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Use of Psychotropic Drugs in Patients with Dementia

A Nationwide Pharmacoepidemiologic Study

PhD thesis by
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GLOBAL EXCELLENCE IN HEALTH

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This thesis was submitted to the Graduate School of Health and Medical Sciences, University of Copenhagen, January 31, 2019

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TABLE OF CONTENTS

Preface and acknowledgements

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Original manuscripts

The following manuscripts form the basis of the thesis:

Study I **Nørgaard A**, Jensen-Dahm C, Gasse C, Hansen HV, Waldemar G.
Time Trends in Antipsychotic Drug Use in Patients with Dementia:
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J Alzheimers Dis. 2016;49(1):211-20. doi: 10.3233/JAD-150481

Study II **Nørgaard A**, Jensen-Dahm C, Gasse C, Hansen ES, Waldemar G.
Psychotropic Polypharmacy in Patients with Dementia: Prevalence and Predictors
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Study III **Nørgaard A**, Jensen-Dahm C, Gasse C, Wimberley T, Hansen ES, Waldemar G.
Impact of Benzodiazepines and Antidepressants on the Mortality in Patients with Dementia on Antipsychotic Treatment
Submitted

Study IV **Nørgaard A**, Jensen-Dahm C, Wimberley T, JH Svendsen, KI Ahmed, TM Laursen, Waldemar G, Gasse C.
Effect of Antipsychotic Drugs on Mortality Risk among Dementia Patients with and without Comorbidities: A Nationwide Study
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Abstract

Neuropsychiatric symptoms are common in patients with dementia and have major negative impact on the quality of life and outcome in patients and caregivers. Antipsychotics, antidepressants, anxiolytics, and hypnotics are often used in the management of these symptoms. While efficacious in some cases, treatment may cause side effects. Increased awareness of the risks may have changed prescription practices over time. Knowledge on the prevalence and consequences of concomitant use of psychotropic drugs is sparse. Using complete, nationwide data, we therefore aimed to investigate time trends in psychotropic drug use in an entire population of patients with dementia as well as the prevalence and predictors of concomitant psychotropic drug use. In Study I, we found a significant reduction in antipsychotic use among patients with dementia from 2000 to 2012. This was accompanied by a decrease in the use of anxiolytics and hypnotics and an increase in the use of antidepressants. In Study II, we found that psychotropic drug classes were frequently combined, with 25% of patients with dementia using at least two different psychotropic drug classes in 2012. Among patients treated with antipsychotics, 75% used another psychotropic drug class during the treatment period. Predictors of filling prescriptions for other psychotropic drug classes among patients already using antipsychotics were nursing home residency, number of non-psychotropic medications, and prior psychiatric diagnosis. So far, knowledge on the mortality risk associated with the use of antipsychotics in combination with other psychotropic drug classes is sparse. In Study III, we found that the combination of antipsychotics and benzodiazepines was associated with over twice the risk of death compared with patients using antipsychotics only. On the other hand, the combination of antipsychotics and antidepressants was associated with a 39% decreased risk of death. In Study IV, we sought to investigate the risk of death associated with antipsychotic treatment comparing users and non-users in the Danish dementia population. Further, we sought to investigate whether patients with pre-existing comorbidity related to the cardiovascular and metabolic systems were at increased compared with patients without these comorbidities. Overall, we found a 35% increased risk of death among patients treated with antipsychotics. The presence of comorbidities did not affect the mortality risk. In conclusion, this thesis provides new insight into psychotropic drug treatment and mortality associated with the treatment in an entire population of patients with dementia. Hopefully, this will encourage further studies to prevent inappropriate prescribing and negative outcomes.

Resumé

Psykiske symptomer og adfærdsforstyrrelser optræder hyppigt hos patienter med demens. Symptomerne udgør ofte en stor belastning for både patienter og pårørende. Antipsykotika, antidepressiva, benzodiazepiner og hypnotika udskrives ofte som et led i behandlingen, men disse farmaka kan have alvorlige bivirkninger. Øget fokus på risici ved psykofarmakologisk behandling kan have påvirket forbruget af psykofarmaka til patienter med demens. Omfanget og konsekvenserne af kombinationsbehandling med flere typer psykofarmaka kendes ikke. Ved hjælp af danske registerdata undersøgte vi derfor udviklingen i forbruget af psykofarmaka samt forekomsten af kombinationsbehandling med forskellige psykofarmaka til patienter med demens. I Studie I fandt vi, at forbruget af antipsykotika var faldet signifikant fra 2000 til 2012. Samtidig var forbruget af benzodiazepiner og hypnotika faldet, mens forbruget af antidepressiva var steget. Studie II viste at 25% af patienter med demens modtog kombinationsbehandling med mindst to typer psykofarmaka i løbet af 2012. Blandt patienter, som modtog antipsykotisk behandling, blev 75% behandlet med en anden type psykofarmaka samtidig. Dette var hyppigst forekommende hos plejehjemsbeboere, samt patienter, der i forvejen havde en psykiatrisk diagnose, og patienter, der i forvejen tog mange forskellige andre typer medicin. Dødeligheden hos patienter med demens, som behandles med antipsykotika i kombination med andre psykofarmaka, er sparsomt undersøgt. I Studie III fandt vi, at patienter i behandling med antipsykotika i kombination med benzodiazepiner havde en dobbelt så høj dødelighed sammenlignet med patienter, som kun fik antipsykotisk medicin. Derimod havde patienter, som blev behandlet med kombinationen af antipsykotika og antidepressiva en lavere dødelighed. I Studie IV undersøgte vi dødeligheden blandt patienter med demens i Danmark, som modtog antipsykotisk behandling, sammenlignet med patienter, som ikke modtog antipsykotisk behandling. Derudover undersøgte vi, om patienter med metaboliske og kardiovaskulære sygdomme havde en øget risiko sammenlignet med patienter uden disse sygdomme. Overordnet fandt vi at dødeligheden var 35% højere for patienter i antipsykotisk behandling, men at tilstedeværelse af metaboliske og kardiovaskulære sygdomme ikke påvirkede dødeligheden. Samlet set beskriver denne afhandling behandlingsmønstre og risici forbundet med psykofarmakologisk behandling i den danske demenspopulation. Denne viden er afgørende for fremtidige studier og tiltag som kan reducere forbruget af psykofarmaka og forebygge alvorlige konsekvenser af behandlingen.

Abbreviations

ATC	Anatomical Therapeutic Chemical
BZDs	Benzodiazepines and related drugs
CI	Confidence interval
DDD	Defined daily dose
FDA	Food and Drug Administration
HR	Hazard ratio
ICD	International Classification of Diseases
OR	Odds ratio
PYs	Person-years
SSRI	Selective serotonin reuptake inhibitor

Introduction

Dementia and neuropsychiatric symptoms

The number of people living with dementia is growing due to population aging, with an estimated nearly 47 million people affected worldwide in 2015, a number that is expected to double every 20 years and to reach over 130 million people in 2050.[1] Dementia is most frequently caused by Alzheimer's disease, vascular dementia, dementia with Lewy bodies and frontotemporal dementia; however, many other diseases can cause dementia. Dementia is characterized by loss of memory and other cognitive functions, loss of ability to perform activities of daily living, loss of emotional control, and altered behavior.

Neuropsychiatric symptoms, often referred to as behavioral and psychological symptoms of dementia, cover a wide range of symptoms affecting emotions, behavior, and perceptions. Almost all patients with dementia experience neuropsychiatric symptoms at some point during the disease progression, and the prevalence of symptoms is often increasing with dementia severity.[2,3] Neuropsychiatric symptoms include, among others, aggression, agitation, anxiety, wandering, sleep disturbances, delusions, hallucinations, and depression.[4] In addition to the cognitive manifestations of dementia, these symptoms markedly add to the personality changes in patients with dementia and can cause serious distress for patients, their families, and caregivers. The personal and economic consequences are of great magnitude as neuropsychiatric symptoms are associated with decreased quality of life, increasing health-care costs, and early nursing home placement.[5,6]

Neuropsychiatric symptoms in dementia are of multifactorial origin. The neurodegeneration and pathophysiological changes in neurotransmitter systems can be a direct cause, and as the disease progresses, more symptoms may arise. Some of these symptoms may be present during most of the duration of the disease. In other cases, the symptoms may by triggered by environmental factors or physical conditions. Genetic and psychological features possibly also influence whether an individual develops the symptoms.[7] Certain aspects of cognitive decline such as misidentification of people and objects, forgetting personal items, and loss of orientation can lead to behavioral symptoms, e.g., agitation, aggression, anxiety, and wandering. Patients with dementia can also develop symptoms due to psychosocial factors and changes in their home or nursing home environment, such as unexpected events and unfamiliar staff. Unmet physiological and psychosocial needs can be expressed as behavioral changes. Pharmacological treatment, particularly drugs affecting the

central nervous system, can have unintended effects and may cause sedation, apathy, sleep disturbances, or agitation. Finally, new or untreated somatic conditions, such as dehydration or pain, can cause neuropsychiatric symptoms.[8]

The management of neuropsychiatric symptoms is complex and will need to target individual symptoms in individual patients. Assessment of symptoms and comprehensive observations form the basis of treatment and prevention. First-line treatment is recommended to be non-pharmacological, the use of guidelines for caregivers becoming more common in assessing and targeting treatment. However, some patients present with extremely aggressive behavior or suffer from severe psychiatric symptoms and may need acute pharmacological treatment.

Antipsychotic drugs

Antipsychotic medication was first discovered and introduced in the 1950s to target psychotic symptoms in patients with schizophrenia and bipolar disease. First-generation antipsychotic drugs were the only alternative for many years. The mechanism of action was the blocking of dopamine receptors, leading to a reduction in hallucinations and delusions. Several, and some rather severe, side effects were soon reported, such as extrapyramidal symptoms, sedation, hypotension, and QT prolongation. In the 1990s, a new generation of antipsychotic drugs was developed and approved for the treatment of psychotic symptoms.[9] The second-generation antipsychotics had comparable efficacy in psychiatric patients. With a modified neurotransmitter receptor blockage mechanism, they were characterized by a more tolerable side effect profile but also marked metabolic side effects.

Even though the pathophysiology and causes of schizophrenia and bipolar disease differ from psychotic symptoms in patients with dementia, antipsychotics have consistently been used off-label to target a range of neuropsychiatric symptoms in dementia, possibly due to the use of the unspecific sedative mechanisms of antipsychotic medication.[10] Accordingly, the use of antipsychotic drugs for patients with dementia is widespread. The prevalence of antipsychotic drug use among patients with dementia has been reported to be 15–32%.[11–13]

The clinical trial evidence for the effect of antipsychotic treatment of neuropsychiatric symptoms in patients with dementia is limited. The best evidence has been found for short-term (roughly defined as 8-12 weeks) use of the first-generation drug haloperidol to manage aggression in patients with

dementia and the second-generation drugs risperidone, aripiprazole, and olanzapine for the management of agitation, aggression, and psychosis.[10,14,15] Treatment beyond 8-12 weeks does not seem to have an effect on neuropsychiatric symptoms.[16] Further, there is evidence suggesting that withdrawal from long-term treatment does not worsen neuropsychiatric symptoms.[17] To sum up, meta-analyses of clinical trials found a small positive effect for aggression and psychosis during short-term antipsychotic treatment. The overall effect, however, is challenged by side effects and adverse events, leading to study conclusions where benefits do not outweigh the risks when treating patients with dementia.[15,18,19]

A few antipsychotic drugs are labelled to treat neuropsychiatric symptoms in dementia. However, other first and second-generation antipsychotics are likely to be used off-label to target varying neuropsychiatric symptoms.[20] By 2018, the Danish Medicines Agency had approved use of haloperidol and risperidone for the indication aggression in Alzheimer's disease under the aforementioned circumstances.[21] In the UK, the labelled indication for risperidone also includes persistent aggression in Alzheimer's disease.[22] In the U.S.A., there are no antipsychotic drugs for treatment of neuropsychiatric symptoms in dementia as labelled indications.[23]

Risks of antipsychotic treatment

In the early 2000s reports started to emerge about the increased risk of cerebrovascular events in patients treated with second-generation antipsychotic drugs in clinical trials.[24] In 2005, the U.S. Food and Drug Administration (FDA) published a statement based on a meta-analysis of 17 double-blind randomized controlled trials testing second-generation antipsychotic drug treatment for patients with dementia. The conclusion was that the treatment was associated with an increased mortality risk of approximately 60–70% compared with placebo. Consequently, a statement was added to second-generation antipsychotic drug labels warning against their use in patients with dementia.[25] In 2008, an additional warning was issued concerning first-generation antipsychotic drugs based on two observational studies[26,27] that found mortality to be similar or even higher than for patients treated with second-generation antipsychotic drugs.[28] The European Medicines Agency warned against using first and second-generation antipsychotics,[29] just as the Danish Health Authority, who published similar warnings in 2004 and 2008 recommending doctors to be cautious when prescribing antipsychotic drugs for patients with dementia.[30]

A number of observational studies focusing on mortality in patients with dementia treated with antipsychotics was published in the 2000s. Large cohort studies from the U.S.A. and Canada also found increased risk of death associated with use of second-generation antipsychotics compared with matched controls not using antipsychotics.[31,32] Another study compared the risk of death associated with first-generation treatment with the risk associated with second-generation antipsychotics and found an increased risk of death among patients treated with first-generation antipsychotics.[33] Further, research indicates an ongoing risk, even if patients are treated for periods longer than 12 weeks. The dementia antipsychotic withdrawal trial (DART-AD), which randomized patients on antipsychotic treatment to either continue or discontinue treatment (placebo), also found increased mortality with long-term treatment (12-54 months).[34]

Increased knowledge about negative aspects of antipsychotic treatment for patients with dementia led to political investigations and initiatives addressing the need to reduce the use of antipsychotic drugs for patients with dementia. In the UK, a report for the Department of Health and Social Care sought to clarify the extent and consequences of antipsychotic use for patients with dementia.[35] The report concluded not only that the prevalence of antipsychotic treatment could be as high as 25% among patients with dementia but also used results from a meta-analysis to calculate the number of patients who would need to be treated to result in one additional death. With an absolute risk difference of 1% over a 6–12-week follow-up, the number needed to harm (defined as additional death) was 100. Based on the estimated number of patients treated with antipsychotic drugs in the UK, this would result in an additional 1800 deaths per year as a direct consequence of antipsychotic treatment.

Trends in the use of antipsychotic drugs for patients with dementia have been studied, but most of these studies aimed at evaluating the effect of a specific intervention. Studies investigating prescription trends between 2001-2011 found an overall decrease in the use of antipsychotic drugs, with some of the trends related to the release of the previously mentioned warnings.[36–40] Changes in other psychotropic drug classes could be expected if antipsychotic drugs were to be substituted with other psychotropics. In some populations, the prescription patterns of other psychotropic drug classes did change over the study period, but with no significant change in relation to the warnings that had been published.[11,36,38,39,41]

To sum up, evidence for the effect of antipsychotic medication for the treatment of neuropsychiatric symptoms is weak, and side effects and adverse events may exceed potential benefits from treatment. According to Danish and international guidelines, treatment with an antipsychotic agent may be necessary in some cases when other non-pharmacological approaches have failed and a patient with dementia suffers from psychosis, is severely distressed, or if the patient, or others, is at risk. The treatment should, however, be of the lowest effective dose and for the shortest period possible.[42,43]

Psychotropic drugs

Other psychotropic drug classes are also used to target the various neuropsychiatric symptoms in dementia. These include anxiolytics, hypnotics, and antidepressants. Anxiolytics may be used in cases of anxiety, severe aggression, and acute psychotic events, while hypnotics may be used to treat sleep disturbances. Antidepressants may be used to treat depressive symptoms, but also agitation and psychosis.

The clinical trial evidence for the efficacy of anxiolytics in patients with dementia is very limited[44] and demonstrates adverse effects, such as sedation and falls.[45] It is recommended to limit the use of anxiolytics to cases of severe anxiety, where other medications have failed and treatment should be short-term.[42] Hypnotics are generally not recommended for patients with dementia, also due to lack of evidence and possible side effects.[46] Identifying the cause of the sleep disturbance, review of medications, and non-pharmacological approaches should be first-line management.

Antidepressant are frequently used for patients with dementia, and there is some evidence for an effect on depression and agitation. Depressive symptoms may, on the one hand, be present before the dementia diagnosis, while depression, on the other hand, may be difficult to diagnose in patients with dementia. A review of the evidence for the efficacy of antidepressants in the treatment of depression concludes that there is only weak evidence; however, the new class of antidepressants, selective serotonin reuptake inhibitors (SSRIs), may be effective. The risk profile of SSRIs is debated, and cognitive and cardiac side effects may challenge the risk-benefit balance.[47–49] Due to the negative effects of antipsychotic treatment, there has been a need for pharmacological alternatives in the management of neuropsychiatric symptoms. A review concluded that SSRIs may be effective

in treating agitation and psychosis in patients with dementia.[50] According to clinical guidelines, SSRIs can be used to target depression, agitation, and psychosis.[42,43]

The mortality risk associated with anxiolytics, hypnotics, and antidepressants has been investigated in observational studies. In a study from the U.S.A., authors compared 180-day mortality for patients initiating antipsychotics or antidepressants with patients not treated with a psychotropic drug. The mortality risk associated with antidepressants was modest but present.[48] The mortality among patients with Alzheimer's disease in a British study was also increased among patients treated with antidepressants before and after the dementia diagnosis.[49] A Canadian study of nursing home residents found a weak association between increased mortality and initiating treatment with an antidepressant compared with second-generation antipsychotics, while initiating benzodiazepines showed a clearer association with increased mortality.[51] Benzodiazepines were also found to be associated with an increased mortality risk in a Finnish study of patients with Alzheimer's disease.[52]

The prevalence of psychotropic drug use has previously been studied in patients with dementia; however, selection bias was present in the studies and they also used varying sample sizes. The prevalence of anxiolytic use has recently been reported between 5–24% and hypnotic use between 7–14%, while antidepressant use have been reported at levels between 32-40%.[38,53–55] Some patients with dementia are, furthermore, treated with more than one psychotropic drug class concomitantly. The prevalence of treatment with combinations of psychotropic drug classes was 30–50% in two nursing home populations,[56,57] and the prevalence of use of three or more different psychotropic drug classes was found to be 14% in a French population of patients with dementia.[54]

Psychotropic polypharmacy and risks

Psychotropic polypharmacy, i.e., concomitant treatment with antipsychotics, anxiolytics, hypnotics, and/or antidepressants for patients with dementia is complex and holds increased risks of adverse events. Patients with dementia are at increased risk of side effects from polypharmacy in general.[58] When psychotropic drugs are combined, this could possibly be problematic due to interactions and the risk of combining, e.g., two drugs that can cause QT prolongation or sedation. On the other hand, the use of polypharmacy can be used to try a lower dose of antipsychotics in combination with, for example, an antidepressant.

A small Finnish study examined the risk of death associated with concomitant use of psychotropic drugs. The mortality risk among patients treated with more than one psychotropic drug was increased compared with patients not using psychotropic drugs, as was the risk of death for patients treated with antipsychotics. In a Swedish case-control study, the authors found an association between psychotropic polypharmacy and increased risk of death. There was also a dose-response relationship with the number of psychotropic drugs.[59]

In other patient populations, the risk of death associated with combining psychotropic drug classes has been studied. Among patients with schizophrenia, the use of antipsychotics in combination with benzodiazepines has been found to be associated with an increased risk of death.[60]

Comorbidity and mortality risk with antipsychotic treatment

The increased mortality among patients with dementia on antipsychotic treatment is well documented. However, it is of great importance to look further into this association by studying the possible mechanisms of action and cause of death. The FDA's meta-analysis pointed towards cardiovascular events and pneumonia as the primary causes of death in patients dying during antipsychotic treatment.[25] Observational studies have looked further into the mechanisms by investigating adverse events and cause of death. Antipsychotics have been linked to an increased risk of arrhythmias and major cardiovascular events,[61–63] which could partly explain the increased mortality. Cerebrovascular events have also been proposed as the link between antipsychotic treatment and mortality. A meta-analysis of trial data found an increased risk of stroke when comparing atypical antipsychotic treatment with placebo.[64] An observational study found an increased risk during antipsychotic treatment that was more pronounced in patients with dementia.[65] A Canadian study compared the risk of cerebrovascular events in patients treated with second-generation antipsychotic drugs with first-generation antipsychotics and found no difference, suggesting there may be a class effect. However, other observational studies have not been able to find an association between antipsychotics and risk of stroke.[66]

Patients with dementia often suffer from other comorbidities due to aging and some comorbidities may act as risk factors for developing dementia.[67] Older patients are at increased risk of side effects such as QT prolongation and hypotension.[68] Comorbidities could potentially influence side effects and the risk of adverse events, and thus, affect the mortality risk among patients treated with

antipsychotics. Most observational studies have adjusted for comorbidities, but in a study of older persons on antipsychotic treatment, there was a greater risk of a major cardiovascular event among those with pre-existing cardiovascular disease.[62] A small Finnish study analyzed whether patients with specific comorbidities had an increased, long-term risk of death during antipsychotic treatment, and the highest risk was found for patients with respiratory disease.[69]

More knowledge is needed

Even though the evidence is weak and knowledge on adverse events and increased mortality has emerged, there may still be frequent use of antipsychotic drugs. Studies on the prevalence of antipsychotic use have been conducted in selected populations, such as nursing home residents, or people with a specific type of health insurance. Further, previous studies on the time trend in use of psychotropic drugs in patients with dementia have mainly focused on evaluating antipsychotic use before and after a specific intervention, such as the FDA warnings. There is a need for knowledge on the use of antipsychotics and other psychotropic drugs in dementia because the management of neuropsychiatric symptoms, to some extent, may express whether adequate care is provided for patients with dementia. A comprehensive analysis of the changes and status of antipsychotic use in dementia care is an important aspect to include when planning future health-care and when monitoring drug use in the field of dementia.

Patients with dementia often suffer from complex neuropsychiatric symptoms, which is why various psychotropic drug classes may be used. The prevalence of concomitant use of psychotropic drugs in a large cohort of dementia patients is widely unexplored. Too little is known about possible negative public health consequences of this prescription practice. Thus, by using extensive population data, including filled prescriptions, it is possible to investigate prevalence, predictors, and the mortality risk associated with psychotropic polypharmacy. In addition, it is important to identify whether some patients with dementia are at a particularly high risk during antipsychotic treatment. There are known cardiovascular and metabolic side effects from antipsychotic drugs and associations with cardiovascular mortality; however, it is unknown whether patients with comorbidities related to the cardiovascular system are at increased risk of death when treated with antipsychotic drugs.

Danish registries provide the opportunity to explore drug utilization and consequences in a dementia population of an entire nation. The registries are unique because of national health-care

coverage and the possibility of linking data from different sources on an individual level with no selection and with nearly complete follow-up. Even though randomized clinical trials and meta-analyses of randomized clinical trial data provide the best evidence, observational studies can be important in studying the consequences of drug use in dementia patients. This group of patients is frail and frequently suffers from comorbid conditions that do not permit participation in traditional clinical trials. Observational studies provide good opportunity for testing hypotheses about treatment patterns and adverse outcomes. Thus, even though causality cannot be established from observational studies, there may be important information and findings from such analyses, as well as the generation of hypotheses for further studies.

Objectives and hypotheses

The overall objective of this PhD thesis was to investigate the use of antipsychotic drugs and other psychotropic drugs in patients with dementia and to study the mortality risk associated with the use of psychotropic drugs. The aim was to clarify areas of inappropriate medication use and to help prevent the negative consequences hereof.

Study I The objective was to investigate time trends of antipsychotic, anxiolytic, hypnotic/sedative, and antidepressant drug use in patients with dementia from 2000-2012.

Hypothesis: use of antipsychotic drugs has decreased among patients with dementia between 2000 and 2012 and there have been compensatory changes in the use of other psychotropic drug classes.

Study II The objective was to investigate the prevalence and predictors of concomitant use of antipsychotic, anxiolytic, hypnotic/sedative, and antidepressant drugs among patients with dementia.

Hypothesis: antipsychotic drugs are frequently used in combination with other psychotropic drug classes and concomitant use is associated with nursing home residency, increasing age, and prior psychiatric disease.

Study III The objective was to investigate the mortality risk among patients with dementia treated with antipsychotics in combination with benzodiazepines and/or antidepressants compared with antipsychotic drugs only.

Hypothesis: concomitant treatment with antipsychotics and other psychotropic drug classes is associated with an increased mortality risk compared with antipsychotic treatment alone.

Study IV The objective was to investigate whether pre-existing comorbidities affect the mortality risk in patients with dementia treated with antipsychotic drugs.

Hypothesis: patients with pre-existing comorbidities are at increased risk of mortality during antipsychotic treatment compared with patients without comorbidities.

Methods

Danish national registries

Data on Danish residents is available from national registries containing demographic and health-care related information. All permanent residents are assigned a unique personal registration number at birth or after immigrating to Denmark, making it possible to link data between registries.[70] For the four studies in this thesis, the following registries were used:

- The Danish Civil Registration System

  Run by Statistics Denmark and contains continuously updated information on date of birth, sex, residence, emigration, and death.[70]
- The Danish National Patient Registry

  Contains data on all hospital admissions (in-patient contacts) since 1977. From 1995 and onwards, the registry also began including data on out-patient contacts and emergency room contacts. The registry contains data on date of contact, diagnoses, and procedures.[71] Between 1977 and 1994 diagnoses were registered according to the International Classification of Diseases (ICD) 8th revision,[72] and as off 1994 and onwards, according to the ICD 10th revision.[73]
- The Danish Psychiatric Central Research Registry

  Established in 1969 with complete data on all psychiatric admissions to psychiatric hospitals from 1970 and onwards.[74] From 1995, the registration of psychiatric in- and out-patient contacts was included in the Danish National Patient Registry.
- The Danish National Prescription Registry

  Since 1994, all filled prescriptions have been registered. Contains data on drug classification according to the Anatomical Therapeutic Chemical (ATC) classification system, date of dispensing, package size, and strength.[75]

Population

The entire elderly Danish population, aged 65 and above, formed the basis for the studies in the thesis. For all four studies the same definition was used to identify patients with dementia in the registries.

Thus, patients with dementia were people who

were registered with a dementia diagnosis (see Table 1 for diagnoses)

and/or

had filled at least one prescription for an anti-dementia drug (ATC: N06D).

Table 1. Diagnoses used for identification of patients with dementia from the Danish National Patient Registry and the Danish Psychiatric Central Research Registry.

	Alzheimer's disease	Vascular dementia	Frontotemporal dementia	Other dementias	Dementia without specification
ICD-8	290.10	293.09-19	290.11	-	290.09-19
ICD-10	F00.0 F00.1 F00.2 F00.9 G30.0 G30.1 G30.8 G30.9	F01.0 F01.1 F01.2 F01.3 F01.8 F01.9	F02.0	G31.8	F03 G31.9

ICD=International Classification of Diseases

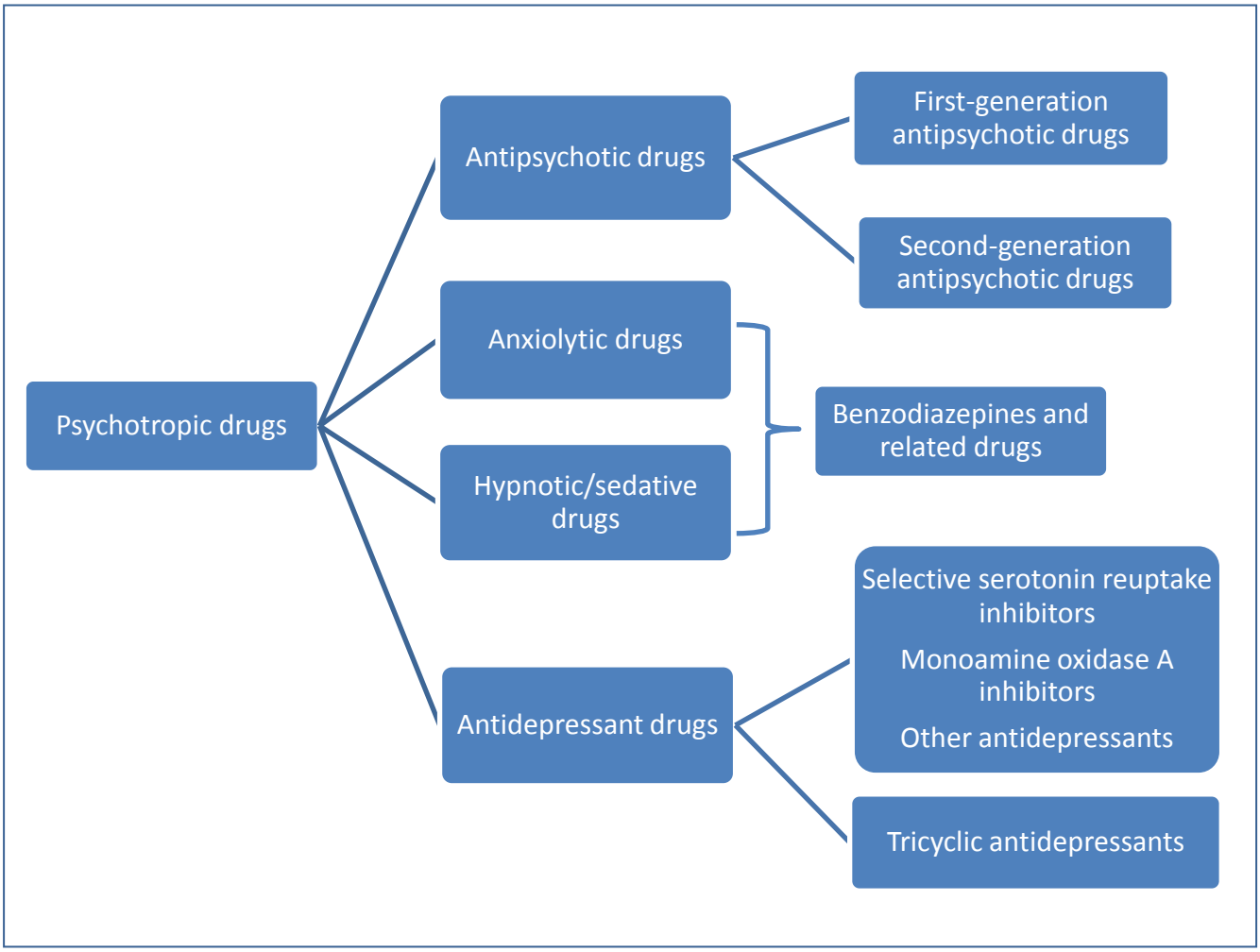
Anti-dementia prescriptions were chosen to capture patients not diagnosed in the secondary sector because the only indication for these drugs is dementia.

The validity of a registered dementia diagnosis in the Danish registries has previously been investigated to enable registry-based research in this field. The study found that dementia diagnoses were correct in 86% of cases.[76] People who had their first registered diagnosis or first filled prescription before age 60, however, were excluded, because previous research found that the validity of a dementia diagnosis in Danish registries was low among younger patients.[77]

Psychotropic drugs

For the four studies in this thesis, the overall term psychotropic drugs include antipsychotics, anxiolytics, hypnotics, and antidepressants (see Figure 1). Lithium was excluded from antipsychotic drugs in all studies because of its main indication as a mood stabilizer. See Study III, Supplementary Material for detailed information on ATC codes of sub groups.

Figure 1. Psychotropic drug classes with sub groups.



The date the prescription was filled was assumed as the first day of treatment. All drugs are registered with a defined daily dose (DDD) which is the average maintenance dose of the drug when used on its major indication in adults.[78] As a result, based on the date the prescription was filled, package size, and strength, it is possible to calculate an assumed treatment period.

Covariates

Factors associated with dementia and psychotropic drug use were included in the studies, some of them as confounders (Table 2 presents specific confounders included in studies I-IV).

Age and sex were obtained from Statistics Denmark. Statistics Denmark generates data-sets with information on residency in nursing homes. Information on hospital admissions and somatic and psychiatric comorbidity was based on registered diagnoses in the Danish National Patient Registry and The Danish Psychiatric Central Research Registry. The number of prescription drugs and other psychotropic drugs was assessed using the Danish National Prescription Registry.

Table 2. Confounders included in multivariate analyses of studies I-IV. All models included age at time of dementia diagnosis and sex.

Study	Confounders
I	Prior psychotic diagnosis Charlson Comorbidity Index score
II	Time since dementia diagnosis Nursing home residency Prior psychiatric diagnosis Charlson Comorbidity Index score Total number of other drugs
III	Calendar year Time since dementia diagnosis at index date Nursing home residency Charlson Comorbidity Index score Prior psychiatric diagnosis Total number of other drugs Prior antidepressant use Prior hospital admission Number of days on antipsychotic treatment
IV	Calendar year Nursing home residency Prior psychiatric diagnosis Charlson Comorbidity Index score (modified) Heart disease Cerebrovascular disease Diabetes mellitus Prior use of benzodiazepines and antidepressants Number of hospitalizations

For further details on definitions and categorizations of continuous variables, please see studies I-IV.

Data analysis

The data management and analyses were performed using SAS statistical software versions 9.3 and 9.4 (SAS Institute Inc., Cary, NC, USA), and R studio. All statistical tests were two-sided, and the significance level was set at a p-value of 0.05.

Study specific methods

All four studies were population-based observational studies. Their specific designs and statistical methods are presented below.

Study I

The study was designed as repeated cross sections of the elderly population. On January 1 of each year from 2000 to 2012, we included all patients with dementia aged 65 and above. Those who had received a dementia diagnosis, or who had filled the first prescription for an anti-dementia drug before age 60, were excluded, leaving the remaining population aged 65 and above on January 1 of each year as the reference population. The outcome of interest was prevalence of users of antipsychotics, anxiolytics, hypnotics/sedatives, and antidepressants among older people with and without dementia. Antipsychotic drugs were divided into two groups: first-generation drugs and second-generation drugs. In Denmark, anti-dementia drugs were introduced from 1997 and onwards and the prevalence of users of anti-dementia drugs was therefore calculated for patients with dementia.

The trend analysis compared prevalence of drug use among patients with dementia between 2000, 2004, 2008, and 2012. The statistical analysis was carried out taking into account that patients could be included multiple times following their sixty-fifth birthday. As a result, the population of patients with dementia was divided into age groups of four-year intervals. Logistic regression analysis was used to assess the probability of receiving a psychotropic drug in 2004, 2008, and 2012 versus 2000. A crude model and an adjusted model including age, sex, prior psychotic diagnosis, and somatic comorbidity (CCI score) was performed. Confounders were chosen based on prior research indicating associations between dementia and psychotropic drug use.

Treatment duration assumed an intake of one DDD per day. Thus, the number of DDDs each patient filled within a year was considered the number of days under treatment. This was then used to calculate the median (25–75% interquartile range) number of DDDs per patient treated with antipsychotics.

Study II

On January 1, 2012, the population of patients with dementia was defined and linked to all filled prescriptions for psychotropic drugs in 2012. Psychotropic drugs were analyzed in the four drug classes: antipsychotics, anxiolytics, hypnotics, and antidepressants. The treatment duration for each prescription was calculated based on one DDD representing one day of treatment. Thus, prescriptions filled in 2011 with a treatment duration continuing into 2012 were also included. Overlapping prescriptions were used to define treatment with multiple psychotropic drug classes (psychotropic polypharmacy). The prevalence of patients with dementia exposed to psychotropic polypharmacy was calculated, as well as the prevalence of patients using antipsychotics in combination with other psychotropic drug classes. Analyses were stratified according to living status (home living versus nursing home residents).

Patient characteristics possibly associated with the prescribing of other psychotropic drug classes, in addition to antipsychotic treatment, were analyzed in a logistic regression model. The outcome was use of antipsychotics in combination with other psychotropic drug classes. The following variables were chosen based on previous literature linking them to antipsychotic use: age, time since dementia diagnosis, nursing home residency, CCI score, prior psychiatric diagnosis, prior psychotic diagnosis, and total number of other drugs used in 2011.[27,79,80] These were all included in a univariate model. Subsequently, a multivariate model including the variables significantly associated with psychotropic polypharmacy was performed to assess factors independently associated with polypharmacy among antipsychotic users.

Study III

The study was designed as a retrospective cohort study. All incident patients with dementia aged 65 and above between January 1, 2009 and December 31, 2013 were identified. Patients who subsequently filled a prescription for an antipsychotic drug between January 1, 2009 and June 30, 2014 were included in the cohort. Index date was defined as the first day of antipsychotic treatment

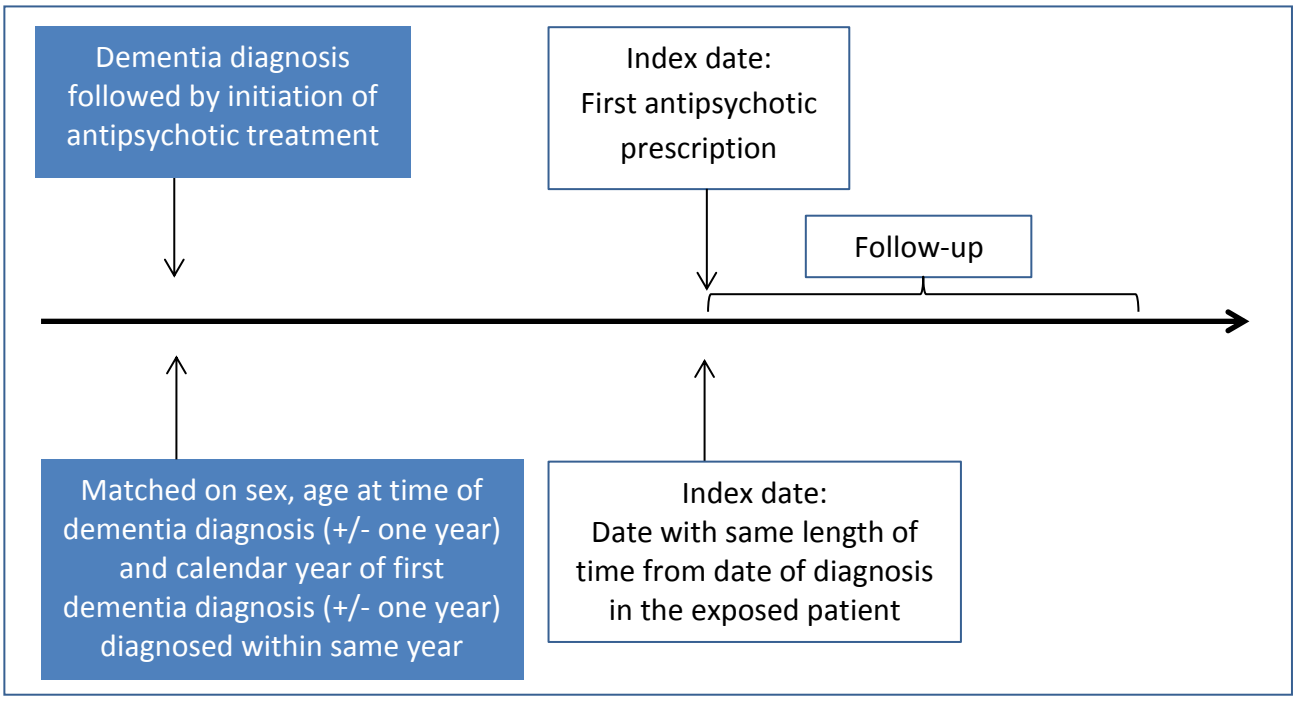
after dementia diagnosis. Two exclusion criteria were applied. First, patients treated with antipsychotic drugs within 180 days prior to the index date were excluded to avoid bias from prevalent users.[81] Second, patients with a hospital admission >30 consecutive days preceding the index date were excluded because data on in-hospital drug treatment is not available in the registries. Exposure to psychotropic drugs during follow-up was divided into antipsychotics, anxiolytics and hypnotics (termed benzodiazepines and related drugs (BZDs)), and antidepressants. Treatment duration for each prescription was calculated to identify overlapping treatments. As the recommended psychotropic drug doses for older patients and patients with dementia differ from their use in adults, the number of DDD per day for antipsychotic drugs, anxiolytics, and tricyclic antidepressants was set at 0.5 DDD, while for hypnotics and other antidepressants it was set at 1.0 DDD.[82] In addition, a grace period of 14 days was added to allow small gaps between prescriptions.[83] If a patient filled prescriptions for other psychotropic drug classes during follow-up, they were classified as concomitant users. Each patient contributed with risk time during each treatment, e.g., risk time during treatment with antipsychotics only and risk time during treatment with antipsychotics in combination with BZDs.

The outcome was 180-day all-cause mortality comparing risk during antipsychotic treatment with risk during antipsychotic treatment in combination with BZDs and/or antidepressants. A Cox regression model was performed to estimate hazard ratios (HRs) with 95% confidence intervals (CI), with time since index date as the underlying time scale. The multivariate model included age, sex, calendar year, time since dementia diagnosis at index date, Charlson Comorbidity Index score, prior psychiatric disease, total number of drugs used (other than psychotropic drugs), previous antidepressant use one year before index date, nursing home residency, hospital admission six months prior to index date, and total number of days on antipsychotic treatment.

Study IV

The study was designed as a matched cohort study. Among all incident dementia patients aged 65-95 years of age, we defined exposed and unexposed subjects. Those who initiated antipsychotic treatment after the diagnosis were defined as exposed subjects. The duration of drug exposure was calculated based on 0.5 DDD per day. We matched up to three unexposed subjects who did not initiate antipsychotic treatment at the time of matching. The index date was the date of first antipsychotic prescription for the exposed subject and a fictive index date was created as the date with the same interval between dementia diagnosis and first antipsychotic prescription of the exposed subject. Exposed and unexposed subjects were excluded if they had filled antipsychotic prescriptions 180 days before the index date. The index date marked start of follow-up (see Figure 2). Unexposed subjects who later filled an antipsychotic prescription were censored, but then included in the analysis as an exposed subject. Follow-up ended at the date of death, emigration, 180 days, at date of initiation of antipsychotic treatment for unexposed subjects, or end of the study period (December 31, 2015), whichever came first. At index date, diabetes, cardiovascular, and cerebrovascular comorbidities were assessed, as well as other confounders (see Table 2).

Figure 2. Matched cohort design.



The outcome was 180-day all-cause mortality, which was assessed by a Cox regression model. The crude mortality rates and crude and adjusted HRs with 95% CI were calculated. The multivariate model included age at time of dementia diagnosis, sex, calendar year, nursing home residency, Charlson Comorbidity Index score, prior psychiatric disease, previous use of antidepressants and BZDs 180 days before index date, and number of hospital admissions within five years before index date. To investigate the influence of specific pre-existing comorbidities, the survival analysis was stratified for diabetes, cardiovascular, and cerebrovascular comorbidities (with adjustment for the comorbidities not under investigation).

Ethical considerations

Statistics Denmark provided access to registry data, which are anonymous. The personal registration number was encrypted.

Studies I-IV were approved by the Danish Data Protection Agency (ID no.: 2007-58-0015/30-0667), Statistics Denmark, and the Danish Health and Medicines Authority (ID no.: 6-8011-907/1). The studies did not require ethical approval or informed patient consent.

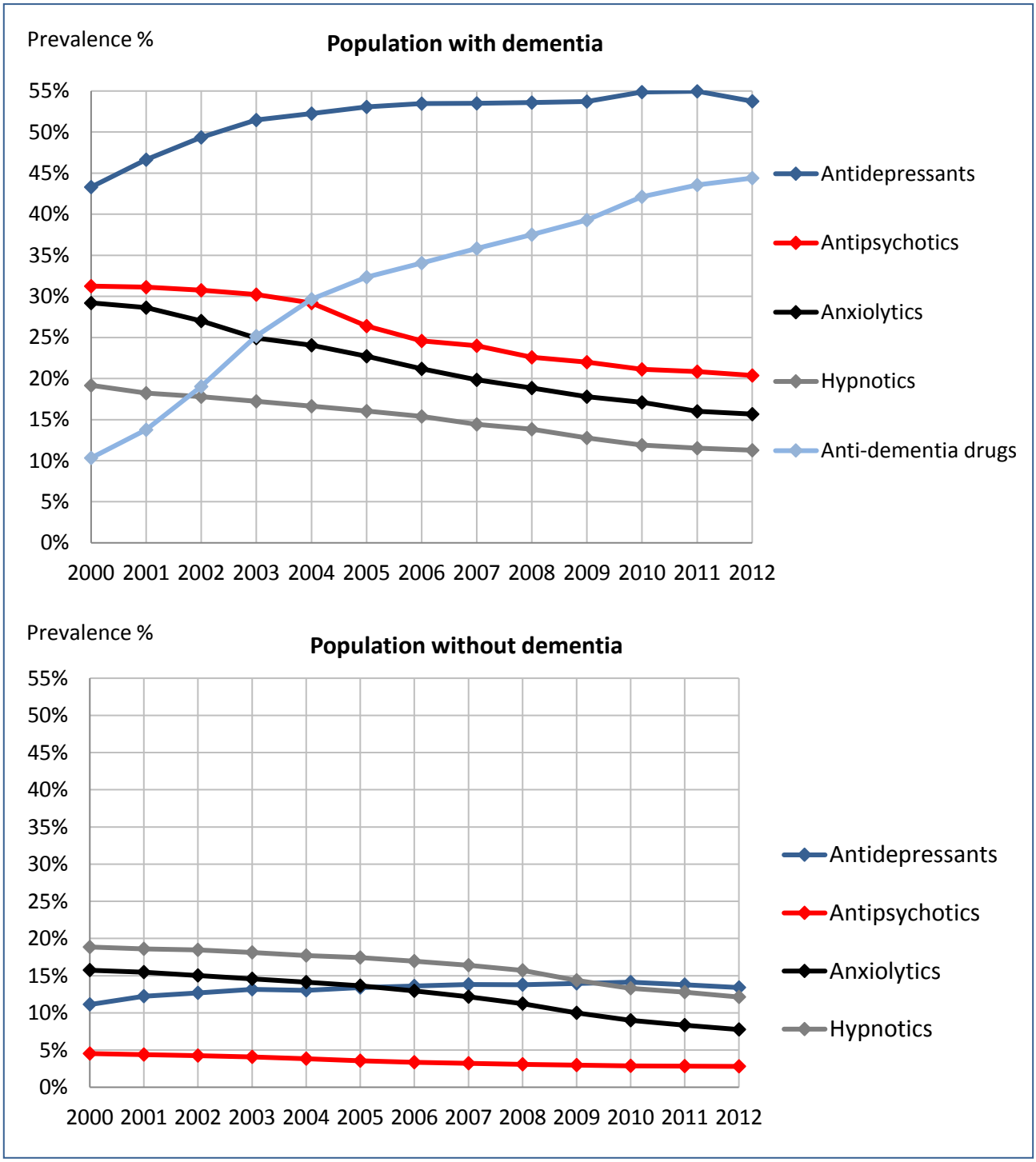
Summary of results

The results presented below are main findings from the four studies. For further details, see studies I-IV.

Study I

In 2000, after excluding 1988 individuals due to early dementia diagnosis, we included 799,914 people aged 65 and above, 19,062 (2.4%) of whom were patients with dementia. After exclusion of early diagnoses, the number of older people/number of patients with dementia (%) increased to 813,648/27,161 (3.5%) in 2004; 860,581/32,260 (3.9%) in 2008; and 972,090/34,553 (3.7%) in 2012. Among patients with dementia the prevalence of antipsychotic drug use decreased from 31.3% to 20.4%. This was the result of first-generation antipsychotic use decreasing from 21.2% to 4.5% while use of second-generation antipsychotics increased initially from 13.4% in 2000 to 22.0% in 2004, followed by a decrease to 17.3% in 2012. From 2000 to 2012, use of anxiolytics decreased from 29.2% to 15.7% and hypnotics/sedatives from 19.2% to 11.3%, while antidepressant use increased from 43.3% to 53.8%. Among older people without dementia, the level of antipsychotic use was lower and showed a decrease from 4.5% in 2000 to 2.8% in 2012. Over the study period, use of anxiolytics decreased from 15.7% to 7.7%, while hypnotics/sedatives decreased from 18.9% to 12.1%. Antidepressant use also increased among older people without dementia, from 11.1% in 2000 to 13.4% in 2012. See Figure 3. The proportion of patients not using any psychotropic drugs increased from 29.8% in 2000 to 33.3% in 2012. Use of anti-dementia drugs increased from 10.3% in 2000 to 44.4% in 2012.

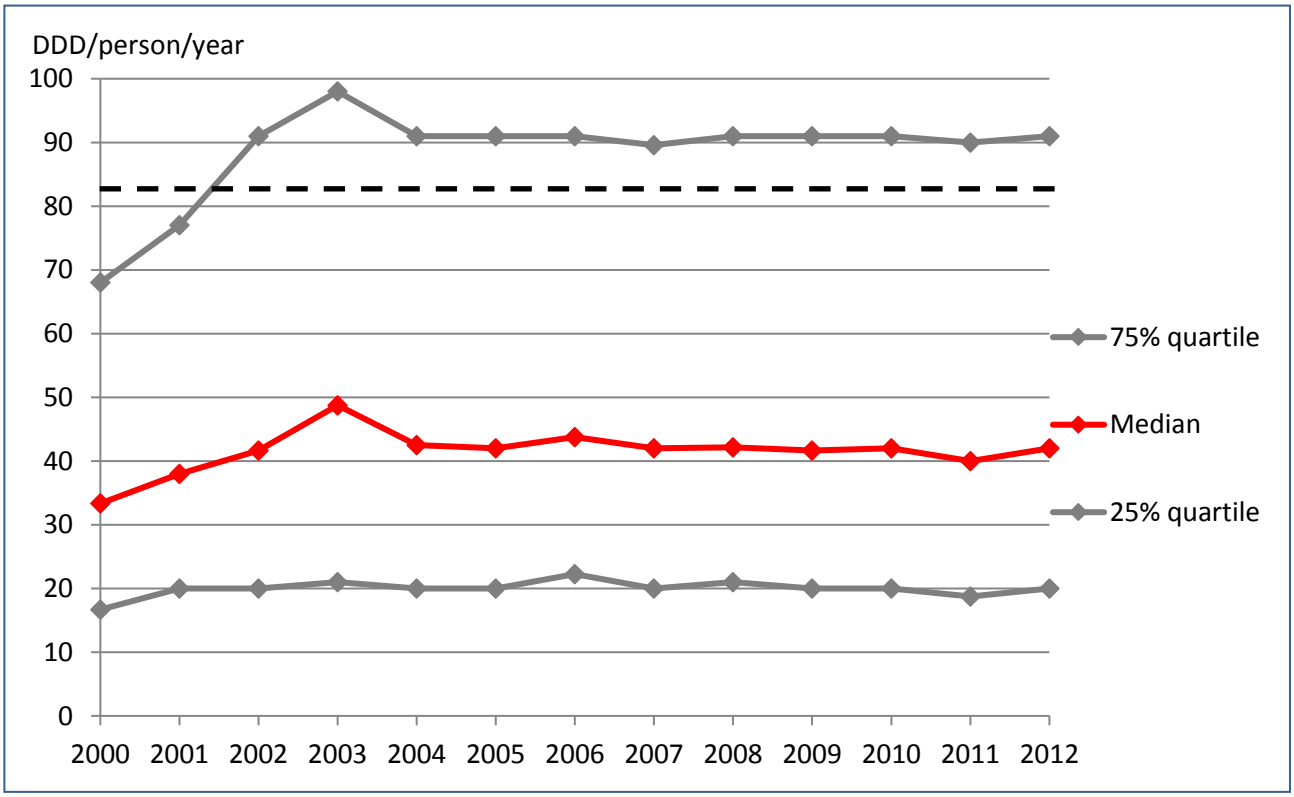
Figure 3. Prevalence of anti-dementia and psychotropic drug use from 2000 to 2012 among the population aged 65 and above with and without dementia. Modified from Nørgaard et al.[84]



The trend analysis found significant changes in antipsychotic use from 2000 to 2012, after adjusting for age, sex, prior psychotic disorder, and CCI score, with the exception of the oldest age group (aged 97–100). The youngest patients (aged 65–68) were 23% less likely to be treated with antipsychotic drugs, while the 89-92-year-olds were 50% less likely to be treated with antipsychotics (50%). See Supplementary Table SA for complete data on trend analysis.

The amount of antipsychotic drug doses filled by patients with dementia increased over the study period, with the largest increase between 2000 and 2003, followed by a stable level between 2004 and 2012; see Figure 4. From 2002–2012, more than a quarter of patients with dementia using antipsychotics had filled doses corresponding to more than 12 weeks of a given year.

Figure 4. Treatment duration of antipsychotic drug use. Defined daily doses (DDD) of antipsychotics prescribed for users of antipsychotics among patients with dementia from 2000 to 2012. The red line indicates median value, and the grey lines indicate 25% and 75% quartiles, respectively. The dotted line marks 84 DDD (12-week) treatment duration. Reprinted from Nørgaard et al.[84]



Study II

The number of patients with dementia included on January 1, 2012 was 34,553. Of those, 17,473 (50.6%) were home living and 17,080 (49.4%) were nursing home residents. Psychotropic polypharmacy occurred in 25.3% (8728) of patients with dementia in 2012 and was more common among nursing home residents (nursing home 30.9% versus home living 19.7%, $p<0.001$). The median number of days that patients were exposed to psychotropic polypharmacy was 50.0 (10–90 percentile range 6.0–278.0). Patients using antipsychotic drugs (7130) were using at least one other psychotropic drug class during the treatment period in 75.8% (5403) of cases. Among patients treated with antipsychotics, the most frequent combination was with antidepressants (67.6%), followed by anxiolytics (19.3%), and hypnotics (14.3%).

Table 3 presents the factors significantly associated with the treatment combination of antipsychotics versus antipsychotics only. Younger age, female sex, patients living in nursing homes, patients with a prior psychiatric diagnosis, and patients using five or more other prescription drugs were most likely to receive a combination of antipsychotics and another psychotropic drug. Time since diagnosis was also associated with the combination of antipsychotics and other psychotropic drugs, which was most evident after five years.

Table 3. Factors associated with concomitant use of antipsychotics with other psychotropics versus antipsychotic monotherapy among patients with dementia in 2012. Reprinted from Nørgaard et al.[85]

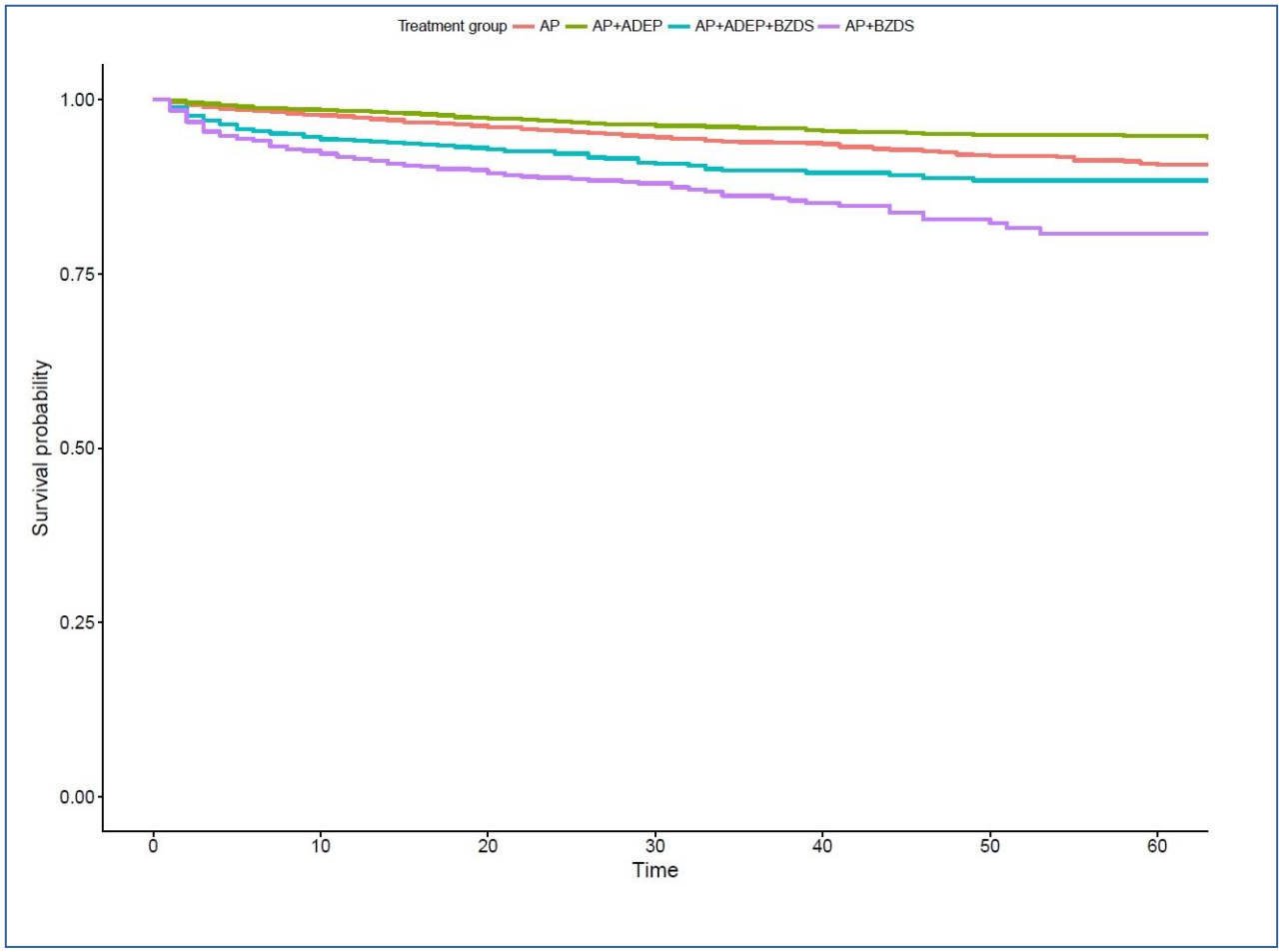
Characteristic	Antipsychotics + other psychotropics. Crude OR (95% CI)	Antipsychotics + other psychotropics. Adjusted*** OR (95% CI)
Age group		
65-74 years	1.00	1.00
75-84 years	0.86 (0.75-0.99) *	0.85 (0.74-0.98) *
≥85 years	0.85 (0.74-0.98) *	0.83 (0.71-0.96) *
Sex (female)	1.21 (1.10-1.34) **	1.13 (1.01-1.25) *
Nursing home resident vs. home living	1.23 (1.11-1.36) **	1.23 (1.11-1.36) **
Time since dementia diagnosis		
<1 year	1.00	1.00
1-3 years	1.28 (1.11-1.48) **	1.33 (1.15-1.54) **
4-5 years	1.18 (1.02-1.38) *	1.20 (1.03-1.40)
>5 years	1.60 (1.38-1.86) **	1.59 (1.36-1.85) **
Number of drugs in 2011 (excluding psychotropic drugs)		
0-1	1.00	1.00
2-4	1.34 (0.99-1.82)	1.27 (0.93-1.74)
5-9	1.63 (1.22-2.17) *	1.54 (1.15-2.08) *
≥10	1.99 (1.48-2.67) **	1.88 (1.39-2.55) **
Somatic comorbidity Charlson Comorbidity Index		
0	1.00	1.00
1	1.13 (0.99-1.28)	1.06 (0.93-1.21)
≥2	1.14 (1.02-1.28) *	1.04 (0.92-1.17)
Psychiatric comorbidity Prior psychiatric disorder (any)	1.76 (1.58-1.95) **	1.71 (1.53-1.90) **

OR=odds ratio; CI=confidence interval.
* $p < 0.05$
** $p < 0.001$
*** Multivariable analysis adjusted for age group, sex, living status, time since dementia diagnosis, number of drugs in 2011, Charlson Comorbidity Index, and prior psychiatric disorder.

Study III

There were 41,494 incident dementia cases between 2009 and 2013. Among those, 10,283 (24.8%) initiated antipsychotic treatment, 160 of whom were excluded due to hospital admissions, and another 2980 were excluded due to recent antipsychotic drug use. For the final analysis, 7143 patients were included. The total follow-up time during treatment with antipsychotics (alone or in combination with other psychotropic drug classes) was 1146 person-years (PYs). During the first 180 days after antipsychotic treatment was initiated, 1787 (25.0%) people died. A total of 831 deaths occurred during treatment with antipsychotics. The crude mortality rate for patients treated with antipsychotics only was 62.3 deaths per 100 PYs, but 194.6 deaths per 100 PYs for patients using combinations of antipsychotics and BZDs, and 40.6 for patients using antipsychotics and antidepressants combined. Figure 5 presents the Kaplan Meier survival curves. Only day 0-60 are presented due to limited power.

Figure 5. Survival 0-60 days after initiation of antipsychotic treatment according to treatment.



AP=antipsychotic; ADEP=antidepressant; BZDS=benzodiazepines and related drugs.

Treatment with antipsychotics in combination with BZDs was associated with an increased 180-day risk of death compared with antipsychotic treatment alone (adjusted HR: 2.19, 95% CI: 1.83-2.63). In contrast, the combination of antipsychotics and antidepressants was associated with a decreased risk of death (adjusted HR: 0.61, 95% CI: 0.50-0.74).

Study IV

A total of 8244 exposed dementia patients were included, while the matching of up to three patients per exposed patient generated 24,730 matched unexposed patients. The study population was followed for 14,285.6 PYs, during which time 5938 deaths occurred (41.6/100 PYs). The crude HR (95% CI) of death within 180 days of mortality for exposed versus unexposed patients was 1.49 (1.41-1.57), while the adjusted HR (95% CI) was 1.35 (1.27-1.43). In the stratified analyses, the highest mortality rate was found for exposed patients with cardiovascular disease; crude mortality rate per 100 PYs (CI) 78.2 (72.9-83.9). Exposed patients without cardiovascular disease had a crude mortality rate per 100 PYs (CI) of 58.3 (55.8-60.9). In the stratified adjusted Cox regression analyses, there was no difference (overlapping CIs) between risk of death in the strata with and without cardiovascular disease. This was also the case for cerebrovascular disease and diabetes; see Table 4.

Table 4. 180-days mortality rates and hazard ratios (HRs) with 95% confidence intervals (95% CI) for antipsychotic treatment (exposed) versus patients not treated with antipsychotics (unexposed) stratified for specific pre-existing comorbidities.

		Crude mortality rate per 100 person-years (CI)	Crude HR (95% CI) *	Adjusted HR (95% CI) **
Cardiovascular disease				
No	Unexposed N=20,649 (83.5%)	36.3 (35.2-37.5)	1.0 (Ref.)	1.0 (Ref.)
	Exposed N=6892 (83.6%)	58.3 (55.8-60.9)	1.55 (1.45-1.66)	1.26 (1.17-1.36)
Yes	Unexposed N= 4081 (16.5%)	50.9 (48.5-53.4)	1.0 (Ref.)	1.0 (Ref.)
	Exposed N=1352 (16.4%)	78.2 (72.9-83.9)	1.41 (1.29-1.53)	1.19 (1.08-1.30)
Cerebrovascular disease				
No	Unexposed N=19,862 (80.3%)	32.9 (31.7-34.1)	1.0 (Ref.)	1.0 (Ref.)
	Exposed N=6512 (79.0%)	55.7 (53.0-58.6)	1.57 (1.47-1.67)	1.41 (1.31-1.50)
Yes	Unexposed N= 4868 (19.7%)	51.0 (48.0-54.2)	1.0 (Ref.)	1.0 (Ref.)
	Exposed N=1732 (21.0%)	68.2 (62.4-74.6)	1.24 (1.16-1.38)	1.17 (1.05-1.32)
Diabetes				
No	Unexposed N=20,658 (83.5%)	34.7 (33.6-36.0)	1.0 (Ref.)	1.0 (Ref.)
	Exposed N=6950 (84.3%)	56.3 (53.6-59.1)	1.50 (1.41-1.59)	1.25 (1.18-1.34)
Yes	Unexposed N= 4072 (16.5%)	44.5 (41.4-47.7)	1.0 (Ref.)	1.0 (Ref.)
	Exposed N= 1294 (15.7%)	69.5 (62.7-77.0)	1.43 (1.26-1.62)	1.15 (1.01-1.32)

* Adjusted for sex and age.

** Adjusted for age at dementia diagnosis, sex, calendar year, nursing home residency, (cardiovascular disease, cerebrovascular disease, and diabetes mellitus),‡ Charlson Comorbidity Index score (excluding dementia, acute myocardial infarction, congestive heart disease, cerebrovascular disease, diabetes, and diabetes with end organ damage), psychiatric comorbidity, treatment with benzodiazepines and antidepressants within 180 days before index date, number of hospitalizations within five years before index date. ‡Not adjusted for the comorbidity in strata of interest.

Discussion

Summary of key findings

The key findings of the thesis are that there have been significant changes in treatment with psychotropic drugs in dementia patients and that antipsychotics are frequently used in combination with other psychotropic drug classes. Further, the combination of antipsychotics and benzodiazepines is associated with an increased mortality risk, while a decreased mortality risk exists for patients treated with antipsychotics in combination with antidepressants. A history of diabetes and cardiovascular and cerebrovascular disease did not influence the increased mortality risk during antipsychotic treatment. In the following, these findings will be discussed, see studies I-IV, however, for further details.

Changes in the use of psychotropic drugs

Prescription guidelines vary between countries; however, internationally, there has been focus on reducing the inappropriate prescribing of antipsychotics for patients with dementia. In 2004, the former UK Committee on Safety of Medicines sent direct instructions to clinicians to warn against the use of antipsychotics for patients with dementia. This was followed by guidelines and reports, including the UK Department of Health's 2009 "Time for Action" report, which launched an ambitious goal of reducing inappropriate prescribing of antipsychotics for patients with dementia. In 2012, the national UK dementia strategy expanded this aim.[86] The result was a marked reduction in the use of antipsychotics for dementia patients in the UK, with prevalence reaching levels of 7–11% based on primary care data.[86–88] In Study I, we also found significant reductions in antipsychotic use among patients with dementia. This may be a consequence of guidelines, warnings, and debate among professionals. Thus, it seems that potential exists to reduce antipsychotic use. We have analyzed the geographical variations in antipsychotic prescription practices in Denmark, with notable findings. With levels of antipsychotics ranging from 7.5%–33.1% between municipalities, the study indicates marked differences in dementia care.[89] This may reflect cultural differences and a lack of knowledge and resources in the management of neuropsychiatric symptoms in dementia care. Thus, antipsychotic treatment levels can be seen as a surrogate marker of adequate care, which is why it is important to continue the monitoring of antipsychotic use.

A reduction in antipsychotic prescriptions may influence the prescribing of other psychotropic drug classes. Interestingly, changes in the use of antipsychotic drugs in Study I were accompanied by

changes in the use of other psychotropic drug classes, with an increase in antidepressant use and a decrease in use of anxiolytics and hypnotics. This is in line with other studies that found an increasing use of antidepressants.[38,39,41] Due to the appearance of evidence that SSRIs have an effect on agitation and psychosis in dementia, [50] we can only speculate that antidepressants, to some extent, have replaced some antipsychotic prescriptions. However, it seems that antidepressant use among older people, in general, has increased over the study period, as observed in other populations.[90] During the same period, initiatives were taken to reduce the use of anxiolytics and hypnotics in the older population, possibly explaining the observed reduction in Study I. The proportion of dementia patients with any psychotropic drug use decreased from 70.2% in 2000 to 66.7% in 2012, suggesting that more patients are managed without psychotropic drugs.

An improvement in the use of antipsychotics in dementia implies not just a reduction in the number of users but also the treatment duration and doses used. Therefore, we examined the median number of DDDs prescribed. The number of DDDs per patient did not decrease during the period of decreasing prevalence, perhaps illustrating that there are now fewer patients with short-term or intermittent use. Notably, 27% of patients treated with antipsychotics had filled prescriptions to cover more than 12 weeks in the period of a year in 2012. Long-term use (>12 weeks) is only recommended for cases of severe and persistent neuropsychiatric symptoms, where other treatments have failed, and antipsychotics have an established effect.[42,43]

Psychotropic polypharmacy

Limited attention has been given to combination treatments with multiple psychotropic drugs. In a French population-based study, 14% of patients with dementia used three or more psychotropic drugs.[54] In a community-based Finnish cohort, 18% of patients with Alzheimer's disease used two or more psychotropic drugs, and in a Canadian population of nursing home residents with dementia, 50% used at least two psychotropic drug classes.[57] This pattern is in line with findings from Study II, where 31% of nursing home residents and 20% of patients living at home used two or more psychotropic drugs. More frequent use of psychotropic polypharmacy among nursing home resident populations may be expected, since increasing neuropsychiatric symptoms is a predictor of nursing home placement.[5] These patients, however, are also frail and may be more susceptible to the adverse effects of psychotropic drugs.[91] We have also presented widespread use of polypharmacy (use of ≥5 different medications) among patients with dementia, which in itself is

associated with negative outcomes.[92] In fact, nursing home residency and increasing number of other prescription drugs were associated with psychotropic polypharmacy in Study II. The Finnish study, subsequently, also found younger age, female sex, and psychiatric disease to be associated with psychotropic polypharmacy three years after dementia diagnosis.[93] The most prevalent combination was antipsychotics and antidepressants, which is in alignment with Study II. There may be plausible reasons to introduce psychotropic polypharmacy in the management of neuropsychiatric symptoms. Patients with agitation and depressive symptoms may benefit from a lower dose of antipsychotics, combined with an SSRI, instead of a higher dose of an antipsychotic drug with respect to effect and in a risk-benefit assessment. On the other hand, adding another psychotropic drug to antipsychotic treatment could introduce possible interactions or an increased risk of adverse events. Surprisingly, 75% of patients with dementia treated with antipsychotics had filled prescriptions for other psychotropic drugs with overlapping treatment periods. It is not possible to rule out that overlapping treatment may represent a switch from one treatment regimen to another. However, the median duration of psychotropic polypharmacy treatment was 50 days, suggesting otherwise.

Mortality risk associated with psychotropic polypharmacy

The high prevalence of combination therapy, largely among patients treated with antipsychotic drugs, leads to safety issues concerning psychotropic polypharmacy. Study III showed an increased risk of death associated with antipsychotic treatment in combination with other psychotropics compared with antipsychotic treatment alone. The extensive literature on antipsychotic treatment and risk of death in patients with dementia generally did not consider concomitant psychotropic drug use in the analyses. Two important observational studies reported that use of other psychotropic drugs was common before the index date.[26,33] However, there was no information about whether these prescriptions continued during follow-up or a description of the potential consequences hereof. A Finnish study found an association between concomitant treatment with several psychotropic drugs and mortality, and a Swedish register-based study found that the number of psychotropic drugs was associated with mortality in a dose-response manner.[59,94] The analyses from Study III suggest an overall increased mortality risk associated with psychotropic polypharmacy. In Study II we found that psychotropic polypharmacy was associated with disease progression, assessed as time since diagnosis. As a result, this measure was therefore included as a

confounder, as neuropsychiatric symptoms increase with disease stage and, at the same time, late stage-dementia is a strong predictor of death.

The increased mortality risk was driven by combinations of antipsychotics and benzodiazepines, whereas patients treated concomitantly with antipsychotics and antidepressants had a lower risk of death compared with patients treated with antipsychotics alone. Interestingly, the combination of antipsychotics and benzodiazepines has been found to increase mortality in schizophrenia patients as well.[60,95] The mechanism for the increased mortality among patients concomitantly treated with antipsychotics and benzodiazepines may be a direct effect due to drug interactions or combinations of side effects from both drug classes. In patients with dementia, benzodiazepines can lead to sedation, falls, and pneumonia[96,97] and the combination with antipsychotic drugs may increase the risk of serious adverse events, subsequently the risk of death. Another possible explanation for the differential risk of death associated with different psychotropic drug combinations is the use of specific combinations for specific patients, that is confounding by indication. Patients with a more severe disease profile and neuropsychiatric symptoms may be treated more often with antipsychotics and benzodiazepines, while patients with agitation, anxiety, or depressive symptoms may be treated with a combination of antipsychotics and antidepressants. As previously shown, the use of SSRIs has increased, and off-label use to treat, e.g., agitation may be the clinician's first choice to avoid antipsychotics, while the combination of antipsychotics and antidepressants may be used to avoid increasing the dose of an antipsychotic drug. There is some evidence for an effect of selective serotonin reuptake inhibitors (SSRIs) on agitation and psychosis.[50] The evidence for an effect of SSRIs and tricyclic antidepressants on depressive symptoms in dementia is, however, limited.[98,99] The Danish national guidelines do not recommend treatment with tricyclic antidepressants but SSRIs can be used to treat behavioral symptoms other than depression when non-pharmacological approaches have failed.[42] The safety profile of antidepressants, however, is under debate. Two observational studies suggest that antidepressants are associated with an increased risk of mortality.[48,49] Future research should address the clinical presentations leading to combination treatment with different psychotropic drug classes, as well as the mechanisms leading to increased mortality.

Identifying patients at high risk

Study IV confirmed an increased mortality risk associated with the initiation of antipsychotic treatment. Further, the presence of comorbidities did not affect the mortality risk. We hypothesized that patients with previous cardiovascular, cerebrovascular, and diabetes diagnoses had a higher mortality risk compared with patients without these comorbidities due to common cardiovascular side effects and adverse events. Few previous studies investigated the effect of comorbidity on risk of mortality and serious adverse events. A meta-analysis suggested that previous cardiovascular disease modified the risk of stroke in patients treated with risperidone.[87] Previous cardiovascular disease has been found not to affect the risk of serious cardiovascular outcomes associated with antipsychotic treatment in an observational study.[100] Methodological issues could explain the varying results. In the latter study, deaths occurring before hospitalization was not included in the analysis, which could bias the results and underestimate the risk associated with antipsychotic treatment.

The 35% increased risk of death among patients treated with antipsychotics is in accordance with other observational studies. The findings regarding comorbidity call for reflection on causal relations, and possible study and data bias. First, there may be other pathways leading to increased mortality among the treated patients than the cardiovascular mechanisms previously proposed.[61–63] Other comorbidities than the ones investigated may show stronger associations with increased mortality risk, e.g., pulmonary disease leading to increased risk of pneumonia and death. In fact, the FDA mentions pneumonia as a leading cause of death during antipsychotic treatment.[25] Investigating pulmonary disease and analyzing cause of death during antipsychotic treatment could be interesting in future studies. Second, our results could reflect that comorbidity status is not associated with an increased risk of death. Dementia and antipsychotic treatment may be more important predictors of mortality, which would reduce the status of cardiovascular comorbidity in the statistical analyses. In other words, all patients with dementia are at increased risk of death during antipsychotic treatment. Third, there is a possibility that under-registration of comorbidities in patients with dementia, that is misclassification, is causing the nondifferential mortality risk between comorbidity strata. This would happen if, e.g., patients with severe cardiovascular disease were not referred for treatment in the secondary health-care sector and therefore included in the stratum without cardiovascular comorbidity. Finally, confounding by indication could be influencing the results. Patients with severe comorbidity may not receive antipsychotic treatment due to

cautious use by clinicians. Qualitative studies of prescription practice could contribute with information about the risk-benefit assessment made by clinicians and point towards future areas to strengthen this practice.

Methodological considerations

In the following, methodological considerations, including strengths and limitations of the four studies, are presented. The aim is to cover some of the key epidemiological concepts of relevance to the study designs, variables, and analyses. Observational studies are conducted in a highly hypothesis-based manner and are based on extensive work conducted prior to the analyses, including taking into account selection bias, confounders, and definition of exposure.

All four studies included a nationwide cohort of patients with dementia. The Danish registries are unique, with complete population data and, in every practical sense, contain complete follow-up. The validity of the dementia diagnosis in the Danish registries has been successfully validated with an accuracy of 86%. However, dementia is underdiagnosed in the registries, an issue that possibly derives from the failure to recognize, or correctly diagnose, dementia, just as it may be due to the fact that some patients with dementia were never referred to secondary health-care for diagnostic evaluation. Numbers from the 2014 Alzheimer Europe Report estimated that around 80,700 people, aged 65 and above, were living with dementia in Denmark in 2012[101] indicating that the Danish registries capture around 43% of dementia cases. The inclusion of patients based on anti-dementia medication only, captured around 11% of our dementia population. As a result, it is only possible for the studies to reflect prescription patterns and the consequences for patients with a registered diagnosis or who underwent anti-dementia treatment. Those who are not captured by the registries may include patients at an early stage who have not yet sought medical evaluation and also patients with late-stage dementia, where a medical evaluation was found to have limited consequences for the patient. It is likely that inclusion of these patients would add a group of patients with few neuropsychiatric symptoms and a group of patients with frequent and complex neuropsychiatric symptoms, thus, affecting the prevalence of psychotropic drug use in opposite directions. In Study III and IV, the risk estimates may be conservative as some patients with severe dementia and psychotropic drug therapy are not included.

Selection bias was eliminated because we were able to include a nationwide dementia cohort. Including data on nursing home residents is of great importance as almost half of the patients with a registered dementia diagnosis were living in a nursing home. These patients have a high prevalence of neuropsychiatric symptoms and a high prevalence of psychotropic drug use. In Study I, some undiagnosed dementia cases were included in the reference population as a relatively small proportion. The validity of registered dementia subtype diagnoses have been found to be low[76] limiting the possibility of investigating treatment patterns and risks across subtypes. Symptoms and management differ, as is seen for Lewy body dementia, where psychosis is prevalent and antipsychotic treatment is poorly tolerated. In Study III and IV, it would have been interesting to test whether treatment and mortality risk differed between diagnostic subgroups.

A confounder is a variable that is unevenly distributed between patient groups (e.g., exposed and unexposed) and associated with both the risk factor and the outcome. Moreover, a confounder is not a step in the causal pathway from exposure to outcome.[102] In Study I, registered diagnoses of somatic comorbidity and psychotic disorders were included as confounders of a possible time trend; that is, comorbidities could be associated with calendar year as well as antipsychotic treatment. This is, however, complex as the practice of registration of comorbid diagnoses may have changed during the study period. Improved treatments and health economic motives are a possible cause for the increasing number of hospital-registered diagnoses. The median Charlson Comorbidity Index score did not increase from 2000 to 2012; however, we did see an increasing number of prescription drugs that was most pronounced for patients with dementia. In Study II, the factors independently associated with the outcome were explored by including confounding factors in the model. However, we did not have data on important factors that could influence the prescribing practices. In a nursing home setting, the staff workload and staff assessment independently determined the use of psychotropics.[103] In Study III and IV, the associations between psychotropic polypharmacy and antipsychotics and risk of death may be influenced by residual confounding. We used time since dementia diagnosis as a proxy for dementia severity because the registry data lack detailed clinical information about disease progression and neuropsychiatric symptoms. Further, we did not have information on indication for treatment, which is one possible way of adding information to the clinical status of patients. Due to the observational study design, we cannot exclude the possibility that some of the association between drug treatment and mortality risk is caused by confounding by indication, which is an important limitation. This would be the case if the observed association

between drug treatment and death is because the indication for drug treatment itself is a cause of the outcome. In other words, patients with severe neuropsychiatric symptoms, who are more likely to be treated with psychotropic drugs, may be at increased risk of death compared with patients with no or few neuropsychiatric symptoms, who are less likely to be treated with psychotropic drugs. We addressed this issue by adjusting for all available important confounders. Another way of addressing confounding by indication would be to use propensity score matching. We cannot dismiss the possibility that some psychotropic drug prescriptions are made as part of an end-of-life treatment. This would increase our mortality risk estimates; however, we did address the issue by excluding injectable drugs, which are most often used in palliative drug regimens. The sensitivity analysis did not alter our results.

The estimation of treatment duration is an important methodological issue. The DDD reflects the use of psychotropic drugs for an adult for the drugs' main indication. Consequently, there may be a discrepancy between standard prescription practices for a patient with schizophrenia and other psychotic disorders and the recommended dose for a patient with dementia. In Study I and II, in addition to presenting treatment duration based on one DDD per day, we used a conservative approach to identify long-term users and to determine the prevalence of polypharmacy. If the actual prescribed dose for patients with dementia is 0.25-0.5 DDD per day, the actual median antipsychotic treatment duration can be as high as 84-168 days in 2012. The appropriateness of these prescription practices must be questioned as guidelines recommend the lowest possible dosage for the shortest possible period of time.[104] In Study II, the analyses were supplemented by sensitivity analyses to evaluate the effect of assessing treatment duration from 0.5 and 0.25 DDD per day. This produced only slightly increase in the number of patients exposed to psychotropic polypharmacy. As the treatment duration is calculated directly from an assumed daily intake, we approached prescription guidelines for patients with dementia by adjusting the DDD for each drug subgroup in Study III and IV. Further, a Finnish study evaluated actual psychotropic drug exposure from prescription data, which also served as a reference for the final decisions. For example, 41% of patients treated with risperidone were actually prescribed 0.5 mg, whereas the DDD for risperidone is set at 5.0 mg.[82] Thus, misclassification of exposure can possibly occur if risperidone exposure were set at one DDD per day, with a shortening of the exposure duration and, consequently, biasing of the risk towards null. Misclassification is always a possibility in pharmacoepidemiology when data is based on prescriptions since there is no information on whether patients comply and consume the

medication. We sought to address this matter by calculating the proportion of patients with antipsychotic use who filled more than one prescription. We found that 86% filled more than one antipsychotic prescription within a year; however, we do not know whether this, for some patients, may reflect discontinuation or switching from one medication to another. In Study II, III and IV the treatment durations were also calculated by adding a grace period to each prescription to avoid censoring due to irregular fillings and missed doses.[83] A misclassification of exposed patients as unexposed patients in Study IV would bias our results towards the null.

Study III and IV investigated the consequences of prescription drug treatment, which is why a new user design was chosen. Patients with prevalent drug use already tolerated the treatment, thus including only incident drug users excluded the possibility of survival bias. This design also prevents bias from variables that were possibly affected by the drug treatment itself, thereby adjusting for a variable on the causal pathway and introducing bias towards null.[81] The mortality outcome in Study III and IV was set at 180 days to make it possible to compare the results with important clinical trial meta-analyses and observational studies. In addition, the hypothesis was that a possible direct medication effect would increase mortality in the relative short term. An important consideration was to censor at the estimated time of discontinuation of treatment in Study III. This was chosen to allow for patients to switch between treatment exposure groups and to introduce an element of self-controlled design;[105] however, this does not exclude the possibility of confounding by indication. In Study IV data was analyzed as intention-to-treat. This method limits the impact of informative censoring because of discontinuation, which can be caused by side effects or a lack of effect from the treatment. If discontinuation is associated with the outcome, censoring may bias the results. On the other hand, in an intention-to-treat analysis the estimates may be conservative due to misclassification of exposure.[106] This analysis made it possible to compare results with meta-analyses and key observational studies.

In Study IV, pre-existing comorbidity was a key object. We used the information available from the registries, that is discharge diagnoses, procedure codes, and antidiabetic medication; however, more detailed information regarding severity may have added to the differentiation of patients into subgroups of comorbidity status. A stratified analysis with a subgroup of patients with severe cardiovascular disease could add information.

Concluding remarks and perspectives

This thesis evaluated the use and consequences of antipsychotics and other psychotropic drugs in a nationwide setting of patients with dementia. The findings suggest that there have been significant changes in the way patients with dementia and neuropsychiatric symptoms are treated since 2000, implying that the potential exists to further reduce the use of antipsychotic drugs. Hence, part of the thesis has contributed to the Danish national dementia strategy, with a national clinical guideline published in 2018 to strengthen appropriate prescribing for patients with dementia.[107] Furthermore, one of three national quality indicators for the dementia strategy is to reduce the use of antipsychotic drugs by 50% by 2025. These initiatives aim at improving dementia care, increasing knowledge in correct use and consequences of antipsychotic treatment, and how to apply alternatives to antipsychotic treatment. In this thesis, we also presented data demonstrating widespread use of psychotropic polypharmacy, and characterized patients treated with antipsychotics in combination with other psychotropic drugs. These findings suggest a need to develop clinical guidelines for concomitant use of psychotropic drugs. Further, we presented evidence to support that combinations of antipsychotics and BZDs increase mortality risk beyond that of antipsychotic treatment alone. Our findings should be tested in other settings; however, we believe that combinations of antipsychotics and benzodiazepines should be used with great caution. As the existing guidelines are restrictive concerning the use of monotherapy, combining these two medications is only appropriate in a few severe cases from a risk-benefit perspective. To identify patients at high risk of mortality, the effect of specific comorbidities was investigated; however, the mortality risk did not differ according to pre-existing comorbidities. On the other hand, this indicates that antipsychotic treatment for dementia patients should be used with caution in all patients regardless of comorbidity status.

There are still many unanswered questions about the neurobiological mechanisms behind neuropsychiatric symptoms in patients with dementia, and these should be further explored to identify new ways of preventing and treating neuropsychiatric symptoms. So far, there is no easy way to manage these symptoms, and pharmacological treatment contains significant risks. Even so, antipsychotic therapy may be the most appropriate method available in severe cases, and few patients need this treatment, including patients with previous psychiatric illness who might still benefit from earlier, and perhaps chronic, psychotropic drug treatment. It is nonetheless important to remember that symptoms such as psychosis and agitation in dementia may originate from other,

and possibly very heterogenous, pathways than in other adult psychiatric populations. In the future, neurogenetics and imaging could lead to individualized treatment strategies when non-pharmacological alternatives have failed.

This thesis brought attention to the management of neuropsychiatric symptoms in patients with dementia. Inappropriate management and prescription practices can have serious negative consequences for patients and caregivers. Thus, future research and health-care planning should continue to focus on ways to improve the lives of patients with dementia and neuropsychiatric symptoms.

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Study manuscripts

Study I

Time Trends in Antipsychotic Drug Use in Patients with Dementia: A Nationwide Study

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Time Trends in Antipsychotic Drug Use in Patients with Dementia: A Nationwide Study

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Abstract.
Background: Antipsychotics are often used to treat neuropsychiatric symptoms in dementia, but the evidence for effect is limited. Antipsychotics have been associated with increased risk of adverse events and mortality in patients with dementia, leading to safety regulations worldwide.
Objective: To investigate time trends in use of antipsychotics and other psychotropic drugs in dementia care.
Methods: The study included longitudinal data on all Danish residents ≥65 years. The study population was defined on January 1 of each year from 2000–2012. Data included prescriptions, discharge diagnoses, and somatic and psychiatric comorbidities. Multivariate time trend analyses of psychotropic drug use in patients with dementia within 4-year age bands were performed.
Results: Overall, among patients with dementia the prevalence of antipsychotic drug use decreased from 31.3% in 2000 to 20.4% in 2012. The decreasing use of antipsychotics was accompanied by decreasing use of anxiolytics and hypnotics/sedatives, but an increase in the use of antidepressants from 43.3% in 2000 to 53.8% in 2012. These changes were significant across almost all age groups. Treatment intensity among patients using antipsychotics increased as the annual median number of defined daily doses (DDD) increased from 33.3 to 42.0 DDD.
Conclusions: The changing patterns of psychotropic drug use may be caused by warnings against use of antipsychotics. Further research is needed to explore the implications for patient safety.

Keywords: Antidepressant drugs, antipsychotic drugs, dementia, neuropsychiatric symptoms, time trend

INTRODUCTION

Neuropsychiatric symptoms are common in patients with dementia and include psychotic, behavioral, and affective symptoms. Up to 90% of the patients will experience one or more of these symptoms during the course of the disease [1]. Neuropsychiatric symptoms and challenging behavior are extremely distressing for patients, family, and professional caregivers and an important predictor of nursing home placement [2]. Antipsychotics are frequently used to treat behavioral symptoms in patients with dementia even though the evidence for effect is limited [3]. While treatment with antipsychotics may be necessary in selected patients, their use, and especially long-term treatment, may be associated with risks of serious adverse events and death [4, 5]. Best practice guidelines recommend non-pharmacological approaches prior to considering treatment of neuropsychiatric symptoms with antipsychotics [6, 7].

In 2005, the U.S. Food and Drug Administration (FDA) issued a warning, based on results from seventeen placebo-controlled trials, stating that the use

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of second-generation antipsychotics in patients with dementia was associated with a 60–70% increased mortality rate. The announcement stressed that antipsychotics were not approved for the treatment of behavioral symptoms in dementia. This was followed by a similar statement in 2008 on first-generation antipsychotics [8], and by a 2009 report from the British Department of Health stating that treating 100 patients with dementia with antipsychotics for one year would result in one death [9]. These warnings have led to safety regulations worldwide, and the Danish Health and Medicines Authority published statements in 2004 and 2008 analogous to the FDA warnings [10, 11].

Our knowledge about the use of psychotropic drugs in routine clinical practice and a possible change in prescription patterns over time is limited. Previous time trend studies in selected populations investigated use of antipsychotics before and after the warnings to evaluate the effect of a specific warning. These studies did not include, however, other confounders, such as somatic and psychiatric comorbidity, that may affect drug use in the population [12–14]. Danish registers provide a unique source for capturing complete data on drug utilization and have the advantage of eliminating selection bias. The primary aim of the present study was to investigate time trends in the use of antipsychotics in dementia care. Our hypothesis was that the prevalence of antipsychotic drug use had decreased from 2000 to 2012 in patients with dementia due to safety regulations and to the ongoing focus on health risks associated with antipsychotics. The secondary aim was to investigate time trends in the use of other psychotropic drugs and anti-dementia drugs to explore whether or not there were any compensatory changes between psychotropic drug classes in patients with dementia.

MATERIALS AND METHODS

Study design

The study was a population-based observational study using data from nationwide Danish registers.

The registers

In Denmark all permanent residents are assigned a personal identification number (CPR number) at time of birth or immigration. This makes it possible to link demographic and medical data from registers at an individual level [15]. The National Patient Registry contains data on all hospital admissions since 1977 and all contacts to outpatient clinics and emergency rooms since 1995 [16]. The Psychiatric Central Registry contains data on all admissions to psychiatric hospitals since April 1, 1969 and all outpatient contacts since 1995 [17]. The diagnoses have been registered from 1970–1993 according to the World Health Organization's (WHO) International Classification of Diseases 8th Revision (ICD-8) and 10th Revision (ICD-10) from 1994 onwards. The Danish National Prescription Registry contains data on all dispensed prescription drugs since 1995. The drugs are registered according to the Anatomical Therapeutic Chemical (ATC) classification system, with information on the date of dispensing, package size, and strength [18].

The study was approved by the Danish Data Protection Agency (ID no.: 2007-58-0015/30-0667), Statistics Denmark, and the Danish Health and Medicines Authority (ID no.: 6-8011-907/1). Danish law did not require ethics committee approval or informed patient consent.

Study population

The population was defined for each year and included all Danish residents aged 65 or older. From January 1, 2000 to December 31, 2012, the annual population was defined at the index date January 1. Thus, an individual could be included at multiple index dates following their sixty-fifth birthday if still alive. Patients with dementia were identified as in and outpatients registered with a dementia diagnosis (Supplementary Table A1 for diagnostic codes) at discharge from a Danish hospital or at an outpatient visit and/or as individuals who had filled at least one prescription for an anti-dementia drug (ATC: N06D). Individuals who had been registered with a dementia diagnosis or filled their first prescription during the 12 months following an index date were not included in the group of patients with dementia until the next index date. Individuals diagnosed or prescribed an anti-dementia drug before age 60 were excluded from the population, because prior research has shown that the validity of dementia diagnoses in this age group is low [19]. The remaining elderly population aged 65 and older without dementia formed the reference population.

Use of psychotropic and anti-dementia drugs

Users of psychotropic drugs were defined as individuals who had filled at least one prescription for a psychotropic drug. Psychotropic drugs were classified according to ATC codes (N05A: antipsychotics;

N05B: anxiolytics; N05C: hypnotics/sedatives; and N06A: antidepressants) [20]. Antipsychotics were categorized as either first-generation (levomepromazine, prochlorperazine, periciazine, haloperidol, melperone, pipamperone, droperidol, chlorprothixene, flupentixol, zuclopenthixol, pimozide, loxapine, and sulpiride) or second-generation drugs (sertindole, ziprasidone, lurasidone, clozapine, olanzapine, quetiapine, asenapine, amisulpride, risperidone, aripiprazole, and paliperidone). Lithium was analyzed separately due to its use as a mood stabilizer. Supplementary Table 2 lists all antipsychotic, anxiolytic, hypnotic/sedative, antidepressant, and anti-dementia drugs available and analyzed. The annual prevalence of patients with dementia and elderly without dementia using psychotropic drugs was calculated according to the population each year.

All drugs are assigned a defined daily dose (DDD) representing the average maintenance dose per day for a drug used for its main indication in adults, defined by WHO. The number of DDDs prescribed within a year was used to evaluate treatment duration. The mean and median DDD for users of antipsychotics among patients with dementia was calculated. As one DDD represents one day of treatment, the number of DDD was used to classify antipsychotic drugs users into two groups comprising short-term (<12 weeks) and long-term (>12 weeks) treatment. Twelve weeks of antipsychotic use was considered long-term treatment, because this duration previously was used to evaluate the efficacy and risks associated with antipsychotics [21].

Comorbidity

We used data from somatic and psychiatric hospital contacts on comorbid conditions that could potentially influence the use of psychotropic drugs. Comorbidity was evaluated at the index date every year. Registered diagnosis codes of 19 chronic somatic diseases constituted the Charlson Comorbidity Index [22]. Psychiatric comorbidity was defined as a registered diagnosis of prior psychotic disorders (one of the following diagnoses: schizophrenia, schizotypal, delusional disorders (ICD-8:295.x9, 296.89, 297.x9, 298.29-298.99, 299.04, 299.05, 299.09, 301.8; ICD-10: F20-29); manic episode and bipolar affective disorder (ICD-8:296.19, 296.39, 298.19; ICD-10: F30-F31)). The total number of different drugs used within one year was used as an indicator of somatic disease not captured by hospital admissions (ATC level 3, e.g., A10A: insulins and analogues) [20].

Statistical analysis

Time trend analysis of prevalent drug use requires independent observations. In order to achieve independency between observations, patients with dementia were divided into age groups at four-year intervals (age 65–68, 69–72, 73–76, 77–80, 81–84, 85–88, 89–92, 93–96, and 97–100). These age groups were used in the trend analysis. Drug use in each age group was compared between 2000, 2004, 2008, and 2012. Thus, an individual could not be represented at more than one point in time in the same age group. Time trend was assessed as the probability of receiving an antipsychotic, first-generation antipsychotic, second-generation antipsychotic, anxiolytic, hypnotic/sedative, and antidepressant in 2000 versus 2004, 2008, and 2012. Logistic regression analyses were performed for all age groups with use of each psychotropic drug class as outcome. We performed a crude analysis with calendar year as the independent variable and evaluated the effect of other covariates independently. Age, gender, psychiatric, and somatic comorbidity were included in the multivariate analysis (adjusted analysis) as potential confounders, because these covariates have been associated with use of antipsychotic and psychotropic drugs in patients with dementia [23, 24]. A p-value of <0.05 was considered statistically significant. During the study period, there were only 114 patients aged $\geq$100; therefore, this age group was not included in the trend analysis.

The data analysis was performed using SAS statistical software, version 9.3 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Study population

Figure 1 shows the selection of the study population aged 65 and older in 2000 and 2012. On January 1, 2000, according to our algorithm, 19, 062 (2.4%) patients with dementia were included, and 780, 852 individuals formed the reference population. On January 1, 2012, the number of patients with dementia had increased to 34,553 (3.5%) and the reference population had grown to 937,537 individuals (Supplementary Figure 1 for data on 2004 and 2008). Data on nursing home placement was available from 2008 and onwards. In 2008, there were 41,234 elderly nursing home residents, 14,632 (35.5%) of whom were patients with dementia. In 2012, out of the 45,584 elderly nursing home residents, 17,080 (37.5%) were patients with

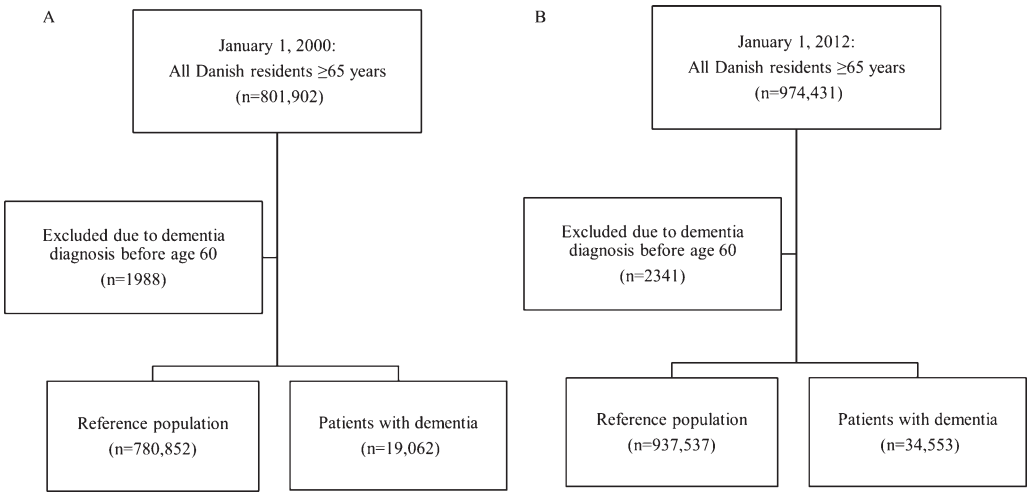

Fig. 1. Study population in 2000 (A) and 2012 (B).

Table 1
Characteristics of the population of patients with dementia and the reference population

Characteristic	2000		2012	
	Patients with dementia (n = 19,062)	Elderly without dementia (n = 780,852)	Patients with dementia (n = 34,553)	Elderly without dementia (n = 937,537)
Age, years	82.2 (77.0–87.1)	74.3 (69.4–80.1)	83.3 (77.6–88.1)	72.7 (68.3–79.1)
Women	12,865 (67.5)	452,822 (58.0)	22,435 (64.9)	512,378 (54.7)
Nursing home resident	NA	NA	17,080 (49.4)	28.504 (3.0)
Total number of drugs used	7.0 (4.0–9.0)	4.0 (2.0–7.0)	9.0 (6.0–12.0)	5.0 (3.0–9.0)
Charlson Comorbidity Index	1.0* (0.0–2.0)	0.0 (0.0–1.0)	1.0* (0.0–2.0)	0.0 (0.0–2.0)
Prior psychotic disorder	1468 (7.7)	11,060 (1.4)	1752 (5.1)	13,545 (1.4)

NA, not available. NOTE. Numbers are given as n (%) and median (25–75% interquartile range) as appropriate. *Index calculated without dementia as one of the comorbidity items.

dementia. Table 1 presents the characteristics of the study populations in 2000 and 2012. The patients with dementia were older and suffered from more comorbidity in 2012 compared to 2000.

Antipsychotic drug use

The annual prevalence of use of first and second-generation antipsychotics and other psychotropic drugs in elderly with dementia and without dementia is displayed in Fig. 2a and b, respectively. From 2000 to 2012 the annual prevalence of overall antipsychotic drug use among patients with dementia decreased from 31.3% to 20.4%. The most noticeable change occurred after 2004. In the reference population, use of antipsychotics decreased from 4.5% in 2000 to 2.8% in 2012. From 2000 to 2004, use of first-generation antipsychotics in patients with dementia decreased from 21.2% to 10.3%, while second-generation antipsychotics increased from 13.4% to 22.0%. From 2004 to 2012, use of both first and second-generation antipsychotics decreased, with first-generation antipsychotics decreasing from 10.3% to 4.5% and second-generation antipsychotics decreasing from 22.0% to 17.3%.

Results from the multivariate trend analysis are presented in Fig. 3 and detailed results can be found in the Supplementary Table 3a–f. From 2000 to 2012, antipsychotic drug use significantly decreased in all age groups, except in the oldest patients aged 97 and older. The largest change was found for patients aged 89–92, who were 50% less likely to receive antipsychotics in 2012 compared to 2000 (adjusted odds ratio (OR) [95% confidence interval (CI)]: 0.50 [0.44–0.56]). The smallest change was in patients between 65–68 years of age, who were 23% less likely to receive an antipsychotic drug in 2012 compared to 2000 (adjusted OR [95% CI]: 0.77 [0.63–0.95]).

Figure 4 shows the treatment duration of antipsychotic treatment in patients with dementia using antipsychotics (excluding lithium). There was a 46.5% increase from 2000 to 2003 (from 33.3 DDD in 2000 to 48.8 DDD in 2003), but from 2003, the median number of DDD per user stabilized at 42.0 DDD in 2012. In 2000, 18.1% of patients with dementia, who used

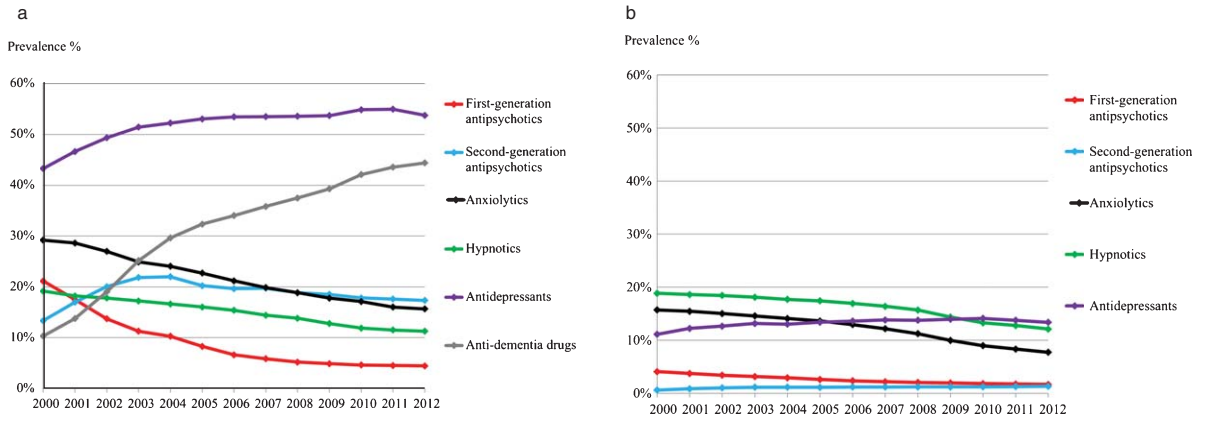

Fig. 2. a. Prevalence of psychotropic drug use in patients with dementia ≥65 years from 2000 to 2012. b. Prevalence of psychotropic drug use in elderly without dementia ≥65 years from 2000 to 2012.

antipsychotics, where long-term users, as they filled prescriptions for more than 84 DDDs (12 weeks). By 2012, long-term use increased to 27.3%.

Use of other psychotropic drug classes

Use of anxiolytics and hypnotics/sedatives almost halved in both groups from 2000 to 2012 (anxiolytics (2000/2012): patients with dementia 29.2%/15.7%, reference population 15.7%/7.7%; hypnotics/sedatives (2000/2012): patients with dementia 19.2%/11.3%, reference population 18.9%/12.1%). The decrease was significant in all age groups in patients with dementia except use of anxiolytic drugs in those ≥97 years of age. The prevalence of antidepressant drug use increased from 43.3% in 2000 to 53.8% in 2012 in patients with dementia, and from 11.1% in 2000 to 13.4% in 2012 in the reference population. Use of antidepressants increased significantly in all age groups, with the largest increase in patients with dementia aged 97–100 (adjusted OR [95% CI]: 2.88 [1.86–4.47]). In 2000, anti-dementia drugs were prescribed for 10.3% of patients with dementia and, 44.4% were in 2012.

The annual prevalence of patients with dementia not using any psychotropic drugs was also calculated. In 2000 29.8% of the patients did not receive any psychotropics, and in 2004 the prevalence was 28.3%. The prevalence of non-users increased to 33.3% in 2012.

DISCUSSION

This study investigated patterns and trends of psychotropic drug use in an entire elderly population for a 13-year period. From 2000 to 2012, the number of users of antipsychotics decreased significantly in patients with dementia to 20.4%, which is a much higher level compared to 2.8% in elderly without dementia. Even more noticeably, treatment intensity increased among patients with dementia using antipsychotics. The decreasing prevalence of use of antipsychotics in patients with dementia was accompanied by a decrease in use of anxiolytics and hypnotics, but an increase in the use of antidepressants and anti-dementia drugs.

Previous studies have reported decreasing use of antipsychotics, but aimed specifically at evaluating the impact of a particular safety warning [12–14, 25, 26] rather than investigating their use over time in dementia care. Studies from France and Scotland that investigated time periods similar to the ones in our study found decreasing use of antipsychotics [13, 14]. However, the authors analyzed the data using a segmented regression analysis design, which did not allow adjustment for variables that might change over time [27]. Furthermore, these studies included selected populations and therefore have limited generalizability. In contrast to our study, an Italian study found that use of antipsychotics increased from 2002 to 2008 [25] in a selected population of users of anti-dementia drugs. Information about other patients diagnosed with dementia who did not receive anti-dementia treatment was missing, which limits the study's generalizability to all patients with dementia. In a study from Germany the authors adjusted for variables that changed over time and found a small, but not significant decrease in the prevalence of antipsychotic drug use [28]. The study consisted of a series of cross-sectional studies of all patients with dementia every year, which created statistical issues as some of the observations were not independent.

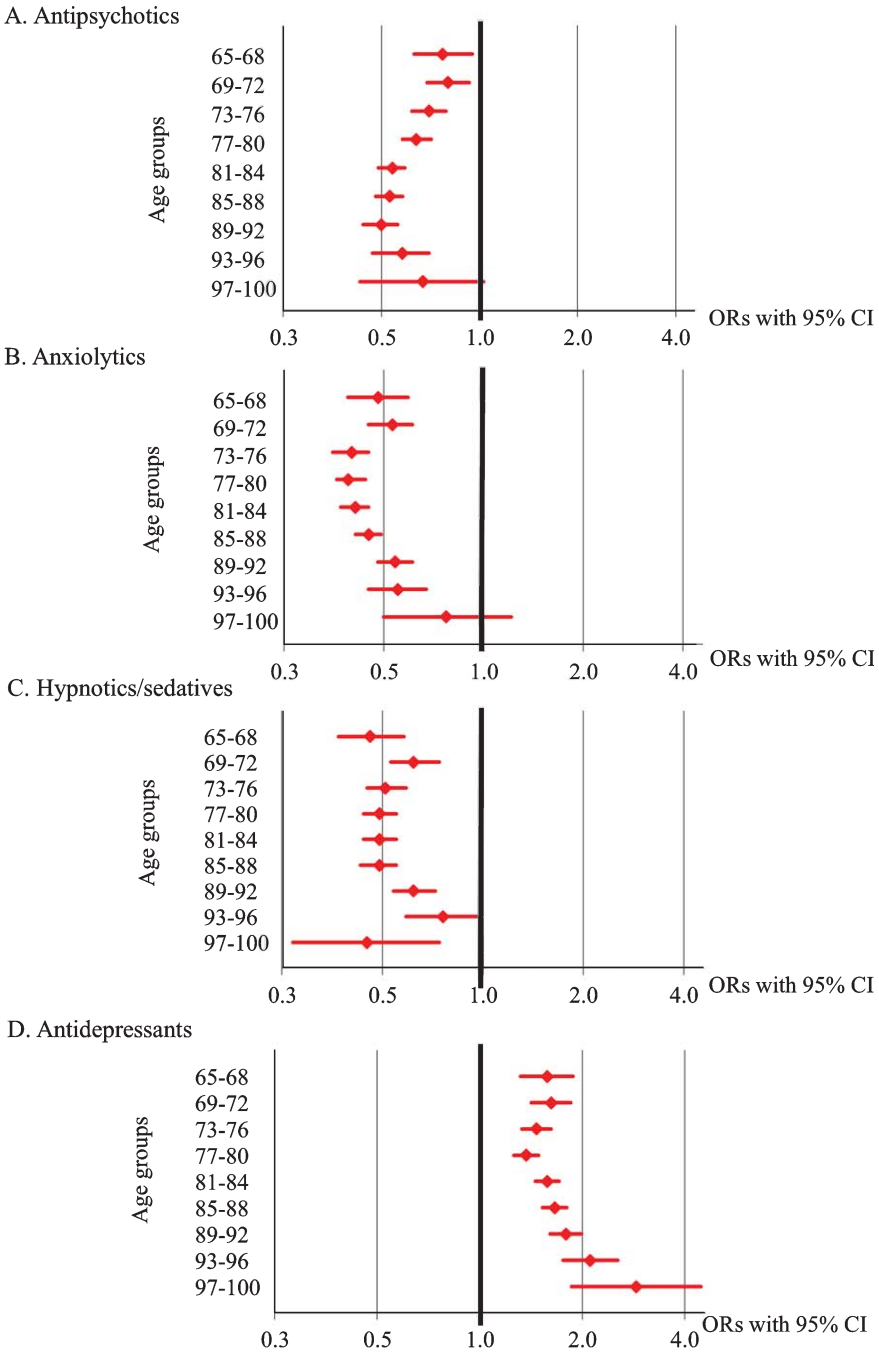

Fig. 3. Time trends in psychotropic drug use in patients with dementia. The figure shows the results of logistic regression analyses comparing use of psychotropic drug classes (A: antipsychotic drugs, B: anxiolytic drugs, C: hypnotic/sedative drugs, D: antidepressant drugs) in patients with dementia in four-year age groups in 2012 versus 2000 (reference), displaying adjusted odds ratios (ORs) and 95% confidence intervals (CI). The adjusted ORs include adjustment for age, gender, prior psychotic disorder, and comorbidity.

Two studies investigating antipsychotic drug use at the time of dementia diagnosis have yielded varying results. A recent study from the UK found decreasing use from 1995 to 2011 of antipsychotics at the day of the first record of a dementia diagnosis and increasing use of antidepressants [29]. A Finnish study of community-dwelling persons reported that from 2005 to 2011 antipsychotic drug use within the first year of

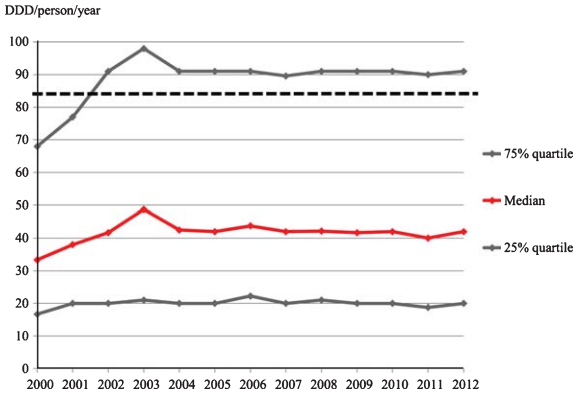

Fig. 4. Treatment duration of antipsychotic drug use. Defined daily doses (DDD) of antipsychotics prescribed for users of antipsychotics among patients with dementia from 2000 to 2012. The red line indicates median value and the grey lines indicate 25% and 75% quartiles, respectively. The dotted line marks 84 DDD (12-week) treatment duration.

a dementia diagnosis increased [30]. However, both studies focused on treatment of prodromal symptoms of dementia and early, possibly more moderate, neuropsychiatric symptoms, whereas our study focused on treatment of neuropsychiatric symptoms at all stages of dementia.

Although we found the percentage of users of antipsychotics to decrease, the treatment intensity increased. In accordance with our study, other studies also found a stable or an increasing volume of antipsychotics prescribed for patients with dementia [13, 28]. These findings could indicate that the decreasing number of patients with dementia using antipsychotics primarily represents a decrease in sporadic or short-term users, an assumption which is supported by an increasing number of long-term users. Current Danish guidelines on antipsychotic drug use stress that antipsychotic treatment in patients with dementia should be prescribed at the lowest possible dosage for the shortest possible period of time [31]. Furthermore, it is recommended that long-term treatment (>12 weeks) is used only in cases of severe neuropsychiatric symptoms after trying non-pharmacological approaches as well as pharmacological alternatives, such as anti-dementia or antidepressants [32]. NHS guidelines also specify the importance of using short-term treatment <12 weeks [7].

Although this study was done in the Danish population, we believe that the implications of our results can be interpreted in the international context. The decreasing use of antipsychotics in Denmark and internationally is most likely the result of public debate and warnings against their use in patients with dementia. Furthermore, the downward trend may have been influenced by emerging studies concluding that the efficacy of antipsychotics is limited and that adverse events often exceed their benefits [33].

The increasing use of antidepressants in our study can be seen in the light of increasing awareness of the risks associated with antipsychotics, which might have created a need for other treatment options for patients with challenging behavior. Only few other studies have investigated potential compensatory changes in the use of other psychotropic drug classes in the light of changing prescription patterns for antipsychotics [14, 34]. In Scotland, use of antidepressants in patients with dementia doubled from 2001 to 2011 [14], but with no evidence of substitution at the time of the warnings. In the US, Kales et al. found no major compensatory changes in any individual psychotropic drug class during the warning period, but changes appeared to be spread over several drug classes [34], and the prevalence of patients not using any psychotropic drugs was constant. In our study the prevalence of non-users increased slightly from 2004 and 2012.

Overall, use of anti-dementia drugs increased from 2000 to 2012. Evidence for the efficacy of anti-dementia drugs in the treatment of neuropsychiatric symptoms is subtle [35], but Danish guidelines recommend trying treatment with anti-dementia drugs in patients with neuropsychiatric symptoms [32]. Thus, an alternative explanation may be that anti-dementia drugs have replaced antipsychotics to some degree. The significant increase in the use of antidepressants could represent a change in the way patients with dementia are treated and suggests that antipsychotics have not merely been replaced by non-pharmacological alternatives. Although the evidence for an effect of antidepressants on depression in patients with dementia is limited [36], there is some evidence that antidepressants can reduce agitation and aggressive behavior [37, 38]. One may speculate that antidepressants are more frequently used for behavioral symptoms like agitation, which raises other concerns regarding the tolerability and risk of adverse events [39]. We do not know whether changes in prescription patterns have had an effect on mortality among patients with dementia and it is also currently unknown whether there has been an effect on the quality of life of the patients.

The major strength of this study is the use of nationwide registers, which captures an entire population, thereby avoiding selection bias. A unique feature is the detailed information on drug utilization in specific age groups. We were able to include prescription data for

nursing home residents, which is of great importance when investigating drug use in patients with dementia. Almost half of the patients with a registered dementia diagnosis were nursing home residents and these patients have a high prevalence of neuropsychiatric symptoms. Furthermore, the Danish registers provide data to investigate the effect of important confounders of a time trend, such as comorbidity and prior psychotic disorder. The validity of dementia diagnoses in the Danish registers has previously been shown to be high [40]. Dementia, however, is underdiagnosed, and some patients with undiagnosed or untreated dementia will have been included in our reference population. In a previous report, we found that in 2003 only 42–78% of dementia cases were registered with a diagnosis in the Danish hospital registers [41]. In addition, in the current study we included patients treated with anti-dementia drugs without a registered dementia diagnosis accounting for 11.7% of patients with dementia in 2012. Our study had further limitations, as some potential confounders were not available for the analysis, i.e., the prevalence of neuropsychiatric symptoms, level of staffing in nursing home and setting (general practice, specialized dementia or psychiatric clinic). Prescription data provides valid information about all redeemed prescriptions, but we did not have information about indications, and we do not know whether patients actually consumed the drugs they purchased. However, 85–86% of patients with dementia using antipsychotics redeemed more than one prescription, which suggests that a high number of the patients consume the prescribed medication.

The number of DDD prescribed was used to evaluate the appropriateness of antipsychotic drug use. We investigated this under the assumption of intake of one DDD per day. In the elderly and especially patients with dementia, prescribing a lower dose of antipsychotics than the standard recommendation is generally advised. Consequently, our results possibly reflect a conservative estimate of the treatment duration. We did not investigate whether users of antipsychotics received several short-term regimens or continuous prescriptions, but in the light of the risk of adverse events, the patients were exposed to a high number of doses either way.

CONCLUSIONS

This study of the entire elderly population of Denmark found a decreasing prevalence of antipsychotic drug users among patients with dementia. There was, however, evidence that many patients continued to be exposed to large amounts of the medication, which is of concern. The observed increasing use of antidepressants may also be a cause of concern, and the fact that more than 50% of all patients with dementia were prescribed antidepressants calls for further investigation. We can only speculate that antidepressants may have replaced some of the prescriptions for antipsychotics, and further research is needed to explore this. The changing patterns of drug use in dementia may be caused by the limited evidence for efficacy of antipsychotics and warnings issued by the authorities.

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Authors' disclosures available online (http://j-alz.com/manuscript-disclosures/15-0481r1).

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: http://dx.doi.org/10.3233/JAD-150481.

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Study I

Time Trends in Antipsychotic Drug Use in Patients with Dementia: A Nationwide Study

Supplementary Material

Supplementary Material

Supplementary Table 1.Diagnoses used for identification of patients with dementia

	ICD-8	ICD-10
Alzheimer's disease	290.10	F00.0, F00.1, F00.2, F00.9, G30.0, G30.1, G30.8, G30.9
Vascular dementia	293.09-19	F01.0, F01.1, F01.2, F01.3, F01.8, F01.9
Frontotemporal dementia	290.11	F02.0
Other dementias	-	G31.8
Dementia without specification	290.09-19	F03, G31.9

ICD, International Classification of Diseases

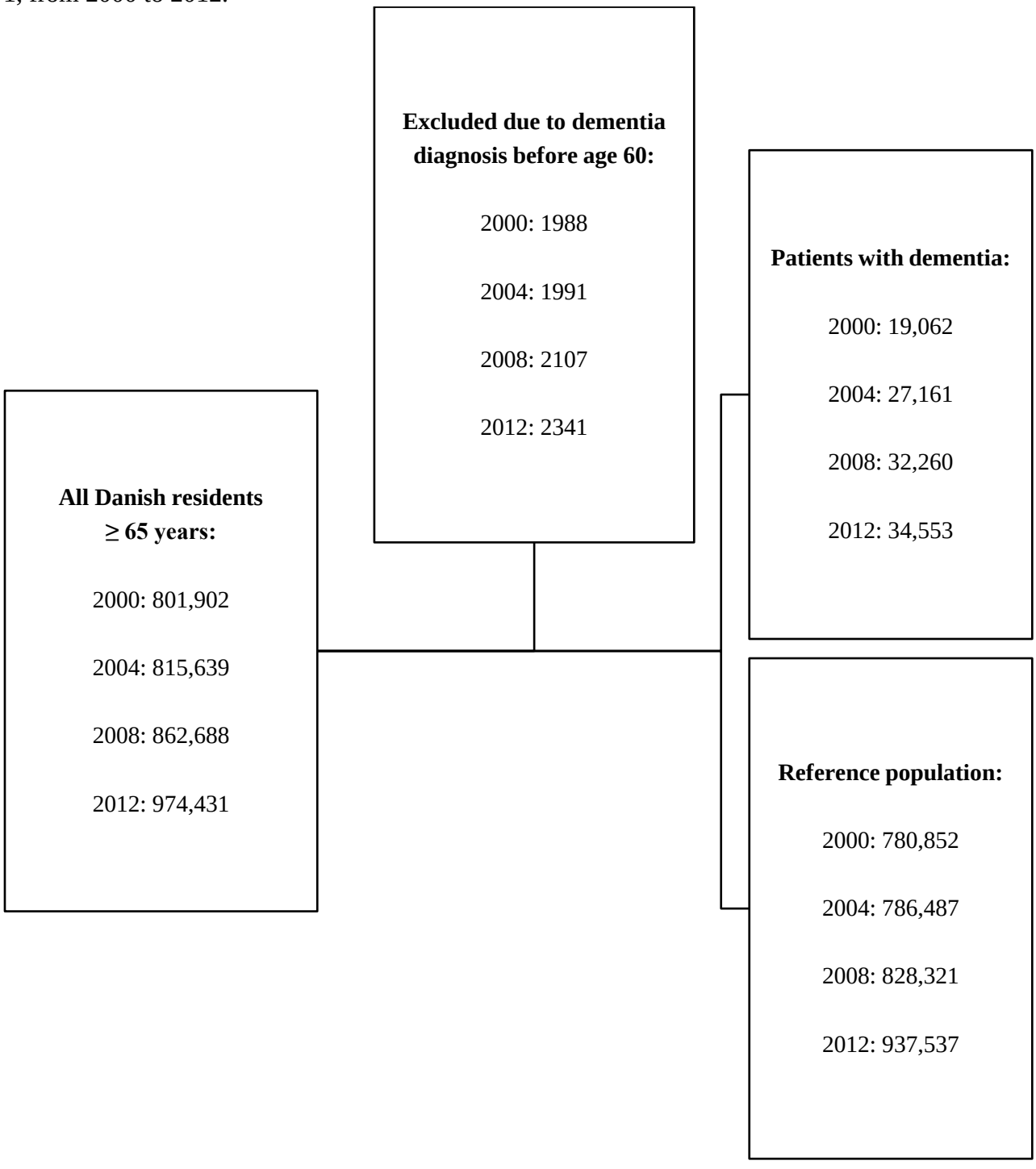
Supplementary Table 2. ATC codes of psychotropic drugs and anti-dementia drugs

N05A Antipsychotics	
N05AA Phenothiazines with aliphatic side-chain	N05AA02 Levomepromazine
N05AB Phenothiazines with piperazine structure	N05AB04 Prochlorperazine
N05AC Phenothiazines with piperidine structure	N05AC01 Periciazine
N05AD Butyrophenone derivatives	N05AD01 Haloperidol
	N05AD03 Melperone
	N05AD05 Pipamperone
	N05AD08 Droperidole
N05AE Indole derivatives	N05AE03 Sertindole
	N05AE04 Ziprasidone
N05AF Thioxanthene derivative	N05AF01 Flupentixol
	N05AF03 Chlorprothixene
	N05AF05 Zuclopenthixol
N05AG Diphenylbutylpiperidine derivatives	N05AG02 Pimozide
N05AH Diazepines, oxazepines, thiazepines and oxepines	N05AH01 Loxapine
	N05AH02 Clozapine
	N05AH03 Olanzapine
	N05AH04 Quetiapine
	N05AH05 Asenapin
N05AL Benzamides	N05AL01 Sulpiride
	N05AL05 Amisulpride
N05AXOther antipsychotics	N05AX08 Risperidone
	N05AX13 Aripiprazole
	N05AX13 Paliperidone
N05B Anxiolytics	
N05BA Benzodiazepine derivatives	N05BA01 Diazepam
	N05BA02 Chlordiazepoxide
	N05BA04 Oxazepam
	N05BA06 Lorazepam
	N05BA08 Bromazepam
	N05BA09 Clobazam
	N05BA12 Alprazolam
N05BB Diphenylmethane derivatives	N05BB01 Hydroxyzine
N05BE Azaspirodecanedione derivatives	N05BE01 Buspirone
N05C Hypnotics and sedatives	
N05CDBenzodiazepine derivatives	N05CD02 Nitrazepam
	N05CD05 Triazolam
	N05CD06 Lormetazepam
N05CF Benzodiazepine related drugs	N05CF01 Zopiclone
	N05CF02 Zolpidem
	N05CF03 Zaleplon
N05CH Melatonin receptor agonists	N05CH01 Melatonin
N06A Antidepressants	
N06AA Tricyclic antidepressants	N06AA02 Imipramin
	N06AA04 Clomipramine

	N06AA09 Amitriptylin
	N06AA10 Nortriptyline
	N06AA12 Doxepin
	N06AA16 Dosulepin
	N06AA21 Maprotiline
N06AB Selective serotonin reuptake inhibitors	N06AB03 Fluoxetine
	N06AB04 Citalopram
	N06AB05 Paroxetine
	N06AB06 Sertraline
	N06AB08 Fluvoxamine
	N06AB10 Escitalopram
N06AF Monoamine oxidase inhibitors, non-selective	N06AF01 Isocarboxazid
N06AG Monoamine oxidase A inhibitors, selective	N06AG02 Moclobemid
N06AX Other antidepressants	N06AX03 Mianserin
	N06AX11 Mirtazapine
	N06AX12 Bupropion
	N06AX16 Venlafaxine
	N06AX18 Reboxetine
	N06AX21 Duloxetine
	N06AX22 Agomelatine
N06D Anti-dementia drugs	
N06DA Anticholinesterases	N06DA02 Donepezil
	N06DA03 Rivastigmine
	N06DA04 Galantamine
N06DX Other anti-dementia drugs	N06DX01 Memantine

ATC, Anatomical Therapeutic Chemical

Supplementary Figure 1. Population of patients with dementia and reference population on January 1, from 2000 to 2012.



Supplementary Table 3a.Time trend analysis for antipsychotic drugs. Logistic regression analysis comparing use of antipsychotic drugs in patients with dementia in four-year age groups in 2004, 2008, and 2012 versus 2000 (reference), displaying age and gender-adjusted odds ratios (ORs) and age, gender, and comorbidity-adjusted ORs and 95% confidence intervals (CI).

Age groups	**Antipsychotic drugs OR (95% CI) (adjusted for age and gender)**	**Antipsychotic drugs OR (95% CI) (adjusted for age, gender, comorbidity, psychosis)**
65-68 years n=4,528	2000: 1.0 2004: 1.02 (0.83-1.25) 2008: 0.82 (0.67-1.01) 2012: **0.77*** (0.63-0.93)	2000: 1.0 2004: 1.09 (0.88-1.34) 2008: 0.87 (0.71-1.08) 2012: **0.77*** (0.63-0.95)
69-72 years n=7,969	2000: 1.0 2004: 0.93 (0.80-1.08) 2008: **0.77*** (0.66-0.89) 2012: **0.73*** (0.63-0.85)	2000: 1.0 2004: 0.97 (0.82-1.13) 2008: **0.82*** (0.71-0.96) 2012: **0.80*** (0.69-0.93)
73-76 years n=13,212	2000: 1.0 2004: 0.94 (0.84-1.05) 2008: **0.73*** (0.65-0.82) 2012: **0.67*** (0.59-0.74)	2000: 1.0 2004: 0.97 (0.86-1.09) 2008: **0.76*** (0.67-0.86) 2012: **0.70*** (0.62-0.79)
77-80 years n=19,659	2000: 1.0 2004: **0.88*** (0.80-0.97) 2008: **0.69*** (0.63-0.76) 2012: **0.60*** (0.54-0.66)	2000: 1.0 2004: **0.91*** (0.83-0.99) 2008: **0.72*** (0.66-0.80) 2012: **0.64*** (0.58-0.71)
81-84 years n=23,797	2000: 1.0 2004: **0.88*** (0.81-0.96) 2008: **0.62*** (0.56-0.67) 2012: **0.51*** (0.47-0.56)	2000: 1.0 2004: **0.90*** (0.83-0.99) 2008: **0.63*** (0.58-0.70) 2012: **0.54*** (0.49-0.59)
85-88 years n=22,764	2000: 1.0 2004: **0.88*** (0.81-0.97) 2008: **0.58*** (0.53-0.64) 2012: **0.50*** (0.46-0.55)	2000: 1.0 2004: 0.92 (0.84-1.01) 2008: **0.61*** (0.56-0.67) 2012: **0.53*** (0.48-0.58)
89-92 years n=14,276	2000: 1.0 2004: **0.89*** (0.79-0.99) 2008: **0.54*** (0.48-0.60) 2012: **0.48*** (0.43-0.54)	2000: 1.0 2004: 0.91 (0.81-1.02) 2008: **0.56*** (0.49-0.63) 2012: **0.50*** (0.44-0.56)
93-96 years n=5,536	2000: 1.0 2004: 1.08 (0.89-1.32) 2008: **0.67*** (0.55-0.82) 2012: **0.54*** (0.44-0.66)	2000: 1.0 2004: 1.15 (0.93-1.40) 2008: **0.72*** (0.59-0.88) 2012: **0.58*** (0.47-0.70)
97-100 years n=1,181	2000: 1.0 2004: 0.89 (0.56-1.41) 2008: 0.70 (0.45-1.09) 2012: 0.67 (0.44-1.02)	2000: 1.0 2004: 0.94 (0.59-1.49) 2008: 0.70 (0.45-1.10) 2012: 0.67 (0.43-1.03)

* $p<0.05$

Supplementary Table 3b.Time trend analysis for first-generation antipsychotic drugs. Logistic regression analysis comparing use of first-generation antipsychotic drugs in patients with dementia in four-year age groups in 2004, 2008, and 2012 versus 2000 (reference), displaying age and gender-adjusted odds ratios (ORs) and age, gender, and comorbidity-adjusted ORs and 95% confidence intervals (CI).

Age groups	**First generation antipsychotic drugs** **OR (95% CI)** **(adjusted for age and gender)**	**First generation antipsychotic drugs** **OR (95% CI)** **(adjusted for age, gender, comorbidity, psychosis)**
65-68 years **n=4,528**	2000: 1.0 2004: **0.56*** (0.44-0.73) 2008: **0.31*** (0.23-0.41) 2012: **0.24*** (0.18-0.32)	2000: 1.0 2004: **0.57*** (0.44-0.74) 2008: **0.30*** (0.23-0.40) 2012: **0.22*** (0.17-0.30)
69-72 years **n=7,969**	2000: 1.0 2004: **0.49*** (0.40-0.59) 2008: **0.24*** (0.20-0.30) 2012: **0.22*** (0.17-0.27)	2000: 1.0 2004: **0.48*** (0.39-0.59) 2008: **0.24*** (0.19-0.31) 2012: **0.22*** (0.18-0.28)
73-76 years **n=13,212**	2000: 1.0 2004: **0.48*** (0.41-0.56) 2008: **0.25*** (0.21-0.30) 2012: **0.22*** (0.19-0.27)	2000: 1.0 2004: **0.48*** (0.41-0.56) 2008: **0.25*** (0.21-0.30) 2012: **0.22*** (0.19-0.27)
77-80 years **n=19,659**	2000: 1.0 2004: **0.44*** (0.39-0.50) 2008: **0.23*** (0.20-0.26) 2012: **0.18*** (0.16-0.21)	2000: 1.0 2004: **0.44*** (0.39-0.50) 2008: **0.23*** (0.20-0.27) 2012: **0.19*** (0.16-0.22)
81-84 years **n=23,797**	2000: 1.0 2004: **0.41*** (0.36-0.46) 2008: **0.18*** (0.16-0.21) 2012: **0.14*** (0.12-0.16)	2000: 1.0 2004: **0.41*** (0.37-0.46) 2008: **0.18*** (0.16-0.21) 2012: **0.14*** (0.12-0.16)
85-88 years **n=22,764**	2000: 1.0 2004: **0.39*** (0.35-0.44) 2008: **0.19*** (0.17-0.22) 2012: **0.16*** (0.14-0.18)	2000: 1.0 2004: **0.40*** (0.35-0.45) 2008: **0.20*** (0.17-0.23) 2012: **0.16*** (0.14-0.18)
89-92 years **n=14,276**	2000: 1.0 2004: **0.36*** (0.31-0.42) 2008: **0.14*** (0.12-0.17) 2012: **0.16*** (0.13-0.19)	2000: 1.0 2004: **0.36*** (0.31-0.42) 2008: **0.15*** (0.12-0.18) 2012: **0.16*** (0.14-0.19)
93-96 years **n=5,536**	2000: 1.0 2004: **0.47*** (0.37-0.61) 2008: **0.20*** (0.15-0.26) 2012: **0.17*** (0.13-0.22)	2000: 1.0 2004: **0.48*** (0.37-0.62) 2008: **0.20*** (0.15-0.26) 2012: **0.17*** (0.13-0.22)
97-100 years **n=1,181**	2000: 1.0 2004: **0.52*** (0.30-0.90) 2008: **0.21*** (0.12-0.39) 2012: **0.12*** (0.06-0.22)	2000: 1.0 2004: **0.54*** (0.31-0.93) 2008: **0.22*** (0.12-0.39) 2012: **0.12*** (0.06-0.23)

* $p<0.05$

Supplementary Table 3c.Time trend analysis for second-generation antipsychotic drugs. Logistic regression analysis comparing use of second-generation antipsychotic drugs in patients with dementia in four-year age groups in 2004, 2008, and 2012 versus 2000 (reference), displaying age and gender-adjusted odds ratios (ORs) and age, gender, and comorbidity-adjusted ORs and 95% confidence intervals (CI).

Age groups	**Second generation antipsychotic drugs OR (95% CI) (adjusted for age and gender)**	**Second generation antipsychotic drugs OR (95% CI) (adjusted for age, gender, comorbidity, psychosis)**
65-68 years n=4,528	2000: 1.0 2004: **1.79*** (1.39-2.29) 2008: **1.59*** (1.25-2.04) 2012: **1.64*** (1.29-2.08)	2000: 1.0 2004: **1.96*** (1.51-2.53) 2008: **1.76*** (1.37-2.27) 2012: **1.77*** (1.38-2.26)
69-72 years n=7,969	2000: 1.0 2004: **1.67*** (1.39-2.00) 2008: **1.62*** (1.35-1.93) 2012: **1.61*** (1.35-1.91)	2000: 1.0 2004: **1.79*** (1.48-2.17) 2008: **1.82*** (1.52-2.19) 2012: **1.85*** (1.54-2.22)
73-76 years n=13,212	2000: 1.0 2004: **1.72*** (1.50-1.97) 2008: **1.51*** (1.32-1.73) 2012: **1.41*** (1.23-1.62)	2000: 1.0 2004: **1.84*** (1.60-2.11) 2008: **1.64*** (1.42-1.89) 2012: **1.56*** (1.35-1.79)
77-80 years n=19,659	2000: 1.0 2004: **1.64*** (1.47-1.84) 2008: **1.46*** (1.30-1.63) 2012: **1.30*** (1.16-1.46)	2000: 1.0 2004: **1.75*** (1.56-1.96) 2008: **1.60*** (1.42-1.79) 2012: **1.45*** (1.29-1.63)
81-84 years n=23,797	2000: 1.0 2004: **1.72*** (1.54-1.92) 2008: **1.43*** (1.28-1.59) 2012: **1.24*** (1.11-1.39)	2000: 1.0 2004: **1.82*** (1.62-2.04) 2008: **1.53*** (1.37-1.72) 2012: **1.36*** (1.22-1.53)
85-88 years n=22,764	2000: 1.0 2004: **1.95*** (1.73-2.19) 2008: **1.50*** (1.33-1.68) 2012: **1.32*** (1.18-1.49)	2000: 1.0 2004: **2.10*** (1.86-2.36) 2008: **1.63*** (1.45-1.83) 2012: **1.45*** (1.29-1.63)
89-92 years n=14,276	2000: 1.0 2004: **2.32*** (2.00-2.71) 2008: **1.61*** (1.38-1.88) 2012: **1.42*** (1.22-1.66)	2000: 1.0 2004: **2.46*** (2.10-2.88) 2008: **1.74*** (1.49-2.04) 2012: **1.54*** (1.32-1.81)
93-96 years n=5,536	2000: 1.0 2004: **2.75*** (2.07-3.64) 2008: **2.06*** (1.56-2.72) 2012: **1.71*** (1.22-1.66)	2000: 1.0 2004: **3.00*** (2.25-4.00) 2008: **2.33*** (1.76-3.08) 2012: **1.93*** (1.45-2.55)
97-100 years n=1,181	2000: 1.0 2004: **2.17*** (1.07-4.42) 2008: **2.64*** (1.35-5.17) 2012: **2.82*** (1.46-5.45)	2000: 1.0 2004: **2.32*** (1.13-4.74) 2008: **2.69*** (1.36-5.29) 2012: **2.84*** (1.46-5.53)

* $p<0.05$

Supplementary Table 3d.Time trend analysis for anxiolytic drugs. Logistic regression analysis comparing use of anxiolytic drugs in patients with dementia in four-year age groups in 2004, 2008, and 2012 versus 2000 (reference), displaying age and gender-adjusted odds ratios (ORs) and age, gender, and comorbidity-adjusted ORs and 95% confidence intervals (CI).

Age groups	**Anxiolytic drugs** **OR (95% CI)** **(adjusted for age and gender)**	**Anxiolytic drugs** **OR (95% CI)** **(adjusted for age, gender, comorbidity, psychosis)**
65-68 years **n=4,528**	2000: 1.0 2004: 0.87 (0.71-1.07) 2008: **0.59*** (0.48-0.72) 2012: **0.50*** (0.41-0.61)	2000: 1.0 2004: 0.87 (0.71-1.07) 2008: **0.58*** (0.47-0.72) 2012: **0.48*** (0.39-0.59)
69-72 years **n=7,969**	2000: 1.0 2004: **0.82*** (0.70-0.96) 2008: **0.63*** (0.54-0.74) 2012: **0.52*** (0.45-0.61)	2000: 1.0 2004: **0.82*** (0.70-0.96) 2008: **0.64*** (0.55-0.74) 2012: **0.53*** (0.45-0.61)
73-76 years **n=13,212**	2000: 1.0 2004: **0.75*** (0.67-0.84) 2008: **0.52*** (0.46-0.58) 2012: **0.40*** (0.35-0.45)	2000: 1.0 2004: **0.75*** (0.67-0.84) 2008: **0.51*** (0.46-0.58) 2012: **0.40*** (0.35-0.45)
77-80 years **n=19,659**	2000: 1.0 2004: **0.75*** (0.68-0.83) 2008: **0.52*** (0.47-0.57) 2012: **0.39*** (0.35-0.43)	2000: 1.0 2004: **0.76*** (0.69-0.83) 2008: **0.52*** (0.47-0.58) 2012: **0.39*** (0.36-0.44)
81-84 years **n=23,797**	2000: 1.0 2004: **0.74*** (0.68-0.81) 2008: **0.53*** (0.49-0.59) 2012: **0.41*** (0.37-0.45)	2000: 1.0 2004: **0.74*** (0.68-0.81) 2008: **0.53*** (0.48-0.58) 2012: **0.41*** (0.37-0.45)
85-88 years **n=22,764**	2000: 1.0 2004: **0.79*** (0.72-0.87) 2008: **0.58*** (0.53-0.64) 2012: **0.45*** (0.41-0.50)	2000: 1.0 2004: **0.79*** (0.72-0.87) 2008: **0.58*** (0.53-0.64) 2012: **0.45*** (0.41-0.49)
89-92 years **n=14,276**	2000: 1.0 2004: **0.74*** (0.66-0.84) 2008: **0.62*** (0.55-0.69) 2012: **0.54*** (0.48-0.62)	2000: 1.0 2004: **0.74*** (0.66-0.84) 2008: **0.61*** (0.54-0.69) 2012: **0.54*** (0.48-0.61)
93-96 years **n=5,536**	2000: 1.0 2004: 0.85 (0.69-1.05) 2008: **0.65*** (0.53-0.79) 2012: **0.56*** (0.46-0.68)	2000: 1.0 2004: 0.86 (0.70-1.05) 2008: **0.64*** (0.53-0.79) 2012: **0.55*** (0.45-0.67)
97-100 years **n=1,181**	2000: 1.0 2004: 0.93 (0.57-1.51) 2008: 0.90 (0.57-1.42) 2012: 0.76 (0.49-1.19)	2000: 1.0 2004: 0.93 (0.58-1.51) 2008: 0.91 (0.58-1.43) 2012: 0.77 (0.50-1.21)

* $p<0.05$

Supplementary Table 3e.Time trend analysis for hypnotic/sedative drugs. Logistic regression analysis comparing use of hypnotic/sedative drugs in patients with dementia in four-year age groups in 2004, 2008, and 2012 versus 2000 (reference), displaying age and gender-adjusted odds ratios (ORs) and age, gender, and comorbidity-adjusted ORs and 95% confidence intervals (CI).

Age groups	**Hypnotic/sedative drugs OR (adjusted for age and gender)**	**Hypnotic/sedative drugs OR (adjusted for age, gender, comorbidity, psychosis)**
65-68 years n=4,528	2000: 1.0 2004: **0.72*** (0.57-0.90) 2008: **0.61*** (0.49-0.77) 2012: **0.49*** (0.39-0.61)	2000: 1.0 2004: **0.72*** (0.57-0.90) 2008: **0.61*** (0.48-0.76) 2012: **0.46*** (0.37-0.58)
69-72 years n=7,969	2000: 1.0 2004: 0.84 (0.71-1.01) 2008: **0.76*** (0.64-0.90) 2012: **0.64*** (0.54-0.76)	2000: 1.0 2004: **0.84*** (0.70-0.99) 2008: **0.75*** (0.63-0.89) 2012: **0.62*** (0.53-0.74)
73-76 years n=13,212	2000: 1.0 2004: **0.78*** (0.69-0.89) 2008: **0.60*** (0.52-0.68) 2012: **0.52*** (0.46-0.60)	2000: 1.0 2004: **0.78*** (0.69-0.89) 2008: **0.59*** (0.51-0.67) 2012: **0.51*** (0.45-0.59)
77-80 years n=19,659	2000: 1.0 2004: **0.86*** (0.77-0.96) 2008: **0.65*** (0.58-0.73) 2012: **0.50*** (0.44-0.56)	2000: 1.0 2004: **0.86*** (0.77-0.96) 2008: **0.64*** (0.58-0.72) 2012: **0.49*** (0.44-0.55)
81-84 years n=23,797	2000: 1.0 2004: 0.92 (0.83-1.03) 2008: **0.70*** (0.63-0.78) 2012: **0.51*** (0.45-0.57)	2000: 1.0 2004: 0.92 (0.83-1.02) 2008:**0.69*** (0.62-0.77) 2012: **0.49*** (0.44-0.55)
85-88 years n=22,764	2000: 1.0 2004: **0.83*** (0.75-0.93) 2008: **0.70*** (0.63-0.78) 2012: **0.51*** (0.46-0.57)	2000: 1.0 2004: **0.82*** (0.73-0.92) 2008: **0.68*** (0.61-0.76) 2012: **0.49*** (0.43-0.55)
89-92 years n=14,276	2000: 1.0 2004: **0.83*** (0.72-0.97) 2008: **0.74*** (0.64-0.85) 2012: **0.65*** (0.56-0.75)	2000: 1.0 2004: **0.82*** (0.71-0.95) 2008: **0.72*** (0.62-0.83) 2012: **0.62*** (0.54-0.72)
93-96 years n=5,536	2000: 1.0 2004: 1.05 (0.81-1.37) 2008: 0.88 (0.68-1.14) 2012: 0.80 (0.62-1.03)	2000: 1.0 2004: 1.04 (0.80-1.36) 2008: 0.85 (0.66-1.11) 2012: **0.76*** (0.59-0.99)
97-100 years n=1,181	2000: 1.0 2004: **0.53*** (0.31-0.92) 2008: **0.53*** (0.32-0.87) 2012: **0.48*** (0.30-0.79)	2000: 1.0 2004: **0.53*** (0.30-0.93) 2008: **0.52*** (0.31-0.86) 2012: **0.45*** (0.27-0.74)

* $p<0.05$

Supplementary Table 3f.Time trend analysis for antidepressant drugs. Logistic regression analysis comparing use of antidepressant drugs in patients with dementia in four-year age groups in 2004, 2008, and 2012 versus 2000 (reference), displaying age and gender-adjusted odds ratios (ORs) and age, gender, and comorbidity-adjusted ORs and 95% confidence intervals (CI).

Age groups	**Antidepressant drugs OR (adjusted for age and gender)**	**Antidepressant drugs OR (adjusted for age, gender, comorbidity, psychosis)**
65-68 years n=4,528	2000: 1.0 2004: **1.52*** (1.26-1.84) 2008: **1.66*** (1.38-1.99) 2012:**1.58*** (1.33-1.89)	2000: 1.0 2004: **1.53*** (1.27-1.85) 2008: **1.67*** (1.39-2.00) 2012: **1.58*** (1.32-1.88)
69-72 years n=7,969	2000: 1.0 2004: **1.41*** (1.23-1.62) 2008: **1.63*** (1.43-1.87) 2012:**1.61*** (1.42-1.84)	2000: 1.0 2004: **1.42*** (1.23-1.63) 2008: **1.64*** (1.44-1.88) 2012: **1.62*** (1.42-1.85)
73-76 years n=13,212	2000: 1.0 2004: **1.30*** (1.18-1.45) 2008: **1.44*** (1.30-1.59) 2012:**1.47*** (1.33-1.63)	2000: 1.0 2004: **1.30*** (1.18-1.45) 2008: **1.43*** (1.29-1.59) 2012: **1.47*** (1.33-1.62)
77-80 years n=19,659	2000: 1.0 2004: **1.39*** (1.28-1.51) 2008: **1.34*** (1.23-1.54) 2012: **1.37*** (1.36-1.49)	2000: 1.0 2004: **1.39*** (1.28-1.52) 2008: **1.34*** (1.23-1.46) 2012: **1.37*** (1.26-1.49)
81-84 years n=23,797	2000: 1.0 2004: **1.53*** (1.41-1.66) 2008: **1.58*** (1.46-1.71) 2012: **1.58*** (1.46-1.71)	2000: 1.0 2004: **1.53*** (1.41-1.66) 2008: **1.58*** (1.46-1.72) 2012: **1.58*** (1.46-1.71)
85-88 years n=22,764	2000: 1.0 2004: **1.40*** (1.29-1.52) 2008: **1.56*** (1.43-1.69) 2012: **1.63*** (1.51-1.77)	2000: 1.0 2004: **1.42*** (1.30-1.54) 2008: **1.58*** (1.45-1.71) 2012: **1.66*** (1.53-1.80)
89-92 years n=14,276	2000: 1.0 2004: **1.58*** (1.41-1.76) 2008: **1.73*** (1.55-1.92) 2012: **1.75*** (1.58-1.94)	2000: 1.0 2004: **1.59*** (1.42-1.78) 2008: **1.76*** (1.58-1.96) 2012: **1.79*** (1.61-1.99)
93-96 years n=5,536	2000: 1.0 2004: **1.90*** (1.56-2.30) 2008: **2.03*** (1.69-2.44) 2012: **2.05*** (1.71-2.46)	2000: 1.0 2004: **1.92*** (1.58-2.34) 2008: **2.08*** (1.73-2.51) 2012: **2.11*** (1.76-2.54)
97-100 years n=1,181	2000: 1.0 2004: **1.52*** (0.94-2.47) 2008: **2.99*** (1.92-4.68) 2012: **2.74*** (1.77-4.25)	2000: 1.0 2004: 1.55 (0.96-2.52) 2008: **3.06*** (1.96-4.79) 2012: **2.88*** (1.86-4.47)

* $p<0.05$

Study II

Psychotropic Polypharmacy in Patients with Dementia: Prevalence and Predictors

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Psychotropic Polypharmacy in Patients with Dementia: Prevalence and Predictors

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Abstract.
Background: Antipsychotics and other psychotropics are frequently used to treat neuropsychiatric symptoms in patients with dementia, even though the evidence for effect is limited. Concerns have been raised about the safety of antipsychotics, but concomitant use of multiple psychotropic drug classes (psychotropic polypharmacy) may also pose a risk for patients.
Objective: To investigate the prevalence and predictors associated with use of psychotropic polypharmacy in patients with dementia.
Methods: A population-based study using nationwide registers. Patients with dementia were identified among all Danish residents ≥65 years on January 1, 2012. Data on prescriptions and comorbidity was included in the analysis. Overlapping prescriptions for different psychotropic drug classes were used to determine psychotropic polypharmacy. A multivariable logistic regression analysis was conducted to evaluate factors independently associated with the prescription of other psychotropic drug classes among patients already using antipsychotics.
Results: Among all patients registered with dementia (34,553), 25.3% (8,728) used ≥2 psychotropic drugs. Among patients treated with antipsychotics 75.8% (5,403) used at least one other psychotropic drug during the antipsychotic treatment period. Nursing home residency, number of non-psychotropic medications used in 2011, and prior psychiatric diagnosis were associated with psychotropic polypharmacy among antipsychotic drug users. The most frequent combination of psychotropic drugs was antipsychotics and antidepressants.
Conclusion: Concomitant use of psychotropic drugs was frequent in dementia patients. Patients living in nursing homes had the highest risk of receiving a combination of antipsychotics and other psychotropic drugs. Concomitant use of psychotropics may cause adverse events, and potential consequences for patients' safety call for further investigation.

Keywords: Antidepressant drugs, antipsychotic drugs, dementia, pharmacoepidemiology, polypharmacy, psychotropic drugs

INTRODUCTION

Antipsychotics are frequently used for patients with dementia [1–4], despite the limited evidence for effect on neuropsychiatric symptoms [5]. Treatment with an antipsychotic may be necessary when patients suffer from severe behavioral symptoms such as aggression and agitation, and there may be a modest effect of antipsychotic treatment on aggression and psychosis, but best practice guidelines recommend non-pharmacological interventions as first line treatment [6, 7]. Antipsychotics have been associated with increased mortality and risk of adverse events such as sedation, extrapyramidal symptoms, stroke, myocardial infarction, and hip fracture [8–10]. A report from

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the British Department of Health also stated that for every 100 patients with dementia treated with antipsychotics for one year, one additional death will result [11]. This has led to warnings and regulations from authorities in various countries on the use of antipsychotics in dementia patients.

We previously found that antipsychotic use decreased among dementia patients, but one in five is still using antipsychotics and for longer periods. Moreover, use of antidepressants is increasing, with anxiolytics and hypnotics/sedatives also frequently used in patients with dementia [12]. These medications have been associated with increased risk of falls, hip fracture, and death [13–15]. Patients with dementia are frail and more prone to side effects [16]. Use of not just one psychotropic drug but combinations of different psychotropic drug classes (psychotropic polypharmacy) is potentially a serious concern for patient safety [17].

In observational studies, concomitant use of psychotropic drugs varied across countries and settings from 14% to 50% [18–22]. However, some studies had limited sample sizes and were based on selected populations, which means it is unknown if these results can be generalized. Interestingly, no previous studies done in larger populations have focused on concomitant use of antipsychotics with other psychotropic drug classes. Danish registers allow for investigation of an entire population, making it possible to avoid selection bias. With a specific interest in the prevalence of concomitant use of antipsychotics with other psychotropic drugs, we aimed to investigate the prevalence of psychotropic polypharmacy in patients with dementia in Denmark, both nursing home residents and those living at home. Our second aim was to investigate the predictors of concomitant use of antipsychotics with other psychotropic drugs in patients with dementia.

METHODS

The register

All Danish residents are assigned a personal identification number (CPR number) at time of birth or immigration. This makes it possible to link demographic and medical data from registers at an individual level [23]. The National Patient Registry contains data on all hospital admissions since 1977 and all contacts to outpatient clinics and emergency rooms since 1995, including dates and discharge diagnoses [24]. The Psychiatric Central Registry contains data on all admissions to psychiatric hospitals since April 1, 1969 and all outpatient contacts since 1995 [25]. The diagnoses have been registered from 1970–1993 according to the World Health Organization's (WHO) International Classification of Diseases 8th Revision (ICD-8) [26] and 10th Revision (ICD-10) from 1994 onwards [27]. Data on all dispensed prescription drugs have been registered in The Danish National Prescription Registry since 1995. The drugs are registered according to the Anatomical Therapeutic Chemical (ATC) classification system [28], with information on the date of dispensing, package size, and strength [29]. Demographic data on sex, living status (nursing home residency), and date of death was provided by Statistics Denmark.

Study population

Among all Danish residents $\geq$65 years and alive on January 1, 2012, we identified patients with dementia as in- and outpatients registered with a dementia diagnosis (see Supplementary Table 1 for diagnostic codes) at discharge from a Danish hospital or at an outpatient visit and/or as individuals who had filled at least one prescription for anti-dementia drugs (ATC: N06D). Individuals registered with a dementia diagnosis or filling their first prescription for anti-dementia drugs before age 60 were excluded, as the validity of register-based dementia diagnosis is low in patients <60 years of age [30]. Time since dementia diagnosis was used as a surrogate marker for dementia severity. The time of diagnosis for patients identified based on anti-dementia medication alone was based on the first redeemed prescription.

Psychotropic drug use

Data on all filled prescriptions for patients with dementia in 2012 were analyzed. Prescriptions filled in 2011 were included in the analysis if the treatment duration included at least one day in 2012. Psychotropic polypharmacy was defined as concomitant use of psychotropic drugs from two or more of the four main groups (ATC codes: N05A: antipsychotics (excluding lithium); N05B: anxiolytics; N05C: hypnotics/sedatives; and N06A: antidepressants). The treatment duration of each prescription was used to identify patients using psychotropic polypharmacy [31]. All drugs are assigned a defined daily dose

Table 1
Baseline characteristics of patients with dementia in 2012 stratified by living status

Characteristic	Home living ($n = 17,473$) n (%)	Nursing home residents ($n = 17,080$) n (%)
Age group		
65–74 years	3,759 (21.5%)	1,923 (11.3%)
75–84 years	7,989 (45.7%)	6,658 (39.0%)
≥85 years	5,725 (32.8%)	8,499 (49.8%)
Sex		
Female	10,401 (59.5%)	12,034 (70.5%)
Male	7,072 (40.5%)	5,046 (29.5%)
Time since dementia diagnosis		
<1 year	4,133 (23.6%)	2,532 (14.8%)
1–3 years	6,161 (35.3%)	5,327 (31.2%)
4–5 years	3,264 (18.7%)	3,933 (23.0%)
>5 years	3,915 (22.4%)	5,288 (31.0%)
Number of drugs in 2011 (excluding psychotropic drugs)		
0–1	822 (4.7%)	371 (2.2%)
2–4	3,659 (20.9%)	2,482 (14.5%)
5–9	7,911 (45.3%)	8,082 (47.3%)
≥10	5,081 (29.1%)	6,145 (36.0%)
Somatic comorbidity		
Charlson Comorbidity Index (excluding dementia)		
0	6,111 (35.0%)	5,911 (34.6%)
1	3,973 (22.7%)	4,294 (25.1%)
≥2	7,389 (42.3%)	6,875 (40.3%)
Cardiovascular disease	7,239 (41.4%)	7,291 (14.0%)
Diabetes	2,542 (14.6%)	2,390 (14.0%)
Psychiatric comorbidity		
Prior psychiatric disorder	3,343 (19.1%)	3,718 (21.8%)
Prior psychotic disorder	657 (3.8%)	797 (4.7%)

(DDD), defined by WHO, representing the assumed average maintenance dose per day for a drug used for its main indication in adults [28]. For the purpose of this study, the number of DDDs per prescription was used to define the duration of treatment (treatment period) for all prescriptions, as one DDD was assumed to represent one day of treatment. If a prescription for an antipsychotic (ATC code: N05A) covered 21.0 DDD, this was registered as 21 days of treatment from the date of dispensation. If the same patients filled a prescription for a drug from another psychotropic drug class during the 21 days covered by the antipsychotic prescription, this was registered as psychotropic polypharmacy. We subsequently calculated the number of days that each patient had used psychotropic polypharmacy. Three sensitivity analyses were performed a) using a minimum of 14 days of overlap in treatment duration to define concomitant use and b) by calculating the antipsychotic treatment duration based on an assumed intake of 0.5 DDD per day; and c) by calculating the antipsychotic treatment duration based on an assumed intake of 0.25 DDD per day.

Comorbidity

Comorbidity was assessed at baseline (January 1, 2012) applying the Charlson Comorbidity Index (CCI) [32, 33], and complemented by specific clinically relevant comorbid conditions, including diabetes, cardiovascular disorders, and psychiatric diagnoses (see Supplementary Table 2 for definitions). Diagnostic codes registered at discharge or at an outpatient visit prior to the index date were used to define comorbidity and diagnoses were used to calculate the CCI score in the study population. Psychiatric comorbidity was defined as a diagnosis registered prior to the dementia diagnosis and defined as either "any psychiatric disorder" or as "a psychotic disorder" (schizophrenia, schizotypal, and delusional disorders; manic episode and bipolar affective disorder). The psychotic disorders were a diagnostic subgroup of "any psychiatric disorder". Diabetes was also identified based on an individual filling at least one prescription for drugs used in diabetes (ATC code A10). The total number of different drugs used in 2011 (excluding psychotropic drugs) was used as an

Table 2
Number of different psychotropic drug classes used among patients with dementia exposed to psychotropic polypharmacy ($n = 8,728$)

	% (n)	Number of days with concomitant use, median (P10; P90)
2 different drug classes	79.1% (6,907)	34.0 (5.0–194.0)
3 different drug classes	18.3% (1,594)	20.0 (3.0–119.0)
4 different drug classes	2.6% (227)	16.0 (2.0–100.0)

(P10; P90): 10–90 percentile range.

indicator of somatic disease not captured by hospital admissions [34]. The different drugs were assessed on the therapeutic level, e.g., antithrombotic agents (ATC level 3: B01A), which means different drugs within the same therapeutic level were not counted separately.

Statistical analysis

Descriptive statistics were used to determine the prevalence of psychotropic drug use. The duration of treatment was not normally distributed and thus calculated as the median with 10–90 percentiles. A logistic regression analysis was performed to evaluate whether potential predictive variables were associated with the prescription of other psychotropic drugs, in addition to antipsychotic treatment. The level of significance for the tested variables was set at a p-value <0.05. Variables that have previously been shown to be associated with the prescription of psychotropic drugs [9, 35–40] were analyzed, and the effect of each variable was initially tested in a univariate analysis. In order to examine factors independently associated with polypharmacy among antipsychotic users, a multivariate logistic analysis was performed that included all covariates significantly associated with the outcome. Age was classified as a categorical variable using three levels (65–74 years, 75–84 years,≥85 years); time since dementia diagnosis was classified using four levels (<1 year, 1–3 years, 4–5 years, >5 years); CCI was classified using three levels (0, 1, ≥2); and the total number of drugs used in 2011 was classified using four levels (0–1 drugs, 2–4 drugs, 5–9 drugs, ≥10 drugs).

Data analysis was performed using SAS statistical software, version 9.3 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Study population

Out of the 974,431 Danish residents aged ≥65 on January 1, 2012, there were 34,553 (3.5%) with dementia and they were included in the study. Majority of patients (88.3%) had been registered with a dementia diagnosis and 4035 (11.7%) were identified based on prescriptions for anti-dementia medication only. Among all individuals identified as patients with dementia 1881 (5.4%) were included based on a first anti-dementia prescription for donezepil (N06DA02), 1451 (4.2%) based on rivastigmine (N06DA03), 333 (1.0%) based on galantamine (N06AD04), and 370 (1.1%) based on memantine (N06DX01). Home living patients with dementia constituted 50.6% (17,473) and 49.4% (17,080) patients were nursing home residents. Table 1 presents the baseline characteristics. Overall, 78.8% (27,219) used five or more drugs (excluding psychotropic drugs); 41.3% (14,264) had at least two registered somatic diagnoses; and 20.4% (7,061) had previously been registered with a psychiatric diagnosis. We excluded 2341 individuals (0.24%) from the entire elderly population who had been diagnosed with dementia before age 60.

Psychotropic polypharmacy among all patients with dementia

Psychotropic polypharmacy with an overlapping treatment duration involving at least two different psychotropic drugs occurred in 25.3% (8,728) of patients with dementia in 2012. Psychotropic polypharmacy was more common among patients living in nursing homes, with a prevalence of 30.9% (5,281), compared to 19.7% (3,447) among patients living at home ($p < 0.001$). Fifty percent of the patients received psychotropic polypharmacy for 50 days or more (median [10–90 percentile range]: 50.0 [6.0–278.0]).

The majority of patients (79.1%) using psychotropic polypharmacy took two different psychotropic drug classes concomitantly and only a few were treated with four psychotropic drug classes (see Table 2). The patients using two psychotropic drugs used concomitant drug therapy for a median number of 34.0 days.

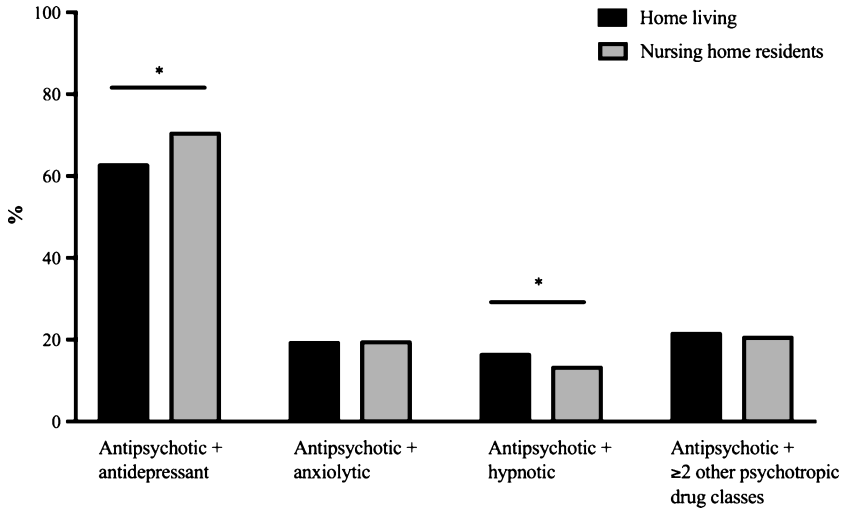

Fig. 1. Psychotropic polypharmacy among patients with dementia treated with antipsychotics in 2012 ($n = 7{,}130$), *p < 0.05.

The most frequent combination was concomitant use of antidepressants and antipsychotics, which occurred in 14.0% (4,819) of patients with dementia, with a median duration of 36.0 days (6.0–169.0). Antidepressants and anxiolytics were prescribed concomitantly for 9.7% (3,347) of patients (median duration of 25.0 days [5.0–175.0] days), and antidepressants and hypnotics were prescribed for 7.1% (2,440) of patients (median duration of 125.0 [10.0–362.0] days). Concomitant treatment with anxiolytics and hypnotics occurred in 2.7% (917) patients (median duration 30.0 [5.0–194.0] days).

Psychotropic polypharmacy in patients using antipsychotics

Among the 7,130 patients treated with antipsychotics in 2012, 75.8% (5,403) used at least one other psychotropic drug during the antipsychotic treatment period with a median treatment duration of 35 days (6–168). Use of antipsychotics in combinations with other psychotropics was more frequent among nursing home residents compared to patients living at home (77.7% versus 72.3% [$p < 0.001$]). Figure 1 presents the prevalence of drug combinations stratified by living status. Antidepressants were prescribed concomitantly for 67.6% (4,819) of all patients using antipsychotics and the combination was more common among nursing home residents compared to patients living at home ($p < 0.001$). Hypnotics were prescribed concomitantly for 14.3% (1,021) of patients using antipsychotics, which was also more common among nursing home residents ($p < 0.001$). Anxiolytics were prescribed for 19.3% (1,378) of antipsychotic users and there was no difference between nursing home residents and patients living at home (nursing home residents: 19.3%, home living: 19.2%, $p = 0.85$). The proportion of patients receiving two other psychotropic drugs in combination with antipsychotic treatment was 20.8% (1,486), also with no difference between nursing home residents and patients living at home (nursing home residents: 20.5%, home living: 21.4%, $p = 0.39$).

Sensitivity analyses

Concomitant treatment may not be clearly defined. Some patients may only use a combination of psychotropic drugs for a few days. This could be the case if patients were switched from one psychotropic drug therapy to another. As a result, we carried out a sensitivity analysis of concomitant drug use that excluded patients with ≤14 days of overlapping treatment duration. The prevalence of patients using at least two different psychotropic drugs decreased from 25.3% (8,728) to 19.7% (6,818), while use of antipsychotics with other psychotropic drugs decreased from 15.6 to 11.9%.

It is generally advised to prescribe lower doses of antipsychotics for patients with dementia than the standard recommendation. As a result, we also carried out a sensitivity analysis to investigate concomitant use based on an assumed intake of 0.5 DDD per day. The prevalence of patients using antipsychotic drugs in combination with other psychotropics increased from 15.6 (5,403) to 15.9%

(5,507) and the median duration of polypharmacy increased from 35.0 days (6.0–168.0) to 70.0 days (12.0–291). When we assumed an intake of 0.25 DDD per day the prevalence increased to 16.4% (5,671) and the median duration of polypharmacy to 121.0 days (17.0–379.0).

Determinants of psychotropic polypharmacy in patients using antipsychotics

Table 3 presents the results from the crude and multivariable regression analysis for determinants for receiving polypharmacy among users of antipsychotics ($n = 7,130$). In the univariate analyses, concomitant use of antipsychotics with other psychotropic drugs versus use of antipsychotics alone was significantly associated with younger age (<75 years), female sex, nursing home residency, number of drugs used in 2011 (≥5 drugs), somatic comorbidity (CCI ≥ 2) and prior psychiatric diagnosis.

The multivariable analysis included all statistically significant variables identified in the univariate analysis. In the full model, the estimate for somatic comorbidity was no longer significantly associated with polypharmacy. All other estimates were attenuated slightly but remained significant, independent predictors of psychotropic polypharmacy.

DISCUSSION

This nationwide population-based study of psychotropic drug use in patients with dementia found that 25% of patients with dementia received treatment with multiple psychotropic drug classes. Furthermore, more than 50% of the patients treated with multiple psychotropic drug classes received the combinations for more than 50 days in 2012. In consideration of the risks associated with antipsychotics, another important finding was that over 75% of patients treated with antipsychotics were exposed to psychotropic polypharmacy.

A recent French population-based study found that during the last four months of 2011, 13.8% of patients with dementia used three different psychotropics [18], which comprised either one from each of three classes (antipsychotics, antidepressants and anxiolytics/hypnotics) or, e.g., two antidepressants and one

Table 3
Factors associated with concomitant use of antipsychotics with other psychotropics versus antipsychotic monotherapy among patients with dementia in 2012

Characteristic	Antipsychotics + other psychotropics Crude OR (95% CI)	Antipsychotics + other psychotropics Adjusted*** OR (95% CI)
Age group		
65–74 years	1.00	1.00
75–84 years	0.86 (0.75–0.99)*	0.85 (0.74–0.98)*
≥85 years	0.85 (0.74–0.98)*	0.83 (0.71–0.96)*
Sex (female)	1.21 (1.10–1.34)**	1.13 (1.01–1.25)*
Nursing home resident versus home living	1.23 (1.11–1.36)**	1.23 (1.11–1.36)**
Time since dementia diagnosis		
<1 year	1.00	1.00
1–3 years	1.28 (1.11–1.48)**	1.33 (1.15–1.54)**
4–5 years	1.18 (1.02–1.38)*	1.20 (1.03–1.40)
>5 years	1.60 (1.38–1.86)**	1.59 (1.36–1.85)**
Number of drugs in 2011 (excluding psychotropic drugs)		
0–1	1.00	1.00
2–4	1.34 (0.99–1.82)	1.27 (0.93–1.74)
5–9	1.63 (1.22–2.17)*	1.54 (1.15–2.08)*
≥10	1.99 (1.48–2.67)**	1.88 (1.39–2.55)**
Somatic comorbidity		
Charlson Comorbidity Index		
0	1.00	1.00
1	1.13 (0.99–1.28)	1.06 (0.93–1.21)
≥2	1.14 (1.02–1.28)*	1.04 (0.92–1.17)
Psychiatric comorbidity		
Prior psychiatric disorder (any)	1.76 (1.58–1.95)**	1.71 (1.53–1.90)**

OR, odds ratio; CI, confidence interval. *$p < 0.05$; **$p < 0.001$; ***Multivariable analysis adjusted for age group, sex, living status, time since dementia diagnosis, number of drugs in 2011, Charlson Comorbidity Index, and prior psychiatric disorder.

from another drug class. This study used data from insurance systems and did not provide information on comorbidities, use of other medications, or living status. Among Ontario nursing home residents with dementia, the use of two or more psychotropics (comprising two kinds of antidepressants or, e.g., one antidepressant and one antipsychotic) increased from 42% in 2004 to 50% in 2013 [22]. Other prior studies investigating concomitant use of psychotropic drugs examined small and selected populations. Two studies from Sweden and Holland found that 20% of patients with dementia used drugs from at least two different psychotropic drug classes [19, 21]. Among UK patients with dementia, 22% used antipsychotics and selective serotonin reuptake inhibitors, while in Sweden 22% of the patients in nursing homes used a combination of antipsychotics and antidepressants [1, 20]. This is close to our findings, which shows that 18.8% of nursing home residents with dementia used a combination of antipsychotics and antidepressants. Some studies focused on drug utilization among nursing home residents, and in a Norwegian sample, 22% used two different psychotropic drug classes, but the study did not include information about dementia diagnoses [41]. Another Norwegian study of three cohorts of nursing home residents found that the most frequent combinations of psychotropic drugs were antidepressants and hypnotics (14% of residents), and antidepressants and anxiolytics (12% of residents) [42]. To our knowledge, predictors of antipsychotic use in combination with other psychotropic drugs among patients with dementia have not previously been investigated. Time since dementia diagnosis was significantly associated with psychotropic polypharmacy during the first years after the diagnosis and again after five years. Affective symptoms, such as depression, are frequent in the early disease stages, while psychotic symptoms more often affect patients in the late stages of the disease. These symptoms may generate a need for drug therapy, and the variation during disease stages may explain the pattern of use of psychotropic polypharmacy associated with dementia severity.

Comorbidity and use of multiple non-psychotropic medications were associated with concomitant use of antipsychotics with other psychotropic drugs. The patients who used the greatest number of medications overall were also most likely to be prescribed a combination of antipsychotics and other psychotropics. This is surprising because, considering the risks of serious adverse events during antipsychotic therapy, comorbidity is a reason for physicians to be even more cautious when prescribing a combination of antipsychotics and other psychotropics. Other studies investigated psychotropic drug use in relation to potentially inappropriate drug use and interactions. A Finnish study from 2003 also found that nursing home residents exposed to potentially inappropriate drugs were more likely to receive psychotropic drugs. Use of more than nine drugs was also associated with use of psychotropics [43].

Patients with a history of a psychiatric disorder were more likely to receive psychotropic polypharmacy than patients without, perhaps due to the high prevalence of depressive disorders prior to onset of dementia [44]. A recent Finish study investigated concomitant use of two or more antipsychotics among patients with Alzheimer's disease living at home [45]. Prior psychotic disorder and depression were associated with use of more than one antipsychotic compared to using one antipsychotic. We did not investigate use of multiple antipsychotics, but this may also be the case in our sample.

Living in a nursing home was also associated with use of antipsychotics in combination with other psychotropics. This is not surprising, as neuropsychiatric symptoms are more common in nursing home residents and a major predictor of nursing home placement [46]. However, use of multiple psychotropic drugs in frail elderly nursing home residents with somatic comorbidities and in those who use multiple other drugs is concerning. We previously found that opioids were also frequently prescribed for frail elderly with dementia and for nursing home residents [47]. These prescription patterns are a concerning trend as this group of patients is at high risk of adverse events. The clinical consequences, however, have only been studied sparsely. Among older adults use of multiple psychotropics was associated with an increased risk of adverse events and death [17].

This is the first study to investigate concomitant use of psychotropic drugs among patients with dementia in an entire elderly population. The use of nationwide registers eliminates selection bias and is a major strength of this study. The inclusion of prescription data on nursing home residents is important, and the registers provide information about a number of possible confounders, such as comorbidity. The method for calculating polypharmacy from register-based data was evaluated by sensitivity analyses. Some patients only received concomitant treatment for a few days, but, according to our data and sensitivity analyses, these comprised only a few patients. On the other hand, the actual dose prescribed may have

been less than 1.0 DDD per day. The antipsychotic drug risperidone, for example, is regularly used in dementia patients and the recommended dose when treating aggression in Alzheimer's disease is 1–2 mg per day, whereas DDD is set at 5 mg. A Finnish study evaluated the validity of a dosage assumption of one DDD per day in people aged ≥75 years and found that the prescribed dose for almost all antipsychotics was below the DDD [48]. Consequently, our estimation of concomitant use may be underestimated. The sensitivity analyses suggest that a prescribed dose of 0.5 DDD or 0.25 DDD per day means that patients may be exposed to psychotropic polypharmacy with antipsychotics for even longer periods.

Studies based on register data are associated with some limitations due to lack of information about clinical rationale for drug prescriptions. There may be residual confounding as we did not have information on neuropsychiatric symptoms, level of staffing in nursing homes, and setting (general practice, specialized dementia, or psychiatric clinic). Moreover, even though prescription data provides valid information on filled prescriptions, there was no information about the indications for drug therapy. We also do not know whether patients actually took the drugs they purchased.

The number of patients with dementia included in this study is somewhat lower than the estimated number of patients >65 years with dementia in Denmark in 2013 which was 80,000 [49]. In a Danish study from 2003, 42–78% of dementia cases were registered with a diagnosis in the Danish hospital registers [50]. Patients not registered with a diagnosis could not be included in the study and we were not able to investigate psychotropic drug use among those patients. It is well known that dementia is underdiagnosed. Some patients may be in the earlier stages of disease and have not yet been diagnosed, some patients may be nursing home residents who are not referred for further diagnostic evaluation and finally, some patients may have been evaluated only by their primary health care general practitioner. Thus, it is important to acknowledge that the findings of this study apply to patients who have been registered with a dementia diagnosis at the hospitals and/or treated with anti-dementia medication. Anti-dementia drugs are indicated for Alzheimer's disease, Parkinson's dementia, and dementia with Lewy bodies, therefore these dementia types may be overrepresented in the subset of the study population identified based on anti-dementia drugs only. CCI score was primarily based on diagnoses in the registers which may give incomplete information on comorbidities. However, the CCI includes chronic conditions registered as main or auxiliary diagnosis since 1977 which increases the likelihood of completeness. Time since diagnosis was used as a surrogate marker for dementia severity in the characterization of the study population. This holds some limitations for two reasons. First, some patients were not registered with a dementia diagnosis in the registers and were included in the study population based on anti-dementia medication use only. For 1.1% of the study population, the first anti-dementia prescription was memantine which is only approved for use in moderate to severe dementia. Thus, the disease duration among these patients would be underestimated. The date of a registered dementia diagnosis may be months or years after the actual onset of disease and may therefore also underestimate dementia severity. Several studies on the risks associated with antipsychotic drug use in patients with dementia have been conducted, and clinical guidelines and warnings aimed to reduce the use of antipsychotics in patients with dementia. We previously found that use of antipsychotics among Danish dementia patients decreased from 31.3% in 2000 to 20.4% in 2012, while antidepressant use increased, with more than 50% of patients with dementia using an antidepressant in 2012 [12]. One may speculate that antidepressants, to some extent, have replaced antipsychotic prescriptions for behavioral symptoms in dementia, but combined use of antipsychotics and antidepressant was also common. Thus, pharmacological treatment of neuropsychiatric symptoms in dementia care is still an important issue that needs to be addressed, and little is known about the use of multiple psychotropic drugs. An important question is whether psychotropic polypharmacy is useful in patients with dementia, and whether it may be associated with harmful consequences. Given the known risks associated with use of antipsychotics and antidepressants [51] but also potential drug interactions, concomitant use may cause adverse events. Even short-term concomitant use may be potentially harmful. Our findings suggest that clinical guidelines should also address common clinical practices of combining several psychotropic drugs and in particular the addition of antipsychotics to an existing psychotropic drug regimen, such as antidepressants.

This study found that use of antipsychotics drugs in combination with other psychotropics is frequent in dementia patients and that some of the frailest elderly living in nursing homes had the highest risk of receiving combinations of psychotropic drugs. This

is concerning as patients with multiple comorbidity and drug use are also the patients most likely to experience side effects and adverse events. The most frequent combination of psychotropic drugs was antipsychotics and antidepressants. Both drug classes have been associated with increased risk of death, but risks associated with concomitant use is unknown. The potential consequences for patient safety call for further investigation.

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SUPPLEMENTARY MATERIAL

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Study II

Psychotropic Polypharmacy in Patients with Dementia: Prevalence and Predictors

Supplementary Material

Supplementary Material

Supplementary Table 1. Diagnoses used for identification of patients with dementia

	ICD-8	ICD-10
Alzheimer's disease	290.10	F00.0, F00.1, F00.2, F00.9, G30.0, G30.1, G30.8, G30.9
Vascular dementia	293.09-19	F01.0, F01.1, F01.2, F01.3, F01.8, F01.9
Frontotemporal dementia	290.11	F02.0
Other dementias	-	G31.8
Dementia without specification	290.09-19	F03, G31.9

ICD, International Classification of Diseases.

Supplementary Table 2. Definition of specific comorbidities

Cardiovascular disease	Considered present if a diagnosis of myocardial infarction, peripheral vascular disease, cerebrovascular disease or hemiplegia was registered in the National Patient Registry under one of the codes to the right	Myocardial infarction: • ICD-8: 410.xx • ICD-10: I21-I23 Peripheral vascular disease: • ICD-8: 440-444.xx ICD-10: I70-74, I77 Cerebrovascular disease: • ICD-8: 430-438.xx • ICD-10: I60-69, G45, G46 Hemiplegia: • ICD-8: 430-438.xx • ICD-10: I60-69, G45, G46
Diabetes	Considered present if one of the codes to the right was registered in the National Patient Registry *or* if a prescription for an antidiabetic was filled the year before (2011)	ICD8: N/A ICD10: E10, E11, E12, E13, E14 ATC: A10

ICD, International Classification of Diseases; ATC, Anatomical Therapeutic Chemical.

Study III

Impact of Benzodiazepines and Antidepressants on the Mortality in Patients with Dementia on Antipsychotic Treatment

Impact of Benzodiazepines and Antidepressants on the Mortality in Patients with Dementia on Antipsychotic Treatment

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ABSTRACT

IMPORTANCE Antipsychotics are known to increase mortality among patients with dementia. Many patients receive concomitant treatment with other psychotropic medications, yet mortality during treatment with antipsychotics in combination with other psychotropic drug classes is unknown.

OBJECTIVE The aim of this study was to investigate the impact of benzodiazepines and antidepressants on the risk of death in patients with dementia initiating antipsychotic drug treatment.

DESIGN A retrospective cohort study using data on all incident dementia cases initiating antipsychotic treatment in Denmark from 2009-2013.

SETTING Population-based study using nationwide registry data.

PARTICIPANTS We identified all incident dementia cases aged 65 and older diagnosed between 2009-2013. Dementia was ascertained by a first-time registered dementia diagnosis in the Danish National Patient Registry or the Psychiatric Central Research Registry and/or a first-time prescription for anti-dementia medication. Patients who initiated antipsychotic treatment were included in the analysis.

MAIN OUTCOME AND MEASURES The 180-day mortality was evaluated by crude and adjusted hazards ratios, comparing periods of antipsychotic treatment with periods of concomitant treatment with benzodiazepines or antidepressants.

RESULTS: Among 41 494 incident dementia cases, 10 291 (24.8%) initiated antipsychotic treatment. After excluding 3140 people due to recent antipsychotic drug use or hospitalization, 7151 people were included in the analysis. The total follow-up time was 1146 person-years and 831 died during antipsychotic treatment. Compared with antipsychotic treatment alone the risk of death increased during antipsychotic treatment in combination with benzodiazepines (adjusted hazard ratio: 2.19, 95% confidence interval: 1.83-2.63), while there was a decreased risk of death during antipsychotic treatment in combination with antidepressants (adjusted hazard ratio: 0.61, 95% confidence interval: 0.50-0.74).

CONCLUSIONS AND RELEVANCE The diverse impact of concomitant use of benzodiazepines and antidepressants on mortality may be due to a direct drug-related effect. Alternatively, the findings could reflect differential mortality associated with different indications for therapy. Although the results cannot prove causality, and there may be residual confounding, clinicians should be cautious when considering the combination of antipsychotics and benzodiazepines in patients with dementia.

Introduction

Neuropsychiatric symptoms in dementia are common and a major burden on patients and caregivers. Antipsychotics are frequently prescribed even though non-pharmacological approaches are recommended as first-line management of neuropsychiatric symptoms.[1–3] Antipsychotic drug treatment may be indicated in selected patients, but the drugs are associated with several side effects, such as sedation, extrapyramidal symptoms, stroke, myocardial infarction, hip fracture, and most importantly an increased risk of death.[4–7] Thus, a risk-benefit assessment should always be included prior to prescribing antipsychotics for patients with dementia.

Aside from antipsychotics, patients with dementia are also prescribed other psychotropic drugs, including benzodiazepines and related drugs (BZDs) and antidepressants. Patients with dementia are frail and more susceptible to side effects from psychotropic drugs.[8] The patterns of psychotropic drug prescription have changed during the last decade, probably due to altered prescription guidelines and warnings against the indiscriminate use of antipsychotics.[3] We previously found that, among dementia patients treated with an antipsychotic drug, 75% also used another psychotropic drug class during the treatment period.[9] Consequently potential psychotropic drug interactions may further increase the risk of adverse events and death.[10] None of the previous large-scale studies on mortality hazards associated with antipsychotic drug use have studied this potential, altered risk.[4–6,11] One study investigated the association between use of multiple psychotropic drugs and mortality in older adults and found an overall association between concomitant prescriptions and increased mortality.[12] However, at present it is unclear whether concomitant treatment with BZDs or antidepressants is associated with an increased risk of mortality when compared with antipsychotic treatment alone.

Observational study designs are crucial to investigate possible negative health outcomes in dementia patients treated with multiple psychotropic drug classes. Danish nationwide registries possess a unique opportunity to investigate prescription patterns in a cohort of dementia patients with complete follow-up. The aim of the present study was to investigate the risk of mortality among new users of antipsychotics, also being treated with BZDs and/or antidepressants and to compare this with the risk of mortality among patients treated with only antipsychotics.

Methods

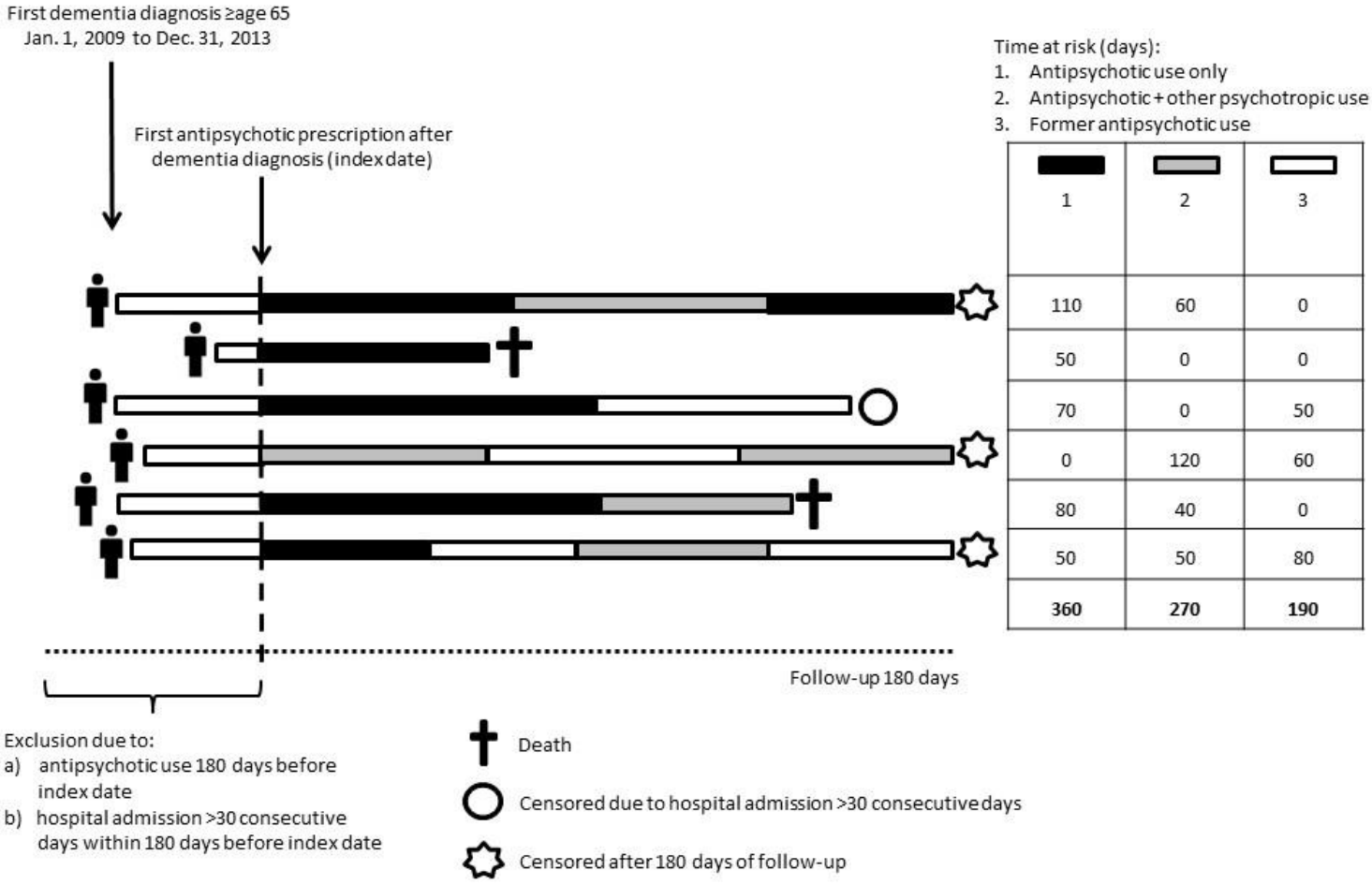
The study was designed as a registry-based nationwide cohort study. In Denmark all individuals are assigned a civil registration number at birth or upon becoming a permanent resident. This number makes it possible to link data from the Danish health registries at an individual level.[13] The registries and data contained within have been described previously.[9]

Study Population

Patients with incident dementia were identified among all Danish residents aged 65 and older. Incident cases of dementia comprised individuals registered with a first-time discharge diagnosis of dementia (diagnostic codes are available in eTable 1 in the supplementary material) from a Danish hospital or at an outpatient visit, and/or individuals who had filled at least one prescription for an anti-dementia drug (Anatomical Therapeutic Chemical (ATC) N06D) between January 1, 2009, and December 31, 2013.

Figure 1 illustrates the study design. Individuals were included in the cohort at the time of the first filled antipsychotic (ATC N05A, excluding lithium: ATC N05AN) prescription (index date) after first dementia diagnosis/anti-dementia drug prescription between January 1, 2009, and June 30, 2014. The first exclusion criterion was use of antipsychotics 180 days prior to the date of first antipsychotic prescription after dementia diagnosis (wash-out period). This new user design was chosen to avoid bias due to inclusion of prevalent users.[14] The second exclusion criterion was individuals admitted to hospital for >30 consecutive days preceding the index date because information about drug use during hospitalization is not available in the national registries.

FIGURE 1. Study Design with Study Subject Examples



Time at risk (days):

1. Antipsychotic use only
2. Antipsychotic + other psychotropic use
3. Former antipsychotic use

1	2	3
110	60	0
50	0	0
70	0	50
0	120	60
80	40	0
50	50	80
360	**270**	**190**

Exposure

Psychotropic drug exposure was defined as use of antipsychotics, BZDs (N05B, N05C), and antidepressants (N06A); see eTable 2 in the supplementary material for ATC codes. As previously described,[9] the duration of each prescription was calculated using the number of defined daily doses (DDDs) per prescription, resulting in an estimated treatment period for every filled prescription. The DDD is defined as the assumed average maintenance dose per day for a drug used for its main indication in adults. However, when used in older adults, the recommended dose is often lower than 1.0 DDD, and research has confirmed this for subgroups of psychotropic drugs.[15] For the main analysis, 0.5 DDD was set as the assumed daily intake for antipsychotics, anxiolytics (N05B), and tricyclic antidepressants. For hypnotics/sedatives (N05C) and all other antidepressants, the assumed daily intake was set at 1.0 DDD. A grace period of 14 days was added to all prescriptions, meaning that individuals who did not fill a new prescription within 14 days after end of treatment were considered as discontinuing treatment. Individuals who filled prescriptions for other psychotropic drug classes, in addition to an antipsychotic during follow-up, were classified as concomitant users. During follow-up each individual was able to contribute with time at risk to specific treatment groups.

Mortality

The outcome of interest was 180-day, all-cause mortality during current use of antipsychotics in combination with BZDs versus current antipsychotic therapy, and during current use of antipsychotics in combination with an antidepressant versus current antipsychotic therapy.

Covariates

Time since dementia diagnosis at index date was used as the marker of dementia severity. Comorbidity (Charlson Comorbidity Index score) was assessed through registered diagnoses at discharge or at an outpatient visit before the index date.[16,17] Psychiatric diagnoses registered before the first dementia diagnoses were used to assess psychiatric comorbidity. To assess comorbidity beyond registered diagnoses in hospital registries, we used data on the total number of drugs used other than psychotropic drugs.[18] The total number of prescription drugs (chemical substance level, ATC level 5) used within three months was included as a time-varying covariate. The first count was applied over a three-month period before the index date. Furthermore, any admission to hospital in the six months prior to the index date was assessed. Use of antipsychotics 10 years before the time of dementia diagnosis was assessed to detect chronic psychiatric illness, and antidepressant drug use one year before the index date was also assessed to describe pre-existing depressive symptoms. The calendar year of the first antipsychotic prescription was included to assess possible changes in

health care practice during the study period. Information on nursing home residency registered the year before the index date was extracted from Statistics Denmark.

Statistical Methods

Individuals were followed from the date of the first antipsychotic filled prescription (index date) until emigration, admission to hospital for >30 consecutive days during follow-up (due to missing information on drug use during admission), or completion of 180 days of follow-up, whichever came first. The mortality rates with 95% confidence intervals (CIs) were calculated per 100 person-years. An extended Cox regression model was performed to calculate hazard ratios for the 180-day risk of mortality. The time since index date was used as the underlying time scale. The full model included the following covariates (defined at index date): age, sex, living status (nursing home resident versus home living), calendar year of first antipsychotic prescription, time since diagnosis, Charlson Comorbidity Index score, psychiatric comorbidity prior to dementia diagnosis (dichotomous), use of antidepressants one year before index date, and hospital admission six months prior to index date (dichotomous). Both the cumulative number of days with antipsychotic treatment and total number of drugs used were coded as time dependent variables. The analysis was also stratified for short versus long-term exposure to combination therapy (>/< 60 days of antipsychotic treatment in combination with other psychotropic drugs).

Sensitivity analyses were performed to test the robustness of the model. An actual consumption of lower or higher doses of psychotropic drugs could change the exposure periods and thus the estimates for risk of mortality. To test the model, exposure was also calculated based on an assumed intake of 0.25 DDD of antipsychotics per day and 1.0 DDD per day. Some patients may have been treated with combinations of psychotropic medication as part of a palliative regimen. Because end-of-life care often includes psychotropic drugs prescribed for subcutaneous administration, we performed a sensitivity analysis that excluded all injectable drugs.

Data analysis was performed using SAS statistical software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

We identified 41 494 people with incident dementia aged 65 and older between 2009 and 2013, of whom 10 291 (24.8%) initiated antipsychotic drug treatment after a dementia diagnosis and thus were included in the study. We excluded 116 individuals due to hospital admissions lasting more than 30 consecutive days preceding the index date. Another 3024 individuals were excluded due to antipsychotic drug use 180 days prior to the first antipsychotic prescription after diagnosis.

This resulted in 7151 individuals with complete follow-up information and total follow-up time of 1146.0 person-years (see Figure 2 for population and Table 1 for baseline characteristics).

FIGURE 2. Selection of Study Cohort

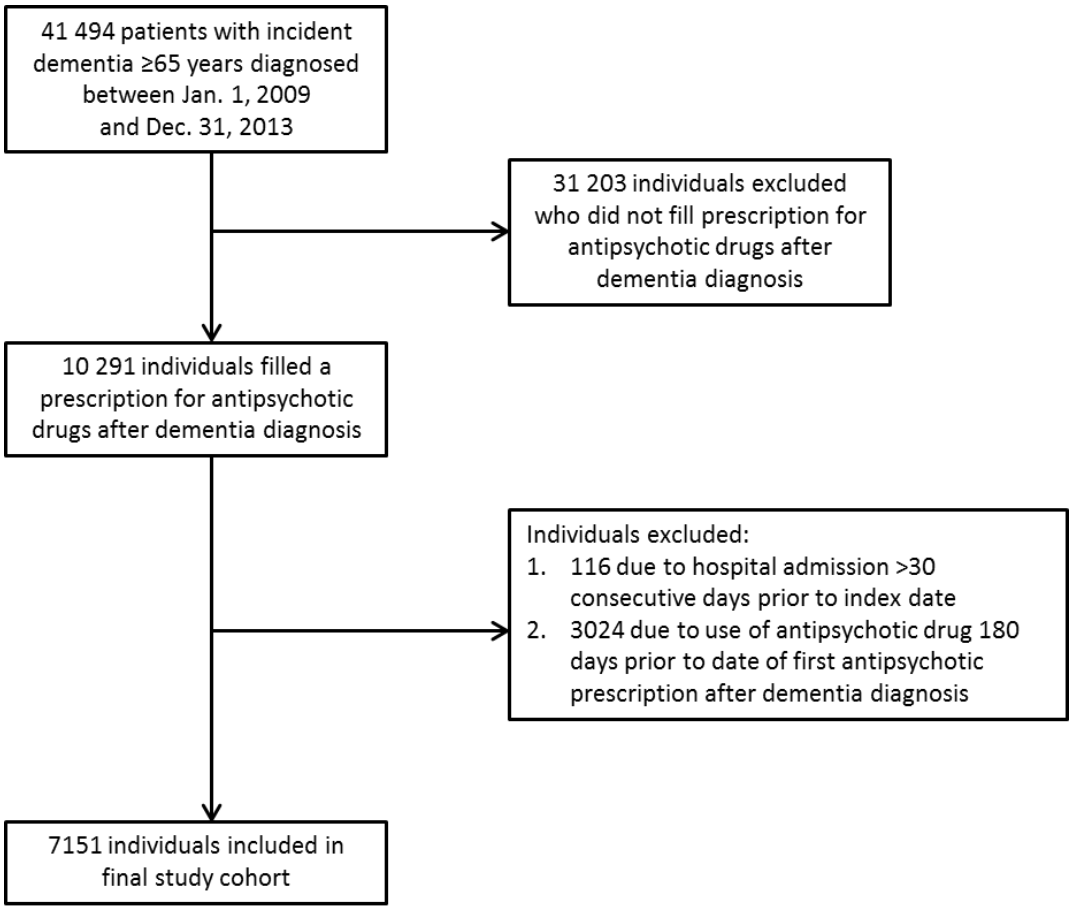


TABLE 1. Baseline Characteristics of the Study Cohort, n=7151

Characteristic		
	Median	**IQR**
Age at time of dementia diagnosis, years	81.9	76.4-86.7
Age at index date, years	83.1	77.7-87.8
Number of drugs other than psychotropic drugs (index date)	6	4-9
Time from dementia diagnosis to first antipsychotic prescription, days	252.0	55.0-643.0
	No.	**%**
Sex (female)	4061	57.0
Nursing home resident	1767	24.7
Charlson Comorbidity Index score (excluding dementia)		
0	2304	32.2
1	1578	22.1
≥2	3269	45.7
Psychiatric disease prior to dementia diagnosis	1432	20.0
Hospital admission six months prior to index date	3525	49.3
Prior antipsychotic use [a]	1114	15.6
Prior antidepressant drug [b]	3965	55.5

Abbreviations: IQR, Interquartile range.

[a] Use of antipsychotic drugs ten years prior to index date.

[b] Use of antidepressant drugs one year prior to index date.

Almost half of the individuals in the study had been hospitalized within the six months prior to antipsychotic treatment. The median time from dementia diagnosis to first antipsychotic prescription was 252 days (interquartile range: 55-643), and 12% (884) filled the first prescription within seven days after a hospitalization. The individual could have one or more periods with antipsychotic treatment during follow-up, and on average, each individual had two to three separate treatment periods. The total follow-up time was 2912.6 person-years, with follow-up time during antipsychotic treatment representing 1146.0 person-years.

During the initial 180 days after the first antipsychotic prescription, 1787 (25.0%) people died, with 831 (46.5%) of the deaths occurring during current antipsychotic treatment periods. The median duration of each treatment period that included at least one antipsychotic drug was 13 (interquartile range: 8-27) days. Table 2 presents time at risk and rates of death for specific combinations of antipsychotics with other psychotropic drug classes in specific treatment groups. Use of antipsychotics in combination with BZDs was associated with more than twice the rate of death (hazard ratio: 2.19, 95% CI: 1.83-2.63) when compared with antipsychotic treatment alone. On the other hand, treatment periods with the combination of antipsychotic and antidepressant drugs showed a 39% decreased mortality rate. For periods with antipsychotic use in combination with both BZDs and antidepressants, we found a lower mortality rate than for the periods with antipsychotics and BZDs, which was still higher than for antipsychotic treatment alone. Stratifying the analyses for duration of exposure to combination therapy showed that the risk of mortality was mainly present during the first 60 days of treatment.

When antipsychotic treatment was discontinued, we found an overall unaltered mortality rate (periods of former antipsychotic treatment) when compared with antipsychotic treatment alone, hazard ratio: 0.99 (95% CI: 0.86-1.14). However, further drug class analyses showed that an increased mortality remained for patients treated with BZDs during antipsychotic treatment breaks. In contrast, patients treated with antidepressants during antipsychotic treatment breaks had a lower mortality compared with antipsychotic use alone.

Sensitivity analyses of a higher or lower antipsychotic dose per day found that HRs were slightly lower when we assumed 0.25 DDD per day of antipsychotic treatment and slightly higher when we assumed an intake of 1.0 DDD per day. When we excluded injectable drugs, the estimates decreased modestly yielding a hazard ratio of 1.85 (CI: 1.50-2.28) for the combination of antipsychotic and BZDs. However, the overall conclusion from the main analysis did not change.

TABLE 2. Follow-up Time and 180-day Mortality Rates and Risk of Mortality for Specific Combinations of Antipsychotics with other Psychotropic Drugs versus Antipsychotic Treatment Alone

	Number (deaths)	Person-years	Rate of death per 100 person-years	95% CI	Crude hazard ratio	95% CI	p-value	Adjusted hazard ratio [a]	95% CI	p-value
Antipsychotic	285	457.74	62.26	55.44-69.93	1.00			1.00		
Antipsychotic + Antidepressant	185	455.30	40.63	35.18-46.93	0.66	0.55-0.79	<.0001	0.61	0.50-0.74	0.0014
Antipsychotic + Antidepressant + BZDs	157	128.09	122.57	104.82-143.32	1.82	1.50-2.22	<.0001	1.41	1.14-1.73	<.0001
Antipsychotic + BZDs	204	104.86	194.55	169.60-233.16	2.77	2.31-3.31	<.0001	2.19	1.83-2.63	<.0001
Total	831	1146.0								

Abbreviations: CI, confidence interval; BZDs, benzodiazepines and related drugs.

[a] Adjusted for age, sex, calendar year, time since dementia diagnosis at index date, Charlson Comorbidity Index score, prior psychiatric disease, total number of drugs used (other than psychotropic drugs), previous antidepressant use one year before index date, nursing home residency, hospital admission six months prior to index date, and total number of days on antipsychotic treatment.

Discussion

This nationwide study of 7151 individuals with dementia initiating antipsychotic treatment found an increased risk of mortality during the 180-day follow-up when antipsychotic drug use was combined with BZDs compared with antipsychotic treatment alone. In contrast, combined prescription of antipsychotics and antidepressants was associated with a decreased risk of mortality.

Several international studies have shown a greater risk of mortality for patients with dementia initiating antipsychotic therapy.[5,19] However, co-medication with other psychotropic drugs was not included in the analyses. Risk comparison between antipsychotic drug classes and other psychotropic drug classes has also been presented, suggesting that not only antipsychotics but also BZDs and antidepressants may yield a risk for patients compared with non-use.[4,20] Our findings suggest that certain combinations increase the risk of mortality among antipsychotic users even further than previously addressed in the literature.

Concomitant prescription of psychotropic drugs has been addressed in patients with schizophrenia. Two observational studies found an increased mortality among patients with schizophrenia using psychotropic drug combinations, i.e. combinations of antipsychotics with benzodiazepines.[21,22] These findings may reflect possible side effects due to drug interactions. Therefore, it is worrying that we find the same risk profile for patients with dementia during antipsychotic and BZDs regimens.

The more than two-fold increase in mortality associated with combining antipsychotics and BZDs may be explained by a direct effect of BZDs on mortality during treatment. If there is a direct effect, this could be mediated by common side effects associated with BZDs, such as sedation and respiratory depression, potentially leading to pneumonia. These side effects may in some cases be reinforced when combined with antipsychotics. Alternatively, the differential mortality in the two groups with and without BZD use may be connected to patient related factors, such as type of neuropsychiatric symptoms or comorbidity, that is, confounding by indication. Antipsychotics and BZDs in combination may be used to treat certain, and maybe more severe, neuropsychiatric symptoms, which in and of itself is associated with increased mortality. We found that 12% of the study population filled the first antipsychotic prescription shortly after a hospitalization, suggesting that they initiated treatment during their hospital stay. Delirium is a common syndrome in dementia and frequent among hospitalized patients, indicating the importance of doing further analyses on this sub group.[23]

We found the highest risk during the first 60 days after the initial antipsychotic prescription, implying that these patients are particularly vulnerable to adverse events relatively shortly after initiation. This suggests that clinicians should consider the risk and benefits before starting antipsychotics and particularly combination therapy of antipsychotics and BZDs.

Interestingly, we found a decreased risk of mortality during combinations of antipsychotic and antidepressant treatment. There are various potential mechanisms to explain this. First, antidepressants may possibly have a direct protective effect on mortality. Second, the profile of the patients may differ between those treated with antipsychotics alone and those treated with antipsychotics and antidepressants in combination. There is ongoing off-label use of both antipsychotics and antidepressants, and some patients with depressive symptoms and agitation or anxiety are treated with an antidepressant in combination with an antipsychotic drug. Clinicians may also choose to combine antipsychotic treatment with an antidepressant to use a lower dose of the antipsychotic drug, thus, yielding a lower risk profile for these patients.

It is not clear whether the increased risk of mortality with antipsychotic use continues after discontinued treatment. Some studies on antipsychotics and the risk of death in patients with dementia have used a follow-up of 180 days after initiation of study medication, but did not differentiate between ongoing and discontinued treatment.[11,19] Our results suggest that there may be an extended risk of mortality window even after discontinuation of antipsychotic treatment or treatment breaks (former antipsychotic use). This seems to be modified, however, by the initiation or continuation of BZDs or antidepressant treatment. The dementia antipsychotic withdrawal trial (DART-AD) investigated mortality in dementia patients discontinuing antipsychotic monotherapy using a randomized placebo-controlled study design and found a better survival rate among those who discontinued treatment compared with those who continued antipsychotic treatment.[24] Further research should address this issue to improve patient care during and after antipsychotic treatment.

The major strength of the present study is the use of nationwide registry data with complete prescription data and diagnoses from the secondary health care sector. The dementia diagnosis has been validated showing that 86% of individuals registered with dementia were diagnosed correctly.[25] The detailed longitudinal data made it possible to assess real-life prescription patterns in the study design. This is in contrast with many other studies, which have only used information about initiation of antipsychotic treatment in their analyses. Our results are important, as a substantial number of patients change treatment during the 180-day follow-up.

This study has important limitations. The nature of an observational study design implies that the results should be interpreted with caution. This study indicates an association between exposure and outcome, but causality cannot be established. It is possible that residual confounding remains. We did, however, control for important confounders in the multivariate analysis. The registry-based data used in this study enables complete population data but cannot provide information on important confounders such as dementia severity and degree of behavioral symptoms. We addressed this by adding time from dementia diagnosis to antipsychotic prescription. It is not possible to determine the actual amount of drug dosages consumed through registry data, but

several sensitivity analyses were performed to assess a possible effect on our results. Our study was designed to describe real-life prescription practices but is also based on certain assumptions, presenting the risk of misclassification of exposure. We based our assumptions on the Danish prescription guidelines for the elderly and individuals with dementia. Further, antipsychotics are known to carry a high-risk profile for some dementia subtypes, such as Lewy body dementia. The registry data did not allow investigation of drug use and risks among patients with specific dementia diagnoses because the validity of dementia subtypes is low.[25] The specific cause of death was not included in this study as the Danish Register of Causes of Death are not sufficiently valid for such analyses. Finally, the generalizability of the present study is limited to patients with a registered dementia diagnosis and patients who used an anti-dementia drug.

Conclusion

In this nationwide observational study of incident dementia patients on antipsychotic treatment, the combination of antipsychotics with BZDs was associated with an increased risk of mortality, while the combination of antipsychotics with antidepressants reduced the risk of mortality. Further research should investigate the background for combining antipsychotic treatment with BZDs and the mechanisms behind the increased mortality. When antipsychotic treatment is judged necessary there is reason to be cautious when prescribing combinations of antipsychotics and BZDs until further evidence exists. For patients with severe behavioral symptoms, clinical guidelines may be needed to address risk-benefit assessment for therapy with combinations of antipsychotics and other psychotropic drugs.

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Study III

Impact of Benzodiazepines and Antidepressants on the Mortality in Patients with Dementia on Antipsychotic Treatment

Supplementary Material

Supplementary Material

eTable 1. Diagnoses Used for Identification of Patients with Dementia

	ICD-10
Alzheimer's Disease	F00.0, F00.1, F00.2, F00.9, G30.0, G30.1, G30.8, G30.9
Vascular Dementia	F01.0, F01.1, F01.2, F01.3, F01.8, F01.9
Frontotemporal Dementia	F02.0
Other Dementias	G31.8
Dementia without Specification	F03, G31.9

Abbreviation: ICD, International Classification of Diseases

eTable 2. ATC Codes of Psychotropic Drugs

Antipsychotics	**Sub Group**	**Generic Name**	**ATC**
	First-generation	Levomepromazine	N05AA02
		Fluphenazine	N05AB02
		Perphenazindeconoate	N05AB03
		Prochlorperazine	N05AB04
		Periciazine	N05AC01
		Haloperidol	N05AD01
		Melperone	N05AD03
		Pipamperone	N05AD05
		Droperidol	N05AD08
		Flupentixol	N05AF01
		Chlorprothixene	N05AF03
		Zuclopenthixol	N05AF05
		Pimozide	N05AG02
		Penfluridole	N05AG03
		Loxapine	N05AH01
		Sulpiride	N05AL01
	Second-generation	Sertindole	N05AE03
		Ziprasidone	N05AE04
		Lurasidone	N05AE05
		Clozapine	N05AH02
		Olanzapine	N05AH03
		Quetiapine	N05AH04
		Asenapine	N05AH05
		Amisulpride	N05AL05
		Risperidone	N05AX08
		Aripiprazole	N05AX12
		Paliperidone	N05AX13
Benzodiazepines and related drugs	**Sub Group**	**Generic Name**	**ATC**
	Anxiolytics	Diazepam	N05BA01
		Chlordiazepoxide	N05BA02
		Oxazepam	N05BA04
		Lorazepam	N05BA06
		Bromazepam	N05BA08
		Clobazam	N05BA09
		Alprazolam	N05BA12
		Hydroxyzine	N05BB01
		Buspirone	N05BE01
	Hypnotics and sedatives	Nitrazepam	N05CD02
		Triazolam	N05CD05
		Lormetazepam	N05CD06
		Zopiclone	N05CF01
		Zolpidem	N05CF02
		Zaleplon	N05CF03

Antidepressants	Sub Group	Generic Name	ATC
	Tricyclic antidepressants	Imipramine	N06AA02
		Clomipramine	N06AA04
		Amitriptyline	N06AA09
		Nortriptyline	N06AA10
		Doxepin	N06AA12
		Dosulepin	N06AA16
		Maprotiline	N06AA21
	Selective serotonin reuptake inhibitors	Fluoxetine	N06AB03
		Citalopram	N06AB04
		Paroxetine	N06AB05
		Sertraline	N06AB06
		Fluvoxamine	N06AB08
		Escitalopram	N06AB10
	Monoamine oxidase inhibitors	Isocarboxazid	N06AF01
		Moclobemide	N06AG02
	Other antidepressants	Mianserin	N06AX03
		Mirtazapine	N06AX11
		Venlafaxine	N06AX16
		Duloxetine	N06AX21
		Agomelatine	N06AX22

Abbreviation: ATC, Anatomical Therapeutic Chemical

Study IV

Effect of Antipsychotic Drugs on Mortality Risk among Dementia Patients with and without Comorbidities: A Nationwide Study

Effect of Antipsychotic Drugs on Mortality Risk among Dementia Patients with and without Comorbidities: A Nationwide Study

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ABSTRACT

OBJECTIVES: To investigate whether comorbidities related to the cardiovascular and metabolic systems affect the mortality risk associated with the initiation of antipsychotic treatment among patients with dementia.

DESIGN: Matched cohort study.

SETTING: Population-based study using nationwide registry data.

PARTICIPANTS: All Danish residents aged 65-95 diagnosed with dementia between 2009 and 2014. Dementia was assessed as a first-time registered dementia diagnosis in the Danish National Patient Register or the Danish Psychiatric Central Research Register and/or a first-time prescription for anti-dementia medication. Patients exposed to antipsychotic medications were matched with up to three unexposed patients.

MEASUREMENTS: Cox proportional hazards models were used to compare risk of death within 180 days after initiation of antipsychotic treatment. The model was adjusted for a range of potential confounders. Analyses were stratified for diabetes, cardiovascular, and cerebrovascular comorbidities.

RESULTS: The study cohort included 8,244 exposed patients and 24,730 unexposed patients. A total of 5,938 patients died during the first 180 days of follow-up. Patients exposed to antipsychotics had a significantly higher adjusted risk of death (hazard ratio: 1.35, 95% confidence interval: 1.27-1.43) than unexposed patients. The elevated risk did not differ between patients with and without diabetes, cardiovascular, and cerebrovascular comorbidities.

CONCLUSION: This nationwide study adds to the evidence on an increased mortality risk associated with antipsychotic treatment and found that caution should be taken for all patient groups regardless of prior comorbid disease related to the cardiovascular and metabolic systems.

Key Words: antipsychotics; dementia; mortality; comorbidity

INTRODUCTION

Antipsychotic drugs are commonly used to treat behavioral and psychological symptoms in patients with dementia. However, the treatment may cause side effects and can lead to serious adverse events and death.[1,2] Analyses of clinical trial data on mortality during antipsychotic treatment led to warnings against antipsychotic treatment for patients with dementia and population-based studies found an increased short term mortality among patients treated with antipsychotic drugs.[3–6]

The side effects of antipsychotic treatment are manifold and include QT prolongation, orthostatic hypotension, sedation, Parkinsonism, and metabolic disturbances. The possible mechanisms leading to increased mortality may be linked to these side effects. QT prolongation may lead to ventricular tachyarrhythmias and sudden cardiac death,[7] orthostatic hypotension may lead to falls and ischemic stroke,[8] and sedation may lead to aspiration pneumonia.[9] Thus, antipsychotic treatment may negatively influence the cardiovascular and metabolic systems, and patients with preexisting cardiovascular comorbidity could be at higher risk of adverse events and death during antipsychotic treatment.

A Danish study of older adults treated with antipsychotics found that people with preexisting cardiovascular disease had a greater risk of major cardiovascular events compared with people without cardiovascular disease.[10] A small Finnish study investigated the mortality risk during antipsychotic treatment among older community-dwelling people in different comorbidity groups. People with respiratory disease at baseline had the highest risk of death associated with antipsychotic treatment.[11]

To date, no large-scale studies have explicitly investigated whether the effect of antipsychotic treatment on the risk of death among patients with dementia varies across groups of patients with or without preexisting comorbidities. In fact, many observational studies have adjusted for comorbidity in the statistical analyses[1,4–6] and, thus, did not evaluate the potential interaction between comorbidity and antipsychotic treatment. Therefore, the aim of this study was to investigate the short-term mortality risk associated with antipsychotic drug treatment in patients with dementia and whether specific preexisting comorbid conditions (cardiovascular disease, cerebrovascular disease, and diabetes) interact with antipsychotic treatment, increasing the mortality rate beyond the risk of death associated with antipsychotic treatment and comorbidity alone.

METHODS

Data Sources

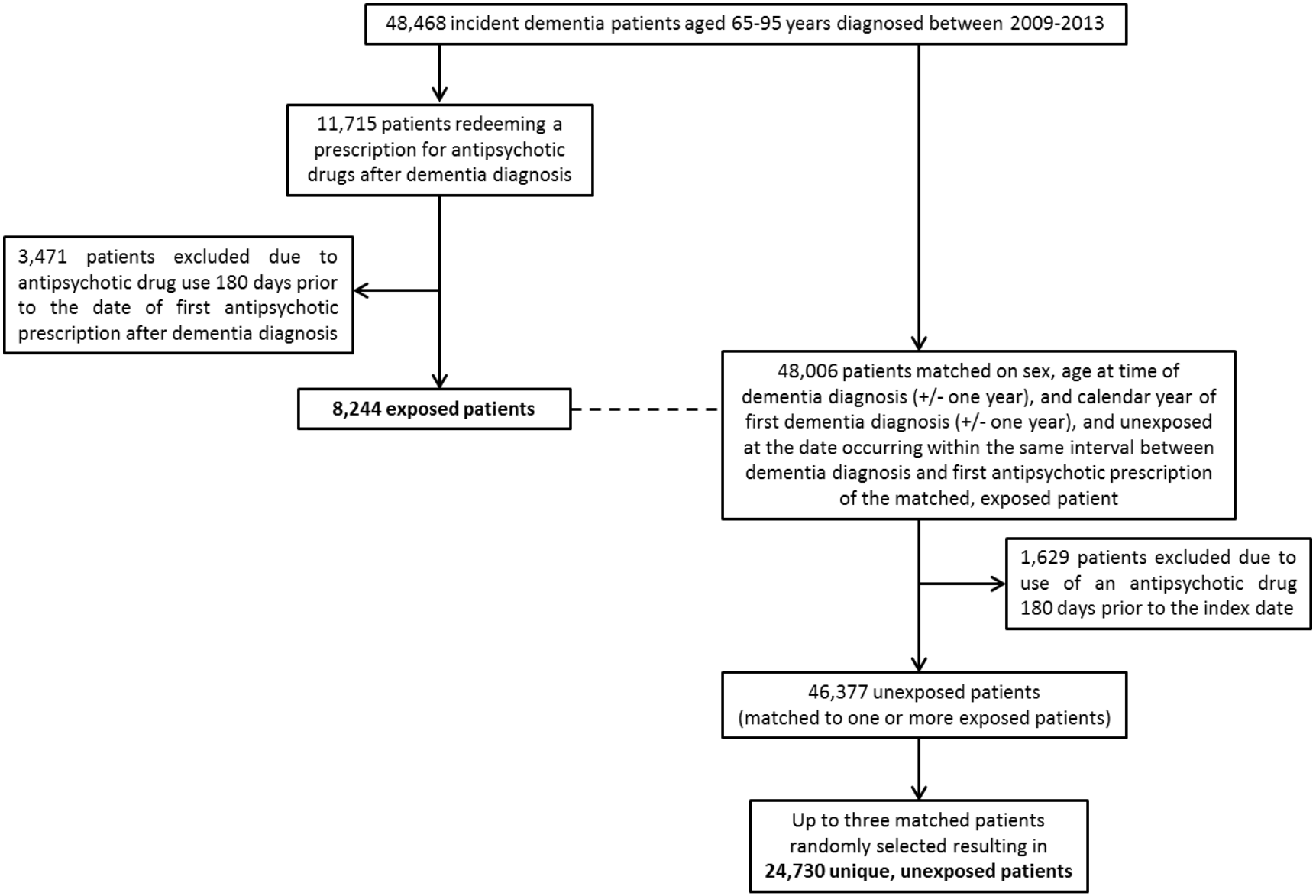
The study used nationwide registry data and was designed as a matched cohort study comparing risk of death among patients exposed to antipsychotic treatment with unexposed patients. All Danish residents are included in the Danish Civil Registration System and assigned a unique personal civil registration number at

birth or after immigrating to Denmark. This allows linkage of data from nationwide registries at an individual level.[12] Statistics Denmark keeps information on date of birth, sex, residence, and vital status. The Danish National Patient Registry includes data on primary and secondary discharge diagnoses of all hospital admissions since 1977, as well as of all contacts to outpatient clinics and emergency rooms since 1995.[13] The Danish Psychiatric Central Research Registry includes data on diagnoses of all admissions to psychiatric hospitals since 1969 and outpatient contacts since 1995.[14] Data on all filled prescriptions since 1995 is included in the Danish National Prescription Registry, with information on the Anatomical Therapeutic Chemical (ATC) classification system code, date of dispensing, package size, and strength.[15] Drugs with an ATC code are assigned a defined daily dose, which is the assumed average maintenance dose per day for a drug used for its main indication in adults.[16]

Study Population

We identified all individuals in Denmark, between 65 and 95 years of age, who were registered with a first-time dementia diagnosis (for diagnosis codes see Supplementary Table S1) and/or had filled their first prescription for antidementia drugs (ATC N06D) between January 1, 2009 and December 31, 2014. We defined exposed patients as those with a prescription for an antipsychotic drug (ATC N05A, excluding lithium) after their first dementia diagnosis or antidementia drug prescription. The date of the antipsychotic prescription was defined as the index date. We then excluded all patients with a prescription for an antipsychotic drug within 180 days before the index date to avoid possible bias from including prevalent users.[17] Incident dementia patients without antipsychotic treatment were matched to exposed patients on sex, age at time of dementia diagnosis (+/- one year), and calendar year of first dementia diagnosis (+/- one year). An index date was created as a date occurring within the same interval between dementia diagnosis and first antipsychotic prescription of the matched exposed patient; thus, unexposed patients were defined as those without antipsychotic use between dementia diagnosis and index date. We excluded unexposed patients with a prescription for an antipsychotic drug within 180 days before the index date. Patients unexposed at the time of matching could be matched to several exposed patients. Unexposed could become exposed later. To restrict unexposed patients to be used only once, we randomly selected up to three unexposed patients to be included in the final analysis (see Figure 1 for study design). Treatment duration for exposed patients was calculated based on an assumed daily intake of 0.5 defined daily dose, based on Danish prescription guidelines and a Finnish registry-based study evaluating psychotropic drug doses.[18]

Figure 1. Flow Diagram of Matched Study Cohort



Outcome of Interest

The study outcome was 180-day mortality. Date of death was assessed through the Danish Civil Registration System.

Comorbidity

The comorbidities under investigation of influencing the association between antipsychotic treatment and mortality were heart disease, cerebrovascular disease, and diabetes mellitus. Comorbidities were assessed at index date. The diagnostic codes, procedure codes and prescription drugs used to define these comorbidities are available in the Supplementary Table S2.

Covariates

Sex, age at time of dementia diagnosis, and living status (nursing home versus home living) were obtained from Statistics Denmark. Other somatic comorbidities were assessed at index date by applying the Charlson Comorbidity Index score, which includes 19 chronic somatic diseases.[19,20] Diagnoses registered at discharge from a hospital or from an outpatient clinic within 10 years before the index date were used. For this study, we excluded dementia, acute myocardial infarction, congestive heart disease, cerebrovascular disease, diabetes, and diabetes with end organ damage from the Charlson Comorbidity Index. Psychiatric comorbidity was defined as any psychiatric diagnosis registered at psychiatric hospitals since 1969 but before the index date. Comorbidity assessment was complemented by the number of somatic hospitalizations for any reason within five years before the index date. Treatment with benzodiazepines and related drugs (ATC N05B and N05C) or antidepressants (ATC N06A) within 180 days before the index date was included as a potential confounder. Calendar year of first dementia diagnosis was included to account for changes in health-care services. In sensitivity analyses, we adjusted for the number of somatic prescription drugs before the index date that could be both a confounder and a mediator of the association between antipsychotic treatment in the strata of comorbidities and the risk of death. The number of prescription drugs (ATC level 5, excluding N05A, N05B, N05C, N06A, N06D, A10) was counted during the three months before the index date.

Statistical Analyses

Descriptive statistics were used to describe the characteristics of the study population. We calculated the crude, 180-day mortality rates. Potential confounders were chosen a priori and included in the multivariate analyses. We performed Cox regression analysis and report crude hazard ratios (HR) and adjusted HR with 95% confidence intervals (CI). Exposed and unexposed patients were followed from the index date until the date of death, emigration, for 180 days, or until the end of the study period (December 31, 2015), whichever

came first. Unexposed patients who became exposed later were censored at the time of first filled antipsychotic prescription. We investigated the potential effect modification by stratification and formal tests of interaction. Consequently, all analyses were stratified according to heart disease, cerebrovascular disease, and diabetes mellitus. The data analyses were performed using SAS statistical software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

We identified 48,468 incident dementia patients aged 65-95 years between 2009 and 2014. We excluded patients treated with an antipsychotic drug within 180 days prior to their first antipsychotic prescription following their first dementia diagnosis (n=5,100). We identified 8,244 patients who initiated antipsychotic treatment during follow-up (exposed patients). Matching of up to three unexposed patients per exposed patient resulted in 24,730 matched patients; see Figure 1. Table 1 presents the characteristics of exposed and unexposed patients with dementia. Exposed patients a psychiatric diagnosis more frequently prior to dementia and had been treated more frequently with benzodiazepines and antidepressants prior to the index date.

Total follow-up time was 14,285.6 person-years, with 5,938 deaths occurring during 180 days follow-up (41.6/100 person-years). In the stratified analyses, the crude 180 day-mortality rate per 100 person-years was lowest for all groups of unexposed patients without comorbidities. The crude mortality rate increased with antipsychotic exposure, and the highest crude mortality rate was found for exposed patients in the strata with comorbidities. Table 2 presents the results from the Cox regression analysis with HRs and 95% CI comparing mortality risk among exposed patients versus unexposed patients. There was a 35% increased risk of death associated with antipsychotic treatment after adjusting for potentially confounding factors. Further adjustment for the number of other medications decreased the HR to 1.23 (95% CI: 1.16-1.31). There was a significant interaction only for cerebrovascular disease on the multiplicative scale. Table 3 presents stratification for pre-existing comorbidities. Overall, there were no differences (overlapping confidence intervals) between risks of death in the strata with and without comorbidities. In the sensitivity analysis, where the number of somatic prescriptions was added to the model, the HRs did not change for strata with or without heart disease and with or without diabetes. When the total number of prescriptions was added, the HR for patients without previous cerebrovascular disease decreased to 1.29 (1.20-1.38), while the HR for patient with previous cerebrovascular disease decreased and became insignificant (HR: 1.09, 95% CI: 0.97-1.23).

Table 1. Characteristics of Exposed and Unexposed Patients

Characteristic	Treated with Antipsychotics (Exposed) n=8,244	Not Treated with Antipsychotics at Beginning of Follow-up (Unexposed) n=24,730
Age at time of dementia diagnosis, years	81.7 (76.2-86.4)	81.7 (76.2-86.4)
Sex (female)	4,671 (56.7%)	14,013 (56.7%)
Nursing home resident	1,995 (24.2%)	5,454 (22.1%)
Other somatic comorbidities, Charlson Comorbidity Index score *		
0	4,563 (55.3%)	13,604 (55.0%)
1	1,307 (15.9%)	4,027 (16.3%)
≥2	2,374 (28.8%)	7,099 (28.7%)
Psychiatric disease prior to dementia diagnosis	1,689 (20.5%)	3,955 (16.0%)
Heart disease	2,512 (30.5%)	7,743 (31.3%)
Cerebrovascular disease	1,732 (21.0%)	4,868 (19.7%)
Diabetes	1,294 (15.7%)	4,072 (16.5%)
Number of hospital admission 5 years prior to index date	4 (2-7)	3 (1-6)
Number of somatic drugs **	6 (3-9)	5 (3-8)
Prior benzodiazepine treatment ***	2,841 (34.5%)	3,158 (12.8%)
Prior antidepressant drug treatment ***	4,442 (53.9%)	5,862 (23.7%)
Time from dementia diagnosis to first antipsychotic prescription, days	261 (54-683)	Not relevant

Numbers are given as n (%) or median (25% quartile to 75% quartile) as appropriate.
*excluding dementia and comorbidities under investigation
**counted at ATC level 5 within 3 months prior to index date excluding N05A, N05B, N05C, N06A, N06D, A10
***redeemed a prescription within 180 days prior to index date

Table 2. Follow-up Time and 180-day Mortality Rates and Hazard Ratios (HRs) and 95% Confidence Intervals (95% CI) of Mortality for Antipsychotic Treatment (Exposed) Vs. Patients Not Treated with Antipsychotics (Unexposed)

	Number of Deaths	Person-years	Crude Mortality Rate per 100 Person-years	Crude HR (95% CI) *	Adjusted HR (95% CI) **	Interaction Term (Heart disease x Antipsychotic Treatment)	Interaction Term (Cerebrovascular Disease x Antipsychotic Treatment)	Interaction Term (Diabetes x Antipsychotic Treatment)
Unexposed n=24,730	3945	10,866.8	36.3 (35.2-37.5)	1.0 (Ref.)	1.0 (Ref.)			
Exposed n=8,244	1993	3,418.8	58.3 (55.8-60.9)	1.49 (1.41-1.57)	1.35 (1.27-1.43)	p=0.2433	p=0.0010	p=0.4913

*Adjusted for sex and age

**Adjusted for: age at dementia diagnosis, sex, calendar year, nursing home residency, heart disease, cerebrovascular disease, diabetes mellitus, Charlson Comorbidity Index score (excluding dementia, acute myocardial infarction, congestive heart disease, cerebrovascular disease, diabetes, and diabetes with end organ damage), psychiatric comorbidity, treatment with benzodiazepines and antidepressants within 180 days before index date, and number of hospitalizations within five years before index date

Table 3. Follow-Up Time and 180-day Mortality Rates and Hazard Ratios (HRs) and 95% Confidence Intervals (95% CI) for Antipsychotic Treatment (Exposed) Vs. Patients Not Treated with Antipsychotics (Unexposed) Stratified for Specific Pre-Existing Comorbidities

		Number of Deaths	Person-years	Crude Mortality Rate per 100 Person-years (95% CI)	Crude HR (95% CI) *	Adjusted HR (95% CI)**
Cardiovascular Disease						
No	Unexposed, n=20,649 (83.5%)	2,286	7,609.0	36.3 (35.2-37.5)	1.0 (Ref.)	1.0 (Ref.)
	Exposed, n=6,892 (83.6%)	1,222	3,418.8	58.3 (55.8-60.9)	1.55 (1.45-1.66)	1.26 (1.17-1.36)
Yes	Unexposed, n= 4,081 (16.5%)	1,659	3,257.9	50.9 (48.5-53.4)	1.0 (Ref.)	1.0 (Ref.)
	Exposed, n=1,352 (16.4%)	771	985.6	78.2 (72.9-83.9)	1.41 (1.29-1.53)	1.19 (1.08-1.30)
Cerebrovascular Disease						
No	Unexposed, n=19,862 (80.3%)	2,898	8,815.2	32.9 (31.7-34.1)	1.0 (Ref.)	1.0 (Ref.)
	Exposed, n=6,512 (79.0%)	1,516	2,719.6	55.7 (53.0-58.6)	1.57 (1.47-1.67)	1.41 (1.31-1.50)
Yes	Unexposed, n= 4,868 (19.7%)	1,047	2,051.6	51.0 (48.0-54.2)	1.0 (Ref.)	1.0 (Ref.)
	Exposed, n=1,732 (21.0%)	477	699.2	68.2 (62.4-74.6)	1.24 (1.16-1.38)	1.17 (1.05-1.32)
Diabetes						
No	Unexposed, n=20,658 (83.5%)	3,169	9,121.4	34.7 (33.6-36.0)	1.0 (Ref.)	1.0 (Ref.)
	Exposed, n=6,950 (84.3%)	1,630	2,896.5	56.3 (53.6-59.1)	1.50 (1.41-1.59)	1.25 (1.18-1.34)
Yes	Unexposed, n= 4,072 (16.5%)	776	1,745.4	44.5 (41.4-47.7)	1.0 (Ref.)	1.0 (Ref.)
	Exposed, n= 1,294 (15.7%)	363	522.3	69.5 (62.7-77.0)	1.43 (1.26-1.62)	1.15 (1.01-1.32)

*Adjusted for: sex and age

**Adjusted for: age at dementia diagnosis, sex, calendar year, nursing home residency, (heart disease, cerebrovascular disease, and diabetes mellitus)‡, Charlson Comorbidity Index score (excluding dementia, acute myocardial infarction, congestive heart disease, cerebrovascular disease, diabetes, and diabetes with end organ damage), psychiatric comorbidity, treatment with benzodiazepines and antidepressants within 180 days before index date, number of hospitalizations within 5 years before index date.

‡Not adjusted for the comorbidity in strata of interest

DISCUSSION

This nationwide study found a 35% increased mortality for patients with dementia treated with antipsychotic drugs. Pre-existing comorbidities related to the cardiovascular and metabolic systems did not influence this mortality risk in our study population.

Previously, both meta-analyses of double-blind randomized placebo-controlled clinical trials and observational studies found an increased mortality risk of 23-54% associated with antipsychotic drug treatment for patients with dementia[1,21]. An analysis of clinical trial conducted by the U.S. Food and Drug Administration concluded that the mortality increased 60-70%.[3] Thus, the overall risk estimates for antipsychotics on the risk of mortality from our nationwide study lie within the lower range of previous findings.

By contrast, the literature on the effect of comorbidities related to the cardiovascular system on the mortality risk with antipsychotic drugs is sparse. So far, a case-control study by Liperoti and colleagues found no additive interaction between pre-existing cardiovascular disease and antipsychotics on the risk of hospitalization for ventricular arrhythmias and cardiac arrest.[22] Their study included nursing home residents only and did not include information on deaths occurring outside the hospital. Another study based on the same data suggested that there may be an effect of pre-existing cerebrovascular disease on the risk of stroke associated with antipsychotic treatment among nursing home residents.[23] These findings, however, maybe biased as the analyses did not find an overall increased risk of cardiovascular and cerebrovascular events associated with second-generation antipsychotics. Another study by Howard and colleagues analyzed data from double-blind randomized placebo-controlled clinical trials of risperidone treatment for dementia patients with behavioral symptoms. The authors found that the increased risk of stroke associated with antipsychotic treatment was modified by pre-existing cardiovascular disease.[24] In contrast, this modification was not found with regard to increased risk of mortality. This is in accordance with our findings that the risk of death associated with antipsychotic treatment did not differ between strata of heart disease, cerebrovascular disease, and diabetes mellitus. One explanation of our findings is that the mechanism of action for the excess mortality with antipsychotic treatment in dementia is not primarily cardiovascular. Thus, dementia and antipsychotic treatment seem to be stronger predictors of mortality than the comorbidities under investigation. It is possible that general side effects of antipsychotic treatment, such as sedation, may lead to inactivity, falls, and pneumonia, eventually causing increased mortality. Another explanation is that some of the comorbid diagnoses included in the Charlson Comorbidity Index, which we used for confounder adjustment in our analyses, have an impact on the mortality risk associated with antipsychotic treatment. For example, pulmonary disease could be an important factor in the association between antipsychotics and

mortality, as reported by the U.S. Food and Drug Administration (FDA) finding pneumonia to be one of the leading causes of death among patients with dementia on antipsychotic treatment.[3]

We cannot exclude the possibility that under-registration of comorbidities may play a role, thus obscuring a link between prior presence of comorbidities and mortality during antipsychotic treatment. We were only able to include comorbidities registered in the secondary health care sector. The patients with dementia who are frail and have multiple comorbidities may not be referred for treatment in hospitals. Examples of unequal treatment of patients with dementia have previously been described, e.g. limited access to treatment for myocardial infarctions and admission to specialized stroke units among patients with dementia compared with older people without dementia.[25,26] This indicates a public health problem and calls for action to secure equal health-care treatment for patients with dementia. Lastly, it is possible that the patients with the most severe comorbid diagnoses within the comorbidity groups were treated with lower doses or not treated at all with antipsychotics as a result of risk-benefit assessments. In fact, some of the cardiovascular diagnoses could constitute contraindications to antipsychotic treatment. This factor could lead to a lower risk among patients with a registered comorbid disease compared with the risk among patients without a registered comorbidity diagnosis. If this is the case, our study would illustrate a clinical movement in the right direction towards safer prescription practices.

Treatment with other somatic medications could potentially act as a confounder. On the one hand pharmacological treatment could illustrate whether comorbidities are well-managed. On the other hand, the prescribing of medications could act as a mediator on the pathway from antipsychotic treatment and comorbidity to death. Therefore, we performed a sensitivity analysis with other medications filled prior to antipsychotic treatment initiation as a confounder, which decreased the risk of death in all strata of comorbidity. In the stratified analysis of cerebrovascular disease, the previously detected increased risk of death associated with antipsychotic treatment among patients with cerebrovascular disease became insignificant when including other medications. Among these patients, it is likely that, e.g., appropriate anticoagulant treatment to prevent further strokes acts as a mediator of the association between antipsychotic, comorbidity, and death, potentially explaining the pattern. The patients with pre-existing cerebrovascular disease could also represent a subgroup of dementia patients, such as vascular dementias, which could have a different mortality risk than other dementia subtypes. However, the registries do not allow for analysis of dementia subtypes due to poor quality of subtype registration. Finally, it is possible that clinicians are more reluctant to prescribe antipsychotics for patients with prior cerebrovascular disease than other comorbidities due to knowledge on risk of stroke with antipsychotic therapy.

The overall increased risk of death associated with antipsychotic drug treatment and among strata of comorbidities should be interpreted in the light of the observational study design. It is not possible to draw

final conclusions regarding causality. We did, however, adjust for a range of potential confounders and the estimates are in range of the results from both meta-analyses of clinical trial data and large observational studies.[1,21] Some important confounders were not available in our study, which could bias the results and increase the risk estimates for the exposed group. We were not able to include information on disease stage and presence of neuropsychiatric symptoms. It is possible that the patients with the most severe neuropsychiatric symptoms and in the latest stages of dementia are overrepresented in the group of patients treated with antipsychotic drugs. These factors are also related to mortality, raising the mortality risk in the exposed group. Such bias due to confounding by indication could explain some of the increased risk of death among patients treated with antipsychotics in our study but also in general in other observational studies. Delirium is associated with both the initiation of antipsychotic treatment and death. The registration of delirium in the registries is, however, not sufficiently valid to be included in the present analysis. In-hospital treatment with antipsychotics is also not available from the prescription registry, but any treatment continued beyond intermittent hospital admissions would be captured by our study design. Residual confounders could be unequally distributed among the comorbidities under investigation, as would be the case if delirium were more prevalent among the exposed patients with previous cerebrovascular disease.[27] Our study was based on the assumption that the patients consumed the prescription drugs. In a previous analysis, 86% of patients treated with antipsychotics filled more than one prescription within a year, suggesting that the majority of patients did consume the drugs.[28]

The major strength of this study is its use of data on a nationwide cohort of unselected incident dementia patients, including people living in nursing homes. Data on prescriptions, diagnoses, and follow-up is, for all practical purposes, complete. Study participants in previous studies differ with respect to disease stage, comorbidities, and nursing home residency, resulting in selection bias. Moreover, the validity of a registered dementia diagnosis in the Danish registries is high.[29] Furthermore, although the number of patients with dementia who are not registered with a diagnosis is unknown, the 2014 Alzheimer Europe Report estimated that around 80,700 people, aged 65 and above, were living with dementia in Denmark in 2012. Thus indicates that the Danish registries capture around 43% of dementia cases.[30]

In conclusion, the results from this nationwide study of incident dementia patients found a 35% increase in mortality among patients initiating antipsychotic treatment. The high risk was not affected by pre-existing comorbidities related to the cardiovascular system, suggesting that clinicians should be cautious when prescribing antipsychotic drugs to all groups of dementia patients. Future research should explore mechanisms for the increased mortality to identify patients at high risk of adverse events. The aim must be to identify those patients who can benefit from antipsychotic treatment with the lowest risk in order to make a risk-benefit assessment at an individual level for best practice of antipsychotic treatment in dementia care.

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Study IV

Effect of Antipsychotic Drugs on Mortality Risk among Dementia Patients with and without Comorbidities: A Nationwide Study

Supplementary Material

Supplementary Material

Supplementary Table S1. Diagnoses Used for Identification of Patients with Dementia

	ICD-10
Alzheimer's Disease	F00.0, F00.1, F00.2, F00.9, G30.0, G30.1, G30.8, G30.9
Vascular Dementia	F01.0, F01.1, F01.2, F01.3, F01.8, F01.9
Frontotemporal Dementia	F02.0
Other Dementias	G31.8
Dementia without Specification	F03, G31.9

ICD = International Classification of Diseases

Supplementary Table S2. Diagnoses used to define cardiovascular disease, cerebrovascular disease, and diabetes. A registered diagnosis <10 years before index date, and prescription <1 year before index date

Cardiovascular Disease		
	Coronary Artery Bypass Grafting (CABG)	KFNA: Connection to coronary artery from internal mammary artery KFNB: Connection to coronary artery from gastroepiploic artery KFNC: Aorto-coronary venous bypass KFND: Aorto-coronary bypass using prosthetic graft KFNE: Coronary bypass using free arterial graft
	Percutaneous coronary intervention (PCI)	KFNG: Expansion and recanalization of coronary artery
	Acute myocardial infarction	I21-25
	Heart failure	I11.0 I50 J81.9
	Cardiomyopathy	I42
	Heart valve disease	I34-I37
	Cardiac implantable electronic device	Pacemaker: BFCA01, BFCA02, BFCA07, KFPE00, KFPE10 Single chamber BFCA03, KFPE20 Dual chamber BFCA04, BFCA05, BFCA06 CRT BFCA0, KFPE96 Unclassified Implantable cardioverter defibrillator (ICD): BFCB00, BFCB02 Single chamber BFCB01 Dual chamber BFCB03 CRT BFCB0, KFPG00, KFPG10, KFPG96 Unclassified
	Tachycardia	I47 I48 I49.0
Cerebrovascular Disease		
	Transient cerebral ischaemic attacks	G45
	Cerebral hemorrhage or infarction	I60-64
Diabetes		
	Diabetes	E10-14
	Drugs used in diabetes	ATC code: A10

ATC = Anatomical Therapeutic Chemical classification system code

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