychotic drug treatment should be as short as possible because of the high risk of side effects, including more rapid progression of the cognitive decline [22]. Antipsychotics should therefore only be offered for people living with dementia who are either at risk of harming themselves or experiencing psychosis [4]. Apparently, psychotropic drugs are prescribed for BPSD due to lack of resources and time to implement nonpharmacological treatment approaches [12, 23]. The highly increased fall risk in elderly individuals with AD can be the result of interaction of several factors including polypharmacy and anticholinergic side effects commonly reported with antipsychotics [9, 24]. Patients with high anticholinergic burden more often terminate treatment with AChEIs early [25]. Of antipsychotics, the atypical substances risperidone and olanzapine currently have the best evidence for efficacy; however, the effects are modest and complicated by an increased risk of stroke [6]. In Norway, only risperidone is approved for the indication psychotic symptoms and agitation [4].

Pain is a very common manifestation in people with dementia that is often neither diagnosed nor treated. Numerous studies have shown that pain sensitivity remains largely intact
with advanced dementia [26]. In addition, the placebo component of analgesic treatment is disrupted in AD patients [27]. Delirium, hearing and vision impairment, falls and injury, incontinence, and pain may coexist with dementia [24], and in severe dementia it may be difficult to communicate symptoms like pain. Therefore, pain and discomfort may trigger behavioral disturbances such as aggression and agitation, and also depression [28]. A clear association has been reported between pain and increased antipsychotic use, which may be related to mistreatment of pain in people with AD [28, 29]. Studies have reported frequent use of opioids in patients with dementia [30]; however, this was not the case in our study. Opioid use was not influenced by AChEI initiation. This was especially apparent in the first 2 years of the study period; the prevalence of weaker analgesics (ATC group N02B) were similar in the study group and in the general population, while a corresponding lower prevalence of opioids was observed. The increasing trend within each age group in the general population can be explained by an increased use with age. The increased prevalence of the use of weaker analgesics (ATC group N02B) observed from 2 years before the introduction of AChEIs will probably not compensate for the reduced use of opioids. The total pattern of analgesic prescription among the AChEI users may indicate an undertreatment of pain in people with dementia. The reason for the possible undertreatment may be that people with dementia underreport pain as a symptom, in addition to the prescribers’ fear of adverse effects of opioids [26]. Paracetamol should always be considered the first-line therapy for pain. In case of moderate to severe pain, low and titrated dosages of an opioid are recommended, and transdermal buprenorphine may be an option [28]. Good evidence indicates that undertreatment of pain is a greater risk factor for the development of delirium than the use of opioids [31]. When prescribing opioids for treating pain in dementia, great consideration should be given to drug selection and dosing frequency [26]. Particularly in older people with dementia, pharmacological treatment should be initiated with great caution. Starting dosage(s) should be low and titrated to response [28].

Data from the NorPD give us a unique opportunity to study drug use patterns, highlighting changes over time in the selected drug groups. The large sample size is a strength in our study. However, patients in institutions are not included in NorPD and therefore not included in the present study. The NorPD does not include data on the use of over-the-counter drugs and herbal drugs. This may lead to an underestimation of weak analgesics in our study as paracetamol in small pack sizes is available as an over-the-counter drug. AChEIs are mainly prescribed for the treatment of AD; however, we did not have information with regard to the clinical presentation of the dementia diagnoses or about the etiology or comorbidities. We did not study benzodiazepines since these drugs are, according to approved indications, mainly used for anxiety and less prescribed for BPSD in Norway. However, as the use of benzodiazepines is rather frequent in this age group, it would have been of interest to study this drug class in more detail. Purchased drugs were used as a surrogate for consumed drugs and may cause overestimation. However, medicine adherence in AChEI users is expected to be good, as caregivers are usually responsible for drug management for patients with dementia.

In conclusion, the study group receiving AChEIs differed from the general population with regard to prevalence of the use of antidepressants, antipsychotics, and analgesics. An increased use of antidepressants and antipsychotics was observed both before and after initiation of AChEIs, which may indicate that behavioral symptoms occur in a preclinical or early phase of AD. The total pattern of analgesic prescription may indicate an undertreatment of pain in people with dementia. Evaluation of depressive and other noncognitive symptoms, as well as pain-related conditions, in people with dementia in an early phase should be prioritized to avoid the unfortunate use of psychotropic drugs and misinterpretation of early symptoms of AD. After the initiation of AChEIs, the indication for continuous use of antidepressants and antipsychotics should be considered.
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Statement of Ethics

The NorPD generated pseudonymous files for research purposes, as regulated by Norwegian law for health registers, hence there was no demand of additional approval by the ethics committee.

Disclosure Statement

The authors have no financial or any other kind of personal conflicts in relation to this paper.

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References


Sex differences in psychotropic and analgesic drug use before and after initiating treatment with acetylcholinesterase inhibitors

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Abstract

Background/aims
The aim was to explore the impact of sex on prevalence, patterns and trends in the prescription of psychotropics and analgesics in users of acetylcholinesterase inhibitors (AChEIs), before and after AChEI initiation, compared to the general population.

Methods
A prospective study applying data from the Norwegian Prescription Database (NorPD) in the period 2004–2016. Prescription of antidepressants, antipsychotics, analgesics including opioids, benzodiazepines and z-hypnotics in persistent AChEI users was studied in a follow-up period from four years before to two years after AChEI initiation in men and women of four age groups: 37–64, 65–72, 73–80 and 81–88 years.

Results
Use of antidepressants, antipsychotics and weaker analgesics increased in both sexes during the follow-up period in 11,764 persistent AChEI users. Women with pre-dementia and dementia stages of AD showed a prescription pattern with more use of psychotropics and opioids than men, except for antipsychotics.

Conclusion
Female sex showed to have a significant influence on the prescriptions of psychotropics and analgesics in AD patients in a pre-dementia and dementia stage. The exception is for antipsychotics, that men used more than women. The prescription pattern showed a higher extent of polypharmacy of psychotropics and/or opioids in women than in men. The total prescription pattern of analgesics could indicate an undertreatment of pain in pre-dementia and dementia stages, most pronounced in men.
Introduction

Alzheimer’s dementia (AD) accounts for 60–80% of people with dementia with a greater proportion and severity of the disease in the higher age groups [1], resulting in 2/3 of patients with AD being women [2].

Approximately 90% of people with dementia develop at least one Behavioral and Psychiatric Symptom of Dementia (BPSD) like depression, agitation, psychosis, apathy or irritability over the course of the disease, symptoms becoming more common as the disease progresses [3]. BPSDs have been associated with sex for its biological characteristics, severity of dementia, and cultural background [4], often reflected in differences in prescription of medications [5]. Besides, disrupted sleep is common.

To stimulate cholinergic transmission, acetylcholinesterase inhibitors (AChEIs) are used in patients with mild to moderate degree of AD [6], with a hypothesized mechanism for improvement in cognition [7]. Some studies have suggested that these medications may alleviate BPSDs as well [8].

However, in most cases psychotropic drugs are used to treat BPSD. Antidepressants and anxiolytics are often used early in the course of AD, whereas antipsychotics are initiated later on [9, 10]. People with dementia use more psychotropics compared to the general population, despite the recommendations of a restrictive use of psychotropics in BPSD [11, 12]. Psychotropic polypharmacy, the use of two or more psychotropic drugs concomitantly, is generally associated with an increased risk of injurious falls, hospitalization and mortality and should be avoided in older persons with dementia [13].

Female sex has been shown to be associated with a higher likelihood of inappropriate drug use [14]. Further, women have an increased risk of polypharmacy [15], are more likely to have functional and cognitive disabilities due to aging and to live alone, known to be associated with depressed mood and over-utilization of psychotropic drugs [16]. Studies have shown that psychotropic drugs are used more common in hospitalised elderly women than in men [16]. However, antipsychotic drug use has been reported to be higher among men with AD and antidepressant drug use higher among women with AD [5, 17]. In Norway, older women living at home are reported to use more opioids and paracetamol than men [18], and female sex has been associated with an increased risk of drug related problems with opioids involved in nursing homes [19].

Thus, the aim was to explore the impact of sex on prevalence, patterns and trends in the prescription of drugs and co-medications of psychotropics and analgesics, as use of antidepressants, antipsychotics, benzodiazepines (BZDs), Z-hypnotics, opioids and weaker analgesics in users of AChEIs, compared to the general population.

Materials and methods

Data

Drug use data were collected from the Norwegian Prescription Database (NorPD) and include sex, age, year of death (when relevant) and information on prescribed drugs dispensed [10]. Drugs dispensed to patients in institutions are not included in the NorPD, making us unable to follow the patients’ drug use in nursing homes. NorPD contains a complete listing of all prescription drugs dispensed by pharmacies in Norway since 2004.

In this study, dispensed drugs represented consumed drugs. The drugs were classified according to the Anatomical Therapeutic Chemical (ATC) classification system version 2017 [20], obtaining date of dispensing, medicinal product name and formulation, ATC-code, number of defined daily doses (DDDs) and the number of tablets/capsules/plasters (allowing us to calculate treatment periods).
We had access to all persons being dispensed at least one prescription of AChEIs (ATC-code N06DA) and the yearly total number of users in the population by sex and one-year age groups (up to and including 89 years).

**Study population**

We used the first prescription of an AChEI as a surrogate marker of the time of the AD diagnosis [11].

The study population consisted of all persistent (see below) AChEI users who initiated AChEI treatment between 1 January 2008 and 31 December 2013 at an age of 88 years or younger, who were alive two years after the year of AChEI treatment initiation, and who were registered in the NorPD the second year after AChEI initiation (not yet in nursing home). They were followed from 4 years (1460 days) before initiation to 2 years (729 days) after initiation. The age limit of 88 was set to make a comparison with the general population possible, for which data with one year age resolution was only available up to and including 89 years. The study population was stratified into four subgroups according to age at initiation. Due to the definition of early onset of dementia the young onset group include persons 37–64 years old. The last three groups were selected to reach equal age spans (65–72, 73–80 and 81–88 years old). Incident use was defined as being prescribed an AChEI drug after more than 365 successive days with no AChEI prescriptions. Some patients were repeated incident users (having several AChEI-free periods of more than 365 days). For each patient we started follow-up at the date of the prescription initiating the longest period with subsequent prescriptions less than 365 days apart (index date). The 'longest period' means the period with the largest number of prescriptions. Treatment length was estimated as the time from index date until the drug dispensed in the last prescription of the longest period was supposed consumed. The earliest possible index date was 1 January 2005. To allow for at least 1 year of follow-up we only included patients with index date before 1 January 2012.

**Sex differences and use of drugs before and after initiation of AChEI**

We studied sex differences in the prescriptions the last four years (365-day periods) before and the first two years after AChEI initiation for the following drug groups: antidepressants (ATC code N06A excluding amitriptyline N06AA09, commonly prescribed for neuropathic pain), antipsychotics (ATC code N05A excluding prochlorperazine N05AB04, commonly prescribed for vertigo), opioids and weaker analgesics (ATC codes N02A and N02B), BZDs (ATC codes N05BA and N05CD) and Z-hypnotics (ATC code N05CF). The day of AChEI initiation was counted as the first day of the first year (365-day period).

Sex differences in prevalence of use of psychotropics and opioids, defined as proportion of users of antidepressants, antipsychotics, BZDs, Z-hypnotics, weaker analgesics and/or opioids, were studied in the cohort during the six years time interval. Use of a given drug class in a given 365-day period was defined as at least one prescription of a drug in the actual drug class in the actual period.

**Incident and persistent use of AChEI**

Incident use was defined as being prescribed an AChEI drug after 365 successive days with no AChEI prescriptions. Since the treatment should, according to Guidelines, be evaluated 90–180 days after initiation, we considered due to possible delay, users who continued treatment 8 months (240 days) after initiation as persistent users [10]. Thus, an incident user was defined as persistent if any of the following was true [9]: i) a new prescription was given between day 210 and day 240 after initiation, ii) drugs for at least 210 days consumption were prescribed.
during the first 210 days from initiation, or iii) the last prescription before day 210 lasted to day 210.

Sex differences and comparison with drug use in the general population

The use of e.g. antidepressants in the study population the first year after initiation of AChEI was compared to the use in the general population as follows: For each of the years 2008–2013, the age- and sex adjusted prevalence of antidepressant use in the general population was computed, using the age- and sex distribution of those initiating AChEI the actual year as reference. The over-all age- and sex adjusted prevalence in the general population was thereafter estimated as $P_{2013} = \frac{\sum_{y=2008}^{2013} u_y}{\sum_{y=2008}^{2013} N_y}$, where $u_y$ and $N_y$ are the age-adjusted number of antidepressant users and the population in year $y$, respectively. When comparing the antidepressant use in AChEI initiators $X$ years before/after initiation with the general population, the dispensing years and the age in the general population was shifted $X$ years. As an example, antidepressant use in in the 81–88 year age group four years before initiation was compared to use in the 77–84 year old persons in 2004–2009 in the general population and antidepressant use in the same age group the second year after initiation was compared to use in the 82–89 year old in 2009–2014 in the general population. Age-adjusted prevalence ratios (PRs) for each sex were calculated by dividing the prevalence in the AChEI users by the age- adjusted prevalence in the general population.

Statistical analysis

R version 3.1.0 [21] was applied for descriptive statistics; proportions with 95% confidence intervals (CIs) were computed for the study population. The CIs were computed using the 'binom.confint' function in the 'binom' package in R with method = "wilson". Age adjusted prevalence rates were computed for the general population with the study population as reference, using the 'ageadjust direct' function in the 'epitools' package in R. The CIs for the general population are very narrow and hence not shown.

Ethics

All the pharmacies in Norway register prescriptions electronically, and the information is sent in monthly reports to NorPD. The patient’s personal ID number and the prescribers ID number are replaced by a unique pseudonym by Statistics Norway. This makes it possible to link drug use to individuals without knowing their identity. Personal information is not disclosed from the NorPD. The database is governed by the national regulation of 17 October 2003 about the collection and processing of health data in the Norwegian Prescription Database. The NorPD generated pseudonymous files for research purposes, as regulated by Norwegian law for health registers [22], hence there was no demand of additional approval by the ethics committee.

Results

The study population consisted of 11,764 persistent AChEI users aged 37–88 years who initiated treatment between 1 January 2008 and 31 December 2013. The percentage of women in the four age groups was 56%, 56%, 61%, and 68%, respectively, and 63% in the full study population. The proportion of the study population receiving at least one prescription of antidepressants, antipsychotics BZDs, Z-hypnotics, opioids and weaker analgesics the four years before initiation of AChEI and the two years after, are shown in Figs 1–6, respectively, together with the age-adjusted proportion of the general population receiving the same drugs.
We found no differences between age-groups related to prescription of the various AChEIs. As donepezil was the first AChEI on the market between 69% (youngest age group) and 72% (oldest age group) used this drug.

Prevalences of use in the general population

Women of the general population showed a higher prevalence of use of antidepressants, antipsychotics, benzodiazepines, z-hypnotics, opioids and weaker analgesics than men. A notable age-related increase in use of these drug groups was observed, especially in women, except for antipsychotics. Within each age-group in Figs 1–6, the change in prevalence over the 6 years covered can be attributed both to a 6 year increase in age and a 6 year increase in calendar year. The change was small for most of the drug groups: In the 37–88 year age group the prevalence for antidepressants increased from 6.5% to 7.2% in men and from 12.5% to 13.3% in women; for antipsychotics it decreased from 2.7% to 2.5% in men and from 3.8% to 3.5% in women; for BZDs it decreased from 10.6% to 9.9% in men and from 20.9% to 19.3% in women; for z-hypnotics it increased from 13.4% to 16.1% in men and from 24.6% to 28.3% in women; for opioids it increased from 15.7% to 16.8% in men and from 21.0% to 22.6% in women. For weaker analgetics, however, the prevalence almost doubled over the 6 years from 7.8% to 13.8% in men and from 13.9% to 23.6% in women. For all of the drug groups except BZDs, the pattern of change was the same in all age groups, but for BZDs the prevalence was stable in the youngest age group (at 6.8% for men and 12.1% for women) but markedly decreasing in the oldest age group (from 13.1% to 11.5% in men and from 23.9% to 21.0% in women). Due to the large sample size, the width of the 95% confidence intervals are less than 0.16 in all cases, and thus all of the changes are statistically significant, but none are large enough to be of any clinical significance.

Prevalences of use in the study population

Women of the study population showed a higher prevalence of use of antidepressants, BZDs, z-hypnotics, opioids and weaker analgesics than men. A notable age-related increase in use of these drug groups was observed, except for antidepressants and antipsychotics.

From four to one year before initiation of AChEI the prevalence of use in the study population overall (age 37–88) compared to the general population was higher for antidepressants, lower for antipsychotics and opioids, and similar for BZDs, z-hypnotics and weaker analgesics. From one year before to two years after initiation, however, the prevalence in the study population was higher than in the general population also for antipsychotics, weaker analgesics, and BZDs (men only), and lower only for opioids. There were some age group specific exceptions to this pattern, though, see details for the different drug groups below.

Antidepressants

The use of antidepressants strongly increased in both genders over the six years interval and was higher in women than in men in all age groups (Fig 1). The use in women increased from 16.2% (95% CI: 15.4%-17.1%) the fourth year before initiation to 34.1% (33.0%-35.2%) the second year after. The corresponding increase in men was from 8.8% (95% CI: 8.0%-9.6%) to 23.7% (22.5%-25.0%). Comparing with the general population, the prevalence ratio (PR) increased from 1.3 to 3.3 over the six years in men and from 1.3 to 2.6 in women. In the youngest age group, the prevalence four year before initiation was about twice as high in the study population as in the general population, whereas in the oldest age group it was about the same in the two populations. In all age groups the prevalence increases strongly the years before...
AChEI initiation, but in the youngest age group there is no significant further increase after initiation.

Antipsychotics

The prevalence of the use of antipsychotics strongly increased in the study population overall (age 37–88) in both sexes from two years prior to the dementia diagnosis and during the two years following initiation of AChEIs (Fig 2). The use in women increased from 3.0% (95% CI: 2.7%–3.4%) the fourth year before initiation to 9.0% (95% CI 8.3%–9.6%) the second year after, respectively. The corresponding increase in men was from 2.2% (95% CI: 1.8%–2.7%) to 9.8% (8.9%–10.7%). Comparing with the general population, the PR in men increased from 0.8 the fourth year before initiation via 1.0 the second year before to 3.9 the second year after initiation, and in women from 0.8 via 1.0 to 2.6. In the youngest age group, the prevalence was higher in the study population than in the general population all six years (although the difference was not statistically significant the first years), whereas in the oldest age group the prevalence in the study population four years before initiation was only about half the prevalence of the general population. Two years before initiation it was still significantly lower (at 2.6% in women and 1.8% in men), but then increased markedly the year before initialization to 5.7% and 4.1% in women and men, respectively, and further to 8.4% and 7.4% the second year after initialization.

BZDs

The prevalence of the use of BZDs was higher in women than in men during the study period (Fig 3), however, continued to rise following AChEI initiation in men, but decreased in women the years after AChEI initiation, compared to the year before. Over the six years the use in women decreased from 21.1 (95% CI 20.2%–22.1%) to 19.0% (18.1%–19.9%), whereas in men it increased from 10.4% (9.6%–11.4%) to 14.0% (13.0%–15.1%). In men, most of the increase occurred from the second to the first year before initiation. Compared to the general population, the use of BZDs was highest in the youngest age group the two years after AChEI initiation.
initiation (average PR of 2.1 for men and 1.4 for women). The PR in the 37–88 age group was stable at 1.0 for women and increased from 1.0 to 1.4 for men.

Z-hypnotics

The prevalence of the use of Z-hypnotics was higher in women than in men in the study population during the study period, however, decreased the second year after AChEI initiation, more strongly in women than in men (Fig 4). The use in women decreased from 25.8% (95%
CI 24.8%–26.8%) to 25.0% (24.0%–26.0%), whereas in men it increased from 13.0% (12.0%–14.0%) to 17.2% (16.1%–18.4%). Compared to the general population the PR was close to 1 for both genders.

**Opioids**

The prevalence of the use of opioids was lower in men than in women in the study population during the study period (Fig 5), and quite stable for both sexes. The use in women increased
from 19.3% (95% CI 18.4%-20.2%) to 19.6% (18.7%-20.5%), whereas in men it decreased from 13.5% (12.5%-14.6%) to 13.1% (12.1%-14.1%). Compared to the general population the PR was stable at 0.9 over the six years for women and decreased from 0.9 to 0.8 for men. The largest difference between the study population and the general population was observed in the oldest age group.

**Weaker analgesics**

The prevalence of the use of drugs of weaker analgesics, mainly consisting of paracetamol, was increasing in the study population during the study period and was higher in women than in men (Fig 6). The first three years it was very close to the prevalence in the general population, but increased more rapidly the last three years, for both women and men. The use in women increased from 13.9% (95% CI 13.1%-14.7%) to 30.6% (29.6%-31.7%) over the six years, and in men from 7.4% (6.7%-8.2%) to 18.2% (17.1%-19.4%). Compared to the general population the PR in the 37–88 year age group increased from 1.0 to 1.3 in women and from 0.9 to 1.3 in men, with all of the increase taking place the last three years. The pattern was similar in the four age groups, except for the youngest group where the increase over the last three years was weaker.

**Psychotropic polypharmacy and opioids**

The proportion of the study population with use of 1 and 2 of the drug groups increased in both sexes the years before AChEI initiation and the first year after, and then flattened out or slightly decreased the second year after in both sexes. The proportion of the study population with concomitant use of 3 and 4 drug groups was low in both sexes (Fig 7). The proportion of women in the study population with use of one drug group increased from 27.1% (95% CI 26.1%-28.1%) four years before AChEI initiation to 35.9% (34.8%-37.0%) the first year after. The corresponding increase in the general population was from 25.5% to 26.0% (Fig 7). The proportion of women with two drug groups increased from 10.3% (9.6%-11.0%) to 17.0
(16.1%-17.8%) in the study population and from 10.7% to 10.8% in the general population. The proportion of men in the study population with use of one drug group increased from 19.7% (18.6%-20.9%) to 30.1% (28.7%-31.5%). The corresponding increase in the general population was from 19.3% to 20.2%. The proportion of men with two drug groups increased from 5.3% (4.7%-6.0%) to 10.8% (9.9%-11.8%) in the study population, whereas it was stable at 5.7% in the general population. The PR between the study population and the general population was in general highest for the young age groups, both for use of 1, 2 and 3 drug groups, in particular so for the years before AChEI initiation (Figs 8 and 9). The proportions with 4 groups were very low and are not shown.

Fig 7. Bullets: Proportion of the study population with concomitant use of exactly 1, 2, 3 or 4 of the drug groups antidepressants, antipsychotics, BZDs and opioids in the 4 years before AChEI initiation and the 2 years after initiation, with 95% confidence intervals. Circles: The corresponding age-adjusted proportion in the general population. Dashed vertical lines indicate AChEI initiation.

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Fig 8. Bullets: Proportion of the study population of men with concomitant use of exactly 1, 2 or 3 of the drug groups antidepressants, antipsychotics, BZDs and opioids in the 4 years before AChEI initiation and the 2 years after initiation, with 95% confidence intervals. Circles: The corresponding age-adjusted proportion in the general population. Dashed vertical lines indicate AChEI initiation. The size of each age group in the study population is given on top.

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Summary

We observed a marked increase in the use of antidepressants, antipsychotics and weaker analgesics in both sexes in AChEI users the last two years prior to AChEI initiation, and the use of these drugs continued to rise the first two years after initiation. However, a decreasing prevalence in the use of BZDs and Z-hypnotics following AChEI initiation in women was observed. Women of the study population had a higher prevalence of use of the studied drug classes compared to the general population except for opioids and Z-hypnotics, and a higher prevalence of use of the studied drug classes than men except for antipsychotics. The prevalence of opioids was lowest in the lowest age group in both sexes.

The highest prevalence rates of antidepressants and antipsychotics were observed in the lower age groups in both sexes, and we observed a tended high use of antipsychotics in men in the lower age groups.

The proportion of the study population with use of a drug in either one or two of the drug groups of antidepressants, antipsychotics, BZDs and opioids increased in both sexes the years before AChEI initiation and decreased slightly from one year after in both sexes, most pronounced in women (Fig 7). As much as 17% of the women and 11% of the men in the study population were prescribed drugs in two of the drug groups the first year after AChEI initiation. Corresponding numbers for one drug group was 36% and 30%, and for three drug groups 5 and 3%, respectively.

Discussion

Female sex showed to have a significant influence on the prescriptions of psychotropics and analgesics in AD patients in a pre-dementia and dementia stage. The exception is antipsychotics that men used more than women. The prescription pattern showed a higher extent of polypharmacy of psychotropics and/or opioids in women than in men.

The increase in prevalence in the use of antidepressants, antipsychotics and weaker analgesics in both sexes in AChEI users with pre-dementia and dementia conditions probably mirrors that BPSD increases in intensity and in symptomatology with increasing severity of AD,
without achieving the desired effect of the initially initiated drug treatment. Thus, the change in prevalence of use of these drug groups appears to take place independently of AChEIs. The higher use of psychotropics in women in the study population indicates that women with AD experience BPSD more frequently than men, as shown in other studies [5]. Older women are likely to have more physical and mental co-morbidities than men and this may in part explain differences in psychotropic medication use between sexes [3]. Severe physical disorders in people with dementia increase the probability of delirium, which is often treated with psychotropic drug.

The proportion of the study population with concomitant use of exactly one, and two of the drug groups of antidepressants, antipsychotics, BZDs and/or opioids decreased from one year following AChEI initiation in women and flattened out in men.

We observed a decreasing prevalence in the use of BZDs and Z-hypnotics in women and in z-hypnotics in men. This may reflect a precaution to reduce the extent of co-medications in people with an AD diagnosis, especially in women.

The high prevalence of use of antidepressants the years before initiation of AChEIs indicates that depression could be a preclinical symptom of AD in both sexes, and possibly that women generally express depressive thoughts better and more often than men. Also, women have been reported to experience depressive symptoms more frequently than men [5], to be more vulnerable to depression than male patients in the mild dementia group [23], to be over-treated with antidepressants and to be prescribed SSRIs more often than men [24]. The increase in prevalence of use might have started more than four years before initiation of treatment with AChEI and is not necessarily related to the initiation. Antidepressants have been reported to be prescribed for other indications than depression in 50% of the cases [25] such as pain and insomnia [26]. According to the national Norwegian dementia guidelines, a SSRI drug should only be offered as additional treatment to patients, when appropriate environmental psychological and/or psychotherapeutic measures have been attempted without achieving the desired effect [11]. The high use in AD patients, especially in women, compared to the general population may be inappropriate, but could also indicate that other treatment strategies have either failed or not been offered. This is worrisome in light of potential severe adverse effects antidepressants may induce [8, 27].

The effect of antipsychotics in BPSD is modest, however, their risk profile is extensive, and a restricted recommended use in Norway for the treatment of BPSD is described in the national dementia guidelines [11]. Despite the recommendation of the national guidelines, the use of antipsychotics in both sexes showed an increasing and high use during the study period. The higher use in men could be explained by the observed differences of BPSD between sexes. Men with dementia are often described as being more physically aggressive compared to women, which may result in more use of antipsychotics in men [5, 17]. The tended high use of antipsychotics in men in the study population in the lower age groups indicates this kind of differences in BPSD. Associations have been found between pain and depression, and depression plays an important role in development of agitation [28]. The use of antipsychotics may therefore be related to pain and depression as agitation often is treated with antipsychotics. Anxiety disorders are the most common psychiatric diseases, and women are twofold more likely than men to develop anxiety at disorder level during lifetime [16], and this is also the case for people with dementia, with anxiety being highly prevalent [29]. Besides, dependency-producing properties of anxiolytics are more pronounced in women than in men [16]. The use of BZDs have been connected to the risk of development of AD, especially the short-acting agents [30], however, another possible explanation is that insomnia could be a prodromal symptom of AD [31].
The use of BZDs and Z-hypnotics was increasing by age, for BZDs especially in women. The high prescription pattern of BZDs for women in particular in the higher age groups, is therefore of concern.

The use of anxiolytics among women has been associated with depressive disorders. This may be due to women tending to have pronounced anxiety symptoms of depression [32], and may suffer from a mixed depression/anxiety condition and that these symptoms are not recognized as early symptoms of AD. Another explanation could be that women in general use more anxiolytics compared to men. We observed an increasing prevalence in the use of BZDs in men from two years before the AD diagnosis, which could indicate that men become more noisy or sleepless at night during the course of the disease.

Women have a much higher prevalence of many pain disorders than men, and sex differences in the use of analgesics probably mirror the higher prevalence of chronic pain in women [33]. The lower use of opioids in men compared to women could reflect an undertreatment of pain, partially explained by the challenges associated with assessing pain, especially in patients with severe dementia, and probably not compensated for by increased use of weaker analgesics, which was strongly increasing in women in the oldest age group. One can ask whether the low use of opioids was related to the tended high use of antipsychotics in men in the lower age groups.

It should be noted that data in the figures of the study population overall (age 37–88) mirror data of the two oldest groups more than the two lower age groups, as the number of subjects in the two oldest groups represent nearly 75% of all subjects in the study population. Thus, the data for the study population overall should be interpreted with that in mind.

Psychotropic polypharmacy is reported to be frequent in AD patients [34], especially in women [35]. Demented women more often concurrently use drugs known to impair cognition [36] compared to men, with a higher risk of adverse events and death [37]. The increased risk may be driven by combinations with BZDs [37]. Other studies show that about 20% of patients with dementia living at home have been reported to be prescribed two or more psychotropic drugs [34] and similar results were found in the study population. As much as 36% of the women and 30% of the men in the study population were prescribed psychotropics and/or opioids one year following AChEI initiation. Although the prevalence of using psychotropics and/or opioids tended to decrease following AChEI initiation, the prevalence rates were still high (17% vs 11%). An important question is whether psychotropic polypharmacy is useful in patients with dementia, given the known risks and potential drug interactions [34], which is of concern especially in women of the study population. Potential pharmacodynamics and/or pharmacokinetic interactions among different drugs may contribute as a potential explanation underlying the decreased occurrence of polypharmacy the second year after initiation of treatment of AD patients with AChEIs. In addition, the findings in this study may not necessarily be generalized to other populations, especially since our data is not based on diagnoses, function or comorbidities.

Strengths and limitations
Data from the NorPD gives us a unique opportunity to study drug use patterns, highlighting changes over time in the selected drug groups. The large sample size and the long study period is a strength in our study. A limitation is that patients in institutions are not included in NorPD and therefore not included in the present study, hence the patients with the most severe symptoms of AD is probably not included in our study. The NorPD does not include data on the use of over-the-counter drugs and herbal drugs which may lead to an underestimation of weak analgesics in our study as paracetamol in small pack sizes are available as over-

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the-counter drugs. AChEIs are mainly prescribed for treatment of AD, however, we did not have information with regard to clinical rationale for prescriptions and indications. Purchased drugs were used as a surrogate for consumed drugs and may cause overestimation. However, medicine adherence in AChEI users is expected to be good, as caregivers usually are responsible for drug management for patients with dementia. We did not study dosage differences between men and women, which could be of relevance due to pharmacokinetic differences between the sexes. Concerning prevalence of psychotropic polypharmacy and opioids, we only record ATC classes and not number of substances. This probably leads to an underestimation of prevalence of polypharmacy. We do not know the duration of symptoms before the diagnosis, and generally, the described increases in prevalence of use of psychotropic drugs might have been started more than four years before AChEI initiation. We also assume younger people to seek medical attention earlier than older people, however, early onset dementia is not always suspected and probably rather interpreted as depression.

Conclusion
In conclusion, the increasing prescription pattern in the use of antidepressants, antipsychotics and weaker analgesics in both sexes during the study period probably mirrors that BPSD, sleep disturbances and pain increase in intensity or in symptomatology with increasing severity of AD, without achieving the desired effect of the initially initiated drug treatment. Female sex showed to have a significant influence on psychotropic prescribing. Women with pre-dementia and dementia stages of AD showed a prescription pattern with more polypharmacy of psychotropics and opioids than men, except for antipsychotics. The total prescription pattern of analgesics could indicate an undertreatment of pain in pre-dementia and dementia stages, most pronounced in men. Sex needs to be taken into consideration in clinical practice in treatment of pre-dementia and dementia conditions, to improve patient outcomes.

Supporting information
S1 Data. Aggregated data supporting Figs 1–9. (XLSX)

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Use of Drugs With Risk of Heart Rate-Related Problems is Common in Norwegian Dementia Patients Treated With Acetylcholinesterase Inhibitors: A Prevalence Study Based on the Norwegian Prescription Database

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Background: Drugs commonly prescribed for heart rate control may induce adverse drug reactions in Alzheimer patients treated with acetylcholinesterase inhibitors (AChEIs). We have studied use of drugs with a known risk of Torsades de pointes (TdP) and drugs used to treat behavioral and psychological symptoms of dementia, as well as a combination of drugs with a known risk of TdP and drugs with a known heart rate-lowering effect, before and after initiating treatment with AChEIs.

Methods: The study applied data from the Norwegian Prescription Database for the period 2004–2016. Prescriptions of concomitant use of drugs in persistent users of AChEIs was studied in a follow-up period from 4 years before to 2 years after AChEI initiation in men and women of two age groups: 37–80 and 81–88 years.

Results: A small number of patients were prescribed haloperidol (~1.5% The second year after AChEI initiation), digoxin/digitoxin (~3%), and verapamil (~1.3%), while a substantial proportion of the patients were prescribed betablockers (~28%) and citalopram/escitalopram (~17%). During follow-up, up to 6% of the study population were prescribed both betablockers and citalopram/escitalopram in addition to AChEIs, a combination that increased over the follow-up period and was observed most frequently in women in the oldest age group.

Conclusions: A large proportion (~44%) of patients treated with AChEIs were prescribed drugs that could cause bradycardia and prolonged time from the start of the Q wave to the end of the T wave (QT interval). Thus, action should be taken to reduce the combination of drugs with risk of bradycardia and prolonged QT interval. Medication review on a regular basis could be an option as an important risk-reducing intervention.
INTRODUCTION

Acetylcholinesterase inhibitors (AChEIs) are usually prescribed early in the course of dementia due to Alzheimer’s disease (AD), and patients who respond well may take these drugs for several years (Hernandez et al., 2009). The target organ for AChEIs is the brain, but as the heart is also rich in cholinesterases, the AChEIs may adversely affect cardiac function due to the cholinergic effects, especially in older patients, resulting in risks of arrhythmias, prolonged time from the start of the Q wave to the end of the T wave (QT-interval), and Torsades de Pointes (TdP) (Isik et al., 2012). Of the AChEIs, only donepezil is classified with a known risk of QT prolongation and TdP (Crediblemeds, 2021). Still, the current knowledge on this topic is limited, and epidemiological studies to examine the comparative risk with use of the different AChEIs are missing (Huang and Alsabbagh, 2020). Effects on the heart is a class effect of the AChEIs (Editorial, 2006) and may result in bradycardia caused by blockade of cholinesterase connected to the vagal nerve, which can cause atrioventricular (AV) or sinoatrial block (Huang and Alsabbagh, 2020). The use of AChEIs has been associated with more than twofold risk of hospitalization due to bradycardia among elderly patients. In addition, those receiving concurrent therapy with negative chronotropic drugs, such as betablockers, digoxin, and verapamil, had an increased risk as well (Park-Wyllie et al., 2009). According to a US study among veterans with AD, patients taking betablockers, with earlier episodes of falls and of myocardial infarction, heart failure, or hypertension have been reported to be most vulnerable for a decrease in heart rate after initiating treatment with AChEIs (Hernandez et al., 2009).

Multiple medical comorbid diseases are common in people with dementia (Chen et al., 2017). Hypertension and cardiovascular disease, which are the most common preexisting comorbidities, are at the same time risk factors of dementia (Ruangritchankul et al., 2020). It is relevant for both sexes to reduce the cardiovascular risk factors to decrease the incidence of dementia (Chêne et al., 2015). As betablockers and cardiotoxic calcium blockers are among the drugs that may increase heart-related problems like hypotension and bradycardia, and because bradycardia in older people is associated with syncope, arrhythmias, and falls, it is important to identify high-risk patients (Hernandez et al., 2009). The most serious adverse effects of digoxin are life-threatening cardiac disorders, and bradycardia is an early warning sign (Editorial, 2009). Through its heart-rate lowering effect, digoxin can cause TdP. The risk increases with coadministration of heart-rate lowering drugs and drugs that can prolong the QT interval, such as AChEIs (Editorial, 2009).

Behavioral and psychological symptoms of dementia (BPSD) are common in people with dementia and often treated with antidepressants and antipsychotics (Norwegian National guideline on dementia, 2021). The frequencies of atypical antipsychotic drugs for treatment of BPSD may be higher than for haloperidol. However, haloperidol was chosen in this study due to its known risk of QT interval prolongation. Among the commonly used agents for treatment of BPSD are escitalopram/citalopram, which also have a known risk of QT-interval prolongation and TdP, like donepezil (Crediblemeds, 2021). A combination of drugs with cardiac activity and AChEIs may explain harmful drug–drug interactions (Pasqualetti et al., 2015), likewise combinations of AChEIs with some psychotropic drugs. It is, therefore, of interest to study the prevalence of relevant drug combinations before and after initiating treatment with AChEIs.

Prescriptions of drugs like betablockers, digoxin, and verapamil can be considered as a proxy for heart disease, and patients with dementia suffering from preexisting cardiac disease, such as heart rate disturbances, are reported to have a higher risk of antipsychotic-induced arrhythmias and sudden cardiac death, related to prolongation of the QT interval (Bilotta et al., 2014). Women will, in general, get cardiovascular disease 6–10 years later than men do and, explained by, different development of blood pressure between the sexes, partly due to women living longer than men (Hestad et al., 2020a). Adverse drug reactions (ADRs) are more common in women than in men, explained by factors such as higher drug levels as a result of pharmacokinetic and pharmacodynamic differences between the sexes and more polypharmacy in women than in men (Rochon et al., 2013; Lucas et al., 2016). The QT interval is generally longer in women, with a higher risk of drug-induced ventricular arrhythmias in women compared with men (Bilotta et al., 2014). Drugs that prolong the QT interval have a greater response in women than in men (Cubeddu, 2016).

Furthermore, age is of interest because aging is associated by pharmacokinetic changes, such as reduced renal excretion and hepatic clearance and altered sensitivity to drugs, such as cardiovascular and psychotropic drugs, and predisposes older persons to ADRs (Rosenthal and Nussinovitch, 2008), in particular, AD patients (Pasqualetti et al., 2015). Systolic blood pressure increases with age in patients with dementia disorders until about 80 years, after which it tends downward (Hestad et al., 2020b), and the association of elevated blood pressure with cognitive performance has been suggested to be different between the two sexes (Hestad et al., 2020a). A large proportion of older adults have complex arrhythmias, and prolongation of the QT interval is related to age-associated degenerative change in the conduction system (Isik et al., 2012).

On this background, the aim was to study changes, from 4 years before to 2 years after initiating treatment with AChEIs, of: 1) the prevalence of use of drugs commonly prescribed for heart rate control and drugs with a known risk of TdP commonly prescribed for treatment of BPSD, 2) the prevalence of combinations of drugs with a known risk of TdP and drugs with a known heart rate-lowering effect, and 3) the differences in prescription patterns of 1) and 2) by age and sex.
MATERIALS AND METHODS

Data
Drug use data were collected from the Norwegian Prescription Database (NorPD). The drugs are classified according to the Anatomical Therapeutic Chemical (ATC) ATC Classification Index with DDDs, 2017 Index with DDDs 2017. The data contain, for each drug dispensation, information about the patient [sex, year of birth, year and month of death (when relevant)] and the drug [date of dispensing, medicinal product name and formulation, ATC-code, number of defined daily doses (DDDs), and the number of tablets/capsules/plasters (allowing us to calculate treatment periods)]. For each dispensing, we had information on the number of tablets/capsules/plasters dispensed. We assumed a consumption of two tablets per day for rivastigmine (ATC code N06DA03) and one tablet per day for the other AChEIs. Drugs dispensed to patients in institutions, e.g., nursing homes, are not included in the NorPD.

We assumed that dispensed drugs were consumed. We had access to all of the above information between January 1, 2004 and December 31, 2016 for all persons being dispensed at least one prescription of an AChEI (ATC-code N06DA) in that period. In addition, the yearly total number of users of all prescribed drugs in the population by gender and 1-year age groups (up to and including 89 years) was available in the same period.

Study population
The study population consisted of all persistent (see below) AChEI users living at home who—at an age of 88 years or younger—initiated AChEI treatment between January 1, 2008 and December 31, 2013. Those who died within 2 years after the year of AChEI treatment initiation, or who were not registered in the NorPD the second year after AChEI initiation (could be in nursing home), were excluded. They were followed from 1,460 days (4 years) before initiation to 729 days (2 years) after initiation. For the general population, data with 1-year age resolution was only available up to, and including, 89 years; hence, the age limit of 88 was set for the study population to make a comparison with the general population possible. Due to the aging process and increased comorbidities, the study population was stratified into two subgroups according to age over and under 80. We used the day of treatment initiation as a surrogate marker of the time of the AD diagnosis (Norwegian National guideline on Dementia, 2021).

A 1-year washout period is commonly used for defining incident drug use. Here, incident drug use was defined as being prescribed an AChEI drug after more than 365 successive days with no AChEI prescriptions, as some patients had several AChEI use periods separated by 365 days without prescriptions. For these, follow-up started at the date of the prescription initiating the longest AChEI use period (index date). Treatment length was computed as the number of days from index date until the drug dispensed in the last prescription of the longest AChEI use period was supposed to be consumed. The earliest possible index date was January 1, 2005. We only included patients with index date between January 1, 2008 and December 31, 2013 to capture drug use 4 years before and 2 years after initiation.

Incident and Persistent Use of Acetylcholinesterase Inhibitors
Incident use was defined as being prescribed an AChEI drug after 365 successive days with no AChEI prescriptions. For patients with incident use more than once (several 365-day periods without AChEI prescriptions), follow-up started at the date initiating the AChEI period with the largest number of subsequent AChEI prescriptions <365 days apart. Treatment with AChEI should be evaluated 90–180 days after initiation according to guidelines; therefore, we considered, due to a possible delay, users who continued treatment 8 months (240 days) after initiation as persistent users (Efjestad et al., 2019). Thus, an incident user was defined as persistent if any of the following was true (Sverdrup Efjestad et al., 2017): 1) A new prescription was given between day 210 and day 240 after initiation, 2) drugs for at least 210-day consumption were prescribed during the first 210 days from initiation, or 3) the last prescription before day 210 lasted to day 210.

Sex Differences and Comparison With Drug Use in the General Population
The use of, e.g., betablockers in the study population the first year after initiation of AChEI was compared with the use in the general population as follows: For each of the years 2008–2013, the age-adjusted prevalence of betablocker use in the general population was computed gender-wise, using the age distribution of those initiating AChEI, the actual year as reference. The overall age-adjusted prevalence in the general population was thereafter estimated as \( \sum_{y=2008}^{2013} N_y \sum_{y=2008}^{2013} N_y \), where \( u_y \) and \( N_y \) are the age-adjusted number of betablocker users and the population in year \( y \), respectively. In the study population, we are able to follow the same individual over a 6-year period. This is not possible in the general population. When comparing the betablocker use in AChEI initiators \( X \) years before/after initiation with the general population, the dispensing years and the age in the general population was shifted \( X \) years. As an example, betablocker use in the 81–88 years age group 4 years before initiation was compared with use in the 77–84-year-olds (as the age group was 4 years younger than the 81–88 group 4 years before, i.e., 77–84-year olds) in 2004–2009 in the general population. Betablocker use in the same age group the second year after initiation was compared with use in the 82- to 89-year olds in 2009–2014 in the general population. Age-adjusted prevalence ratios (PRs) for each gender were calculated by dividing the prevalence in the AChEI users by the age-adjusted prevalence in the general population.

The proportions of the study population and the general population receiving at least one prescription of haloperidol, citalopram/escitalopram, verapamil, betablockers, diuretics, and digitoxin/digoxin the 4 years before initiation of AChEI and the 2 years after were studied. Digitoxin has been the preferred digitalis drug in Norway, but was replaced with...
digoxin following a period with delivery problems in 2011. The two generics have about the same pharmacological profile (Haga et al., 2016).

**Drugs or Drug Groups**

Prevalence of haloperidol (ATC code N05AD01), citalopram (N06AB10) or escitalopram (N06AB04), verapamil (C08DA01), betablockers (C07), and digitoxin/digoxin (C01A) was studied in the 4 years before and the 2 years after initiation of AChEIs (prevalence of use in each of the six 365-day periods during the 6 years of follow-up).

In addition, we studied prevalence of concomitant use of betablockers + citalopram or escitalopram, and of verapamil + citalopram or escitalopram in the 4 years before and the 2 years after initiation of AChEIs. Citalopram/escitalopram were selected as drugs with known risk of TdP, commonly used in the treatment of BPSD.

**Statistical Analysis**

R versions 3.1.0–4.0.2 (R Core Team, 2014) were applied for descriptive statistics; proportions with 95% confidence intervals (CIs) were computed for the study population. The CIs were computed using the “binom.confint” function in the “binom” package in R with method = “wilson.” Age-adjusted prevalence rates were computed for the general population with the study population as reference, using the “ageadjust direct” function in the “epitools” package in R. The CIs for the general population are very narrow and, hence, not shown.

**Ethics and Data Protection Regulations**

All the pharmacies in Norway register prescriptions electronically, and the information is sent in monthly reports to NorPD. The personal ID number of the patient and the ID numbers of the prescribers are replaced by a unique pseudonym by Statistics Norway. This makes it possible to link drug use to individuals without knowing their identity. Personal information is not disclosed from the NorPD. The database is governed by the national regulation of October 17, 2003 about the collection and processing of health data in the Norwegian Prescription Database. The NorPD generated pseudonymous files for research purposes, as regulated by Norwegian law for health register (FOR-2003-10-17-1246, 2003); hence, there was no demand of additional approval by the ethics committee. According to the national regulations for the NorPD at the study start, approval by an ethical committee was only necessary for studies where NorPD was linked to other registers. No other registers are involved in this study. Thus, no ethical committee has been contacted for this study. The data holder of NorPD, the Norwegian Institute of Public Health, has approved a full Data Protection Impact Assessment (DPIA) of the project.

**RESULTS**

The study population consisted of 11,764 persistent AChEI users aged 37–88 years who initiated treatment between January 1, 2008 and December 31, 2013. The percentage of women was 59% in the 37–80 age group and 68% in the 81–88 age group, in all 63%. The proportion of the study population receiving at least one prescription of haloperidol/citalopram/escitalopram, verapamil, betablockers, and digitoxin/digoxin the 4 years before initiation of AChEI and the 2 years after, are shown for men and women separately in Figures 1–5, respectively. The age-adjusted proportion of men and women in the general population receiving the same drugs are, for comparison, shown in the same figures. Of the men and women in the study population, 43.4% and 43.9%, respectively, received a prescription in at least one of the five drug groups the second year after AChEI initiation (Supplementary Figure S1; Supplementary Table S1). The corresponding proportions in the age-adjusted general population were 38.6% and 36.9%. Proportions of men and women of the two age groups of the study population who used combinations of verapamil and citalopram/escitalopram and of betablockers and citalopram/escitalopram, respectively, are shown in Figures 6, 7, in addition to the age-adjusted proportion of men and women in the general population receiving the same combinations.

We found no differences between the two age groups related to prescription of the various AChEIs. As donepezil was the first AChEI on the market, between 74.0% (youngest age group) and 75.2% (oldest age group) used this drug.

**Prevalence of Use in the General Population**

A change in prevalence in the general population over the 6 years of follow-up can mainly be explained by the 6 years increase in age. Women of the general population showed a slightly higher prevalence of use of citalopram/escitalopram than men. Men of the general population showed a slightly higher prevalence of use of digitoxin/digoxin and betablockers than women. A notable age-related increase in the use of verapamil, betablockers, and digoxin/digoxin was observed in both sexes. The change during follow-up was small: In the 37- to 88-year age group, the prevalence for verapamil decreased from 1.7% to 1.4% in men and from 1.9% to 1.7% in women; for betablockers, it increased from 29.4% to 34.6% in men and from 26.1% to 30.9% in women; for digoxin/digitoxin, it decreased from 3.4% to 3.3% in men and increased from 2.5% to 2.8% in women. For haloperidol and citalopram/escitalopram, no specific sex differences were observed during the study period. For all drugs, the pattern of change was the same during the study period in the different age groups and between the two sexes. Age-specific proportions (37–80 and 81–88 years) are shown in Table 1 and Supplementary Table S1.

**Prevalence of Use in the Study Population**

Women of the study population showed a higher prevalence of use of citalopram/escitalopram and verapamil than men. A notable age-related increase in the use of betablockers and digitoxin/digitoxin was observed. During the study period, the prevalence of use in the study population overall (age 37–88) compared with the general population was higher for haloperidol and citalopram/escitalopram, but lower for verapamil,
betablockers, and digoxin/digitoxin in women. There were some age group-specific exceptions to this pattern, though, see details for the different drug groups below and in Table 1 and Supplementary Table S1.

**Haloperidol**

The prevalence of use of haloperidol strongly increased in both genders from 2 years prior to introduction of AChEIs in both sexes (Figure 1); however, it slightly decreased in the 81–88 age group in women in the last year of the study period. Regarding the use in men, the 37- to 80-year group increased from <0.3% in the fourth year before initiation to 1.4% (1.1%–1.9%) in the second year after, and the corresponding increase in the 81- to 88-year old was from <0.3% in the fourth year before initiation to 1.6% (1.1%–2.4%) in the second year after (exact numbers not shown due to

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**FIGURE 1** Open circles: Proportion of men and women, respectively, of the study population who filled at least one prescription of haloperidol (ATC N05AD01) in the 4 years before acetylcholinesterase inhibitors (AChEI) initiation and the 2 years after with 95% confidence intervals. Years with less than five users in one or both of the age groups are not shown. Bullets: The corresponding age adjusted proportion in the general population. Dashed vertical lines indicate AChEI initiation. The size of each age group in the study population is given on top.

**FIGURE 2** Open circles: Proportion of men and women, respectively, of the study population who filled at least one prescription of citalopram or escitalopram (ATC N06AB04 or 10) in the 4 years before AChEI initiation and the 2 years after with 95% confidence intervals. Bullets: The corresponding age adjusted proportion in the general population. Dashed vertical lines indicate AChEI initiation. The size of each age group in the study population is given on top.
<5 users in one or both of the age groups). Regarding the use in women, the 37- to 80-year group increased from 0.2% (95% CI: 0.1%–0.4%) in the fourth year before initiation to 1.6% (1.2%–2.0%) in the second year after, and the corresponding increase in the 81- to 88-year old was from 0.2% (95% CI: 0.1%–0.4%) in the fourth year before initiation to 1.4% (1.1%–1.9%) in the second year after. Compared with the general population, the prevalence ratio (PR) in men increased from <1 to 2.9 in the 81- to 88-year old. In women, the PR increased from 0.9 to 6.2 over the 6 years in the 37- to 80-year old and from 0.4 to 2.6 in the 81- to 88-year old.

**Citalopram and Escitalopram**
The prevalence of use of citalopram and escitalopram strongly increased in both sexes over the 6-years interval and was higher in women than in men in the two age groups (Figure 2). Regarding the use in men, the 37- to 80-year
group increased from 4.5% (95% CI: 3.8%–5.3%) in the fourth year before initiation to 15.4% (14.1%–16.7%) in the second year after, and the corresponding increase in the 81- to 88-year old was from 3.0% (95% CI: 2.2%–4.0%) in the fourth year before initiation to 12.7% (11.1%–14.5%) in the second year after. Regarding the use in women, the 37- to 80-year group increased from 8.3% (95% CI: 7.5%–9.1%) in the fourth year before initiation to 21.0% (19.8%–22.2%) in the second year after, and the corresponding increase in the 81- to 88-year old was from 7.4% (95% CI: 6.5%–8.3%) in the fourth year before initiation to 18.4% (17.1%–19.8%) in the second year after. Compared with the general population, the PR in men increased from 1.7 to 4.8 over the 6 years in the 37- to 80-year old and from 0.8 to 3.0 in the 81- to 88-year old. In women, the PR increased from 1.7 to 3.5 over the 6 years in the 37- to 80-year old and from 1.2 to 2.5 in the 81- to 88-year old.
Verapamil
The prevalence of use of verapamil slightly decreased prior to introduction of AChEIs in both sexes (Figure 3). The use in men in the 37- to 80-year group decreased from 1.4% (95% CI: 1.0%–1.9%) in the fourth year before initiation to 1.0% (0.7%–1.4%) in the second year after, and the corresponding decrease in the 81- to 88-year old was from 2.0% (95% CI: 1.4%–2.9%) in the fourth year before initiation to 1.7% (1.2%–2.5%) in the second year after. Regarding the use in women, the 37- to 80-year group decreased from 1.3% (95% CI: 1.0%–1.7%) in the fourth year before initiation to 1.1% (0.8%–1.4%) in the second year after, and the corresponding decrease in the 81- to 88-year old was from 1.9% (95% CI: 1.5%–2.5%) in the fourth year before initiation to 1.9% (1.4%–2.4%) in the second year after. Compared with the general population, the PR decreased in men from 1.01 to 0.79 over the 6 years in the 37- to 80-year old and increased from 0.84 to 0.95 in the 81- to 88-year old. In women, the PR decreased from 0.96 to 0.78 over the 6 years in the 37- to 80-year old and increased from 0.74 to 0.86 in the 81- to 88-year old.

Betablockers
The prevalence of use of betablockers slightly increased in both sexes from 4 years prior to introduction of AChEIs (Figure 4), more or less in parallel with the general population, but decreased in both sexes from 1 year prior to introduction of AChEIs. Regarding the use in men, the 37- to 80-year group increased from 26.5% (95% CI: 24.9%–28.1%) in the fourth year before initiation to 28.8% (27.2%–30.5%) 1 year before, and thereafter, it decreased to 27.9% (26.3%–29.6%) in the second year after. The corresponding increase in the 81- to 88-year old was from 32.5% (95% CI: 30.2%–35.0%) in the fourth year before initiation, via 36.6% (34.2%–39.1%) 1 year before, to 35.3% (32.9%–37.7%) in the second year after. Regarding the use in women, the 37- to 80-year group increased from 21.2% (95% CI: 20.0%–22.5%) in the fourth year before initiation to 24.4% (23.0%–25.5%) 1 year before, and thereafter, it decreased to 23.2% (22.0%–24.5%) in the second year after. The corresponding increase in the 81- to 88-year old was from 29.5% (95% CI: 27.9%–31.1%) in the fourth year before initiation, via 33.6% (32.0%–35.3%) 1 year before, to 31.8% (30.2%–33.5%) in the second year after. Compared with the general population, the PR decreased in men from 1.01 to 0.87 over the 6 years in the 37- to 80-year old and from 0.97 to 0.85 over the 6 years in the 81- to 88-year old. In women, the PR decreased from 0.97 to 0.89 in the 81- to 88-year old.

Digoxin/Digitoxin
The prevalence of use of digoxin/digitoxin slightly increased in both sexes in the study population overall (Figure 5), and the prevalence of use was higher in men than in women. The use in men in the 37- to 80-year group increased from 2.2% (95% CI: 1.8%–2.8%) in the fourth year before initiation to 2.8% (2.3%–3.5%) in the second year after. The overall increase in the 81- to 88-year old was from 4.3% (95% CI: 3.4%–5.4%) in the fourth year before initiation to 5.2% (4.2%–6.5%) in the second year after. The use in women in the 37- to 80-year group increased from 1.2% (95% CI: 0.9%–1.6%) in the fourth year before initiation to 1.6% (1.3%–2.0%) in the second year after, and the corresponding increase in the 81- to 88-year old was from 2.4% (95% CI: 1.9%–3.0%) in the fourth year before initiation, flattening out from 1 year before to 3.6% (3.0%–4.3%) in the second year after. Compared with the general population, the PR in men increased from 1.00 to 1.15 over the 6 years in the 37- to 80-year old and from 0.77 to 1.08 in the 81- to 88-year old.
TABLE 1 | Prevalences of use of the studied drugs during follow-up time by age and sex. (−) and after (+) AChEI initiation

<table>
<thead>
<tr>
<th>Years before (−)</th>
<th>Men</th>
<th>Women</th>
<th>Men</th>
<th>Women</th>
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<tbody>
<tr>
<td>−4 year</td>
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<td>+2 year</td>
<td>−4 year</td>
<td>−1 year</td>
</tr>
<tr>
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<td>0.33</td>
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<tr>
<td>Prop</td>
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<td>0.51</td>
</tr>
<tr>
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<td>1.08</td>
<td>0.76</td>
</tr>
<tr>
<td>Citalopram/escitalopram</td>
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<td>30.1</td>
<td>25.3</td>
</tr>
<tr>
<td>Prop</td>
<td>28.8</td>
<td>32.2</td>
<td>26.2</td>
<td>23.9</td>
</tr>
<tr>
<td>Ratio</td>
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<td>1.06</td>
<td>1.00</td>
<td>1.05</td>
</tr>
<tr>
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<td>1.06</td>
</tr>
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<td>0.98</td>
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<td>Ratio</td>
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<td>1.02</td>
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</table>

Note. Proportion (%) of men and women, respectively, of the study population (SP) who filled at least one prescription of the studied drugs in the fourth and first years before AChEI initiation and the second year after, and corresponding proportion in the age adjusted general population (GP), and prevalence ratios between SP and GP. Confidence intervals are given in Supplementary Table S1.

Combinations of Verapamil and Citalopram/Escitalopram

The proportion of the study population overall using combinations of verapamil and citalopram/escitalopram was very low, particularly in men (Figure 6). The use in men in the study population overall increased from <0.1% in the fourth year before initiation (<5 users) to 0.3% (0.2%–0.5%) in the second year after. The use in women in the study population overall increased from 0.1% (95% CI: 0.1%–0.3%) in the fourth year before initiation to 0.3% (0.2%–0.5%) in the second year after. Compared with the general population, the PR increased in men from <1 to 4.4 over the 6 years in the 37- to 88-year old. In women, the PR increased from 1.1 to 2.5 in the 37- to 88-year old over the 6-year interval.

Combinations of Betablockers and Citalopram/Escitalopram

The proportion of the study population using combinations of betablockers and citalopram/escitalopram increased over the study period in the age group 37–88 and was higher in women than in men (Figure 7). The use in men in the study population overall increased from 1.0% (95% CI: 0.8%–1.7%) in the fourth year before initiation via 3.1 (2.6%–3.7%) in the first year before to 4.0% (3.4%–4.6%) in the second year after. The use in women in the study population overall increased from 2.1% (95% CI: 1.8%–2.4%) in the fourth year before initiation to 4.7% (4.3%–5.2%) in the first year before, and thereafter, it flattened out to 4.9% (4.4%–5.4%) in the second year after. For the use in men, the 37- to 80-years group increased from 1.2% (95% CI: 0.9%–1.7%) in the fourth year before initiation to 4.2% (3.5%–4.9%) in the second year after. For the use in men, the 81- to 88-year group increased from 0.6% (95% CI: 0.3%–1.2%) in the fourth year before initiation to 3.7% (2.9%–4.8%) in the first year before and 3.6% (2.8%–4.7%) in the second year after. For the use in women, the 37- to 80-years group increased from 1.9% (95% CI: 1.5%–2.4%) in the fourth year before initiation to 4.6% (4.0%–5.3%) in the first year before, and thereafter, it decreased to 4.2% (3.6%–4.9%) in the second year after. The corresponding increase in the 81- to 88-year old was from 2.5% (95% CI: 2.0%–3.1%) in the fourth year before initiation to 4.9% (4.2%–5.7%) in the first year before and 5.8% (95% CI: 5.0%–6.6%) in the second year after. Compared with the general population, the PR increased in men from 1.0 to 2.8 over the 6 years in the 37- to 88-year old. In women, the PR increased from 1.3 to 2.1 in the 37- to 88-year old over the 6-year interval.

DISCUSSION

In users of AChEIs, a high prevalence of use of betablockers and of citalopram/escitalopram was found. The prevalence of use of haloperidol and citalopram/escitalopram was higher in the study
population compared with the general population. The prevalence of use of verapamil was low in the general population and even lower in the study population, and use of the digitalis drugs was flattening out in the study population following introduction of AChEIs. The proportion of the study population with concomitant use of betablockers and citalopram/escitalopram was higher in women than in men. We have searched the literature, and unfortunately, we could not find any comparative studies.

Haloperidol
Haloperidol has been shown to be used with a higher frequency in patients having a significantly greater risk of QT prolongation and TdP (older, medically ill, hospitalized patients) than other antipsychotics (Beach et al., 2018). The overall low prevalence of use of haloperidol reflects the restricted use of typical antipsychotics in dementia. However, the prevalence of use in the study population was higher than in the general population, and the use is not in accordance with the Norwegian National guideline on dementia, 2021. The increase in both sexes from 2 years prior to the dementia diagnosis may reflect an increase in the severity of the BPSD symptoms during the course of the AD.

Citalopram and Escitalopram
The strong increase in the prevalence of use of citalopram and escitalopram in both sexes over the 6-year interval may indicate that incidence of depression has increased, or that symptoms of depression are more often treated with an antidepressant, especially in women. It could also be that these drugs were used to treat other BPSDs due to the restricted use of antipsychotics. The prescription pattern was not markedly influenced by initiation of AChEIs. Citalopram has, together with warfarin, shown to be the most frequently observed substance causing clinically relevant drug–drug interactions in hospitalized people with dementia, partly explained by the prolongation of the QT interval not seen among other selective serotonin reuptake inhibitors (SSRIs) (Sönnertam et al., 2018). The high prevalence of use is therefore a concern, especially in women being more sensitive to ADRs. Norwegian National guideline on dementia, (2021) recommend only a restricted use of SSRIs in AD. According to these guidelines, an SSRI drug should be offered as additional treatment of depression, not of BPSD in general, and only when appropriate environmental psychological and/or psychotherapeutic measures have been attempted without achieving the desired effect.

Verapamil
The low prevalence of use of verapamil in the general population, which is even lower in the study population, reflects that this class IV antiarrhythmic drug is not the first drug of choice in treating heart frequency problems. Patients taking verapamil must be carefully monitored with regard to adverse effects like bradycardia, and interactions may be enhanced by verapamil being an inhibitor of p-glycoprotein. As an example, we can expect a much higher bioavailability of digoxin when accompanied by verapamil. The decrease in prevalence of use in both sexes of the study population from 2 to 3 years before the AD diagnosis indicates that the drug is prescribed with caution, possibly because of the known risk profile and/or ADRs.

Betablockers
The increase in the prevalence of the use of betablockers probably reflects the increase in cardiovascular disease among older people, especially in older people with dementia, as shown in the 81- to 88-year old in both sexes. From the aspect of risks, even the smallest doses of betablockers may induce severe bradycardia and disorders of AV conduction in the more sensitive elderly patients, which can clinically be manifested as vertigo and falls with possible serious injury. Such effects may be enhanced by the administration of other medication with effects on the heart (Kubesova et al., 2013), and thereby explain the reduction in the prevalence of use of betablockers in both sexes and age groups after AChEI initiation.

Digoxin/Digitoxin
Digoxin is a cardiac glycoside that is commonly used among older adults in the treatment of congestive heart failure and atrial fibrillation. However, since AChEIs and digoxin can interact to give changes in the heart rate or cardiac conduction, co-prescription of digoxin with AChEIs have the potential to increase the risk of ADRs (Bentué-Ferrer et al., 2003). The potentially life-threatening cardiac adverse effects of digoxin like bradycardia could easily occur due to the narrow therapeutic window of digoxin (Editorial, 2009). The prevalence of use of the digitalis drugs was flattening out in the study population following introduction of AChEIs, especially in the older age group in women, which indicates a restricted use in people with dementia. This could be explained by ADRs, especially in older women, and fewer patients with indications for use of these drugs.

Drug combinations
The small but higher proportion of the combination of verapamil and citalopram/escitalopram in the study population compared with the general population, especially in the higher age group following initiation of AChEIs, possibly reflects the high and increasing prevalence of use of citalopram/escitalopram in the study population. The proportion of the study population with concomitant use of betablockers and citalopram/escitalopram was higher in women than in men. A reduced prevalence was observed in women in the 37- to 80-year old group, while the prevalence of use seemed to continue to increase in men. However, in the oldest age group, the prevalence of use declined in men following initiation of AChEIs, while it increased in women. This could reflect that women get cardiovascular disease later than men do, and that treatment in this group both with betablockers and citalopram/escitalopram was considered to be important.

CONCLUSION
As people with AD, and especially women, are at high risk for fall-related injuries and syncope, the use of AChEIs should be initiated with caution because of associations with increased rates of bradycardia, syncope, pacemaker insertion, and hip fracture in older adults with dementia (Cronin and Kenny, 2010). Thus, AChEIs should not be a standard treatment of patients with dementia, but decision on prescribing should be weighed on the expected risk profile of each individual, and AChEI therapy should be reconsidered if little or no cognitive improvement is observed.
early in therapy (Park-Wyllie et al., 2009). Cardiovascular side effects should be monitored, which is specifically important in patients already taking drugs that often cause bradycardia (Mohammad et al., 2017). The use of two or more drugs that prolong the QT interval should be avoided, or if required, monitored closely. Betablockers should not be prescribed in patients with long QT or during treatment with QT prolonging drugs (Cubeddu, 2016).

In summary, with regard to potential ADRs, even the low prevalence of use of haloperidol is concerning. The high prevalence of use of betablockers may give rise to bradycardia and disorders of AV conduction, and induce vertigo and falls, as well as interactions with other drugs with effects on the heart. Due to the high prevalence of use of citalopram/escitalopram, especially in women, a substantial proportion of the patients are at risk of developing pharmacodynamic interactions, especially when combined with AChEIs and betablockers.

Strengths and Limitations
Using data from the NorPD, we had no access to clinical diagnoses like depression, congestive heart failure and atrial fibrillation, or adverse effects. However, we aimed to explore the association between the use of AChEIs and prescription of drugs with effect on the heart. Data from the NorPD gives us a unique opportunity to study drug use patterns, highlighting changes over time in selected drug groups. The large sample size and the long study period is a strength in our study. In Norway, patients in nursing homes more often use antidementia drugs than people living at home (Fog et al., 2019), and the NorPD do not include patients in nursing homes. AChEIs are mainly prescribed for treatment of AD; however, we did not have information with regard to the clinical rationale for prescriptions including etiological diagnoses, severity of the symptoms, and ADL dependency. Purchased drugs were used as a surrogate for consumed drugs and may cause overestimation. However, medicine adherence in AChEIs users is expected to be good, as caregivers usually are responsible for drug management for patients with dementia. We did not study dosage differences between men and women, which could be of relevance due to pharmacokinetic differences between the sexes; however, even small doses of the studied drugs may cause serious ADRs in the study group. Medicine use was quantified up to 4 years prior to AChEI initiation, and as only a 1-year wash-out was used to define initiation, the study population included 494 patients who used AChEIs 2–4 years prior to index date. However, the majority of these (61%) had <4 prescriptions in this period, and we have included the 494 in the analysis. Only persistent users were included, and people who were still alive at 2 years post-initiation. People who developed a cardiovascular issue or had a cardiovascular event (potentially due to co-prescribing of medicines associated with cardiovascular problems) might have discontinued AChEIs before they fulfilled the persistence criteria, or have been more likely to die the two first years after AChEI initiation. This could lead to bias in who is included in the study (e.g., people with lower rates of use of the medicines of interest being excluded). There have been no changes in guidelines related to the drugs being studied since 2013. Hence, the therapy that was valid that time is still valid today.

Decisions about prescribing medicines among patients with dementia may be complicated by conflicting recommendations in prescribing guidelines as indicated in this study. A small number of patients treated with AChEIs were prescribed haloperidol, diphenylbutylpiperazine, and verapamil, while a substantial proportion were prescribed betablockers and citalopram/escitalopram. Prevalence of use of betablockers was reduced by initiation of AChEIs in both sexes. Up to 6% of the study population were prescribed combinations of betablockers and citalopram/citalopram in addition to AChEIs, a combination increasing over the study period and observed most frequently in women in the oldest age group, being the most sensitive group to ADRs. About 44% of the patients were prescribed a drug in at least one of the studied drug groups during the second year after AChEI initiation. The present findings suggest the need for careful medication review with focus on bradycardic and prolonged QT interval in patients treated with AChEIs as an important risk-reducing intervention.

DATA AVAILABILITY STATEMENT
The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

ETHICS STATEMENT
Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS
AE conceived the idea for this article and drafted the first version of the manuscript. HI-H, KE, and HB contributed with ideas and supervision. VH performed the statistical analysis. All authors participated in writing the article and approved the final version to be submitted for consideration for publication.

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SUPPLEMENTARY MATERIAL
The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2021.791578/full#supplementary-material

Supplementary Table S2 | Data. Aggregated data supporting Figures 1–7.
REFERENCES


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