Association of Benzodiazepines and Antidepressants With 180-Day Mortality Among Patients With Dementia Receiving Antipsychotic Pharmacotherapy:

A Nationwide Registry-Based Study

Ane Nørgaard, MD, PhD[a,*]; Christina Jensen-Dahm, MD, PhD[a]; Christiane Gasse, RPharm, PhD[b,c,d]; Theresa Wimberley, MSc, PhD[b]; Elsebet Steno Hansen, MD, PhD[a]; and Gunhild Waldemar, MD, DMSc[a]

ABSTRACT

Objective: Antipsychotic drugs are known to increase mortality among patients with dementia. Many patients receive concomitant treatment with other psychotropic agents. The aim of this retrospective cohort study was to investigate the impact of benzodiazepines and antidepressants on the risk of death in patients with dementia initiating antipsychotic drug treatment.

Methods: Nationwide registry data on all incident dementia cases among individuals aged 65 years and older in Denmark between 2009 and 2013 for which antipsychotic treatment was initiated were used. The 180-day mortality was evaluated by crude and adjusted hazard ratios (HRs, including adjustment for somatic and psychiatric comorbidity, other prescription drugs, nursing home residency, and time since diagnosis), comparing periods of antipsychotic treatment with periods of concomitant treatment with benzodiazepines or antidepressants.

Results: Among 41,494 incident dementia cases, antipsychotic treatment was initiated for 10,291 (24.8%). After 3,140 people were excluded due to recent antipsychotic drug use or hospitalization, 7,151 people were included in the analysis. The total follow-up time during current antipsychotic treatment was 1,146 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 HR = 2.19; 95% CI, 1.83–2.63), while there was a decreased risk of death during antipsychotic treatment in combination with antidepressants (adjusted HR = 0.61; 95% CI, 0.50–0.74).

Conclusions: 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.

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[a]Danish Dementia Research Centre, Department of Neurology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

[b]National Centre for Register-based Research, Aarhus University, Aarhus, Denmark

[c]Department of Affective Disorders, Aarhus University Hospital Psychiatry, Aarhus, Denmark

[d]Centre for Integrated Register-based Research at Aarhus University (CIRRAU), Aarhus, Denmark

**Corresponding author:* Ane Nørgaard, MD, PhD, Department of Neurology, Danish Dementia Research Centre, Rigshospitalet, University of Copenhagen, Blegdamsvej 9, 2100 Copenhagen Ø, Denmark (ane.noergaard.christensen.02@regionh.dk).

Neuropsychiatric symptoms in dementia are common and a major burden on patients and caregivers. Antipsychotics are frequently prescribed even though non-pharmacologic 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 often 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[9] previously found that, among dementia patients treated with an antipsychotic drug, 75% also received an agent from another psychotropic drug class during the treatment period. Consequently, potential psychotropic drug interactions may further increase the risk of adverse events and death.[10] None of the previous large-scale studies[4–6,11] on mortality hazards associated with antipsychotic drug use have studied this potential, altered risk. One study[12] 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. However, at present it is unclear whether concomitant treatment with BZDs or antidepressants is associated with an increased risk of death 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

Clinical Points

- Patients with dementia are often treated with antipsychotics in combination with other psychotropics; however, little is known about the safety of this practice.
- This study found an increased mortality when antipsychotics were combined with benzodiazepines but a lower mortality when antipsychotics and antidepressants were combined.
- The findings suggest that combination treatment with antipsychotics and benzodiazepines should be used with caution in patients with dementia.

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 death among new users of antipsychotics also being treated with BZDs and/or antidepressants and to compare this with the risk of death 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 years and older. Incident cases of dementia comprised individuals registered with a first-time discharge diagnosis of dementia (diagnostic codes are available in Supplementary Table 1) from a Danish hospital or at an outpatient visit and/or individuals who had filled at least 1 prescription for an antidementia drug (Anatomical Therapeutic Chemical [ATC] code 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/antidementia drug prescription between January 1, 2009, and June 30, 2014. The first exclusion criterion was use of antipsychotics 180 days prior to the index date (washout period). This new user design was chosen to avoid bias due to inclusion of prevalent users.[14] The second exclusion criterion was admission to hospital for > 30 consecutive days preceding the index date because information about drug use during hospitalization is not available in the national registries.

Exposure

Psychotropic drug exposure was defined as use of antipsychotics, BZDs (N05B, N05C), and antidepressants (N06A); see Supplementary Table 2 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 (eg, selective serotonin reuptake inhibitors [SSRIs]), 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 with any period of filled prescriptions for other psychotropic drug classes, in addition to an antipsychotic during the 180-day follow-up, were classified as concomitant users. During follow-up, each individual was able to contribute with time at risk to specific treatment groups.

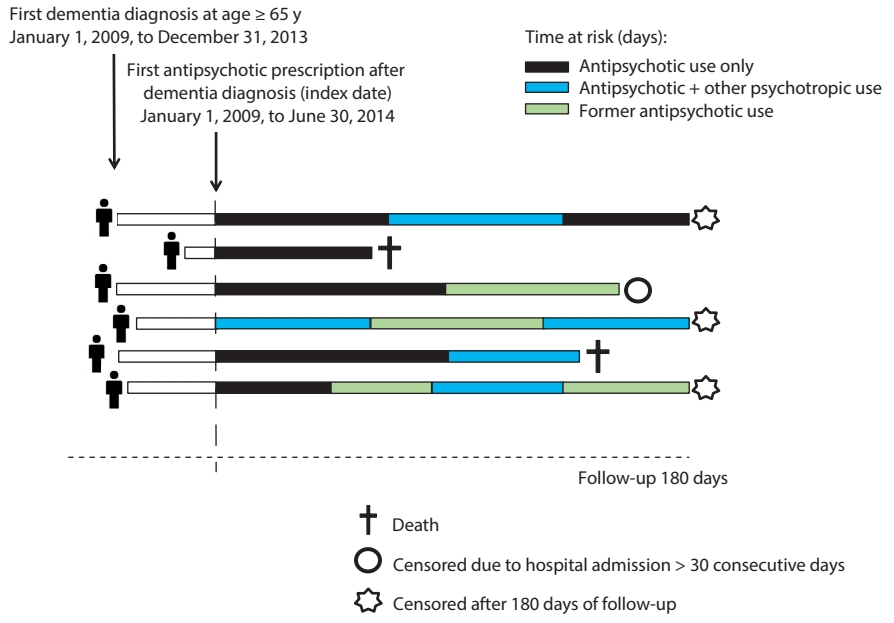
Mortality

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[16,17] score) was assessed through registered diagnoses at discharge or at an outpatient visit before the index date. Psychiatric diagnoses registered before the first dementia diagnoses were used to assess psychiatric comorbidity and included as a covariate. Thus, patients with a history of psychiatric illness were not excluded. 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 number of prescription drugs (chemical substance level, ATC level 5) used within 3 months was included as a time-varying covariate. The first count was applied over a 3-month period before the index date. Furthermore, any admission to hospital in the 6 months prior to the index date was assessed. Use of antipsychotics 10 years before the time of dementia diagnosis was assessed as a proxy for conditions such as anxiety and insomnia as well as psychotic depression and primary psychotic disorders treated with antipsychotics. Antidepressant drug use 1 year before the index date was assessed as a proxy for anxiety and depression treated in the primary care sector. 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

Figure 1. Study Design With Study Subject Examples

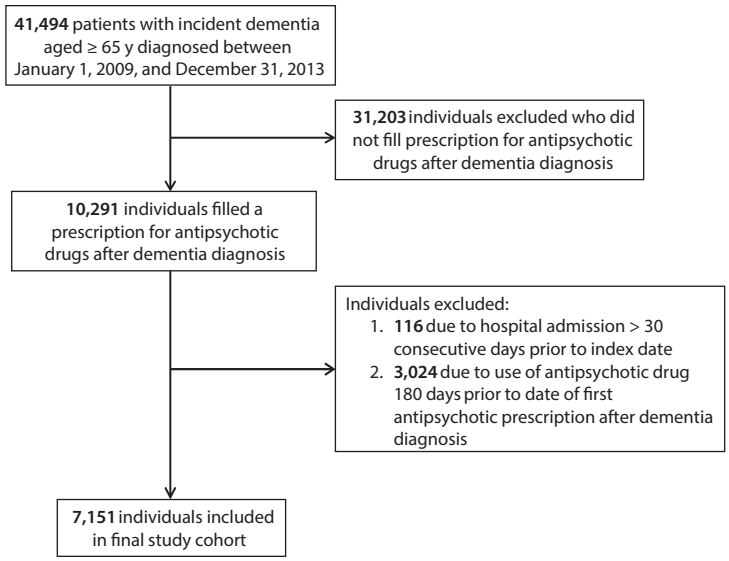


residency registered before the index date was extracted from Statistics Denmark. Please see Supplementary Table 3 for detailed definitions of covariates.

Statistical Methods

Individuals were followed from the date of the first filled antipsychotic 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 (HRs) for the 180-day risk of death. 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 (continuous), psychiatric comorbidity prior to dementia diagnosis (dichotomous), use of antidepressants 1 year before index date, and hospital admission 6 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 or ≤60 days of antipsychotic treatment in combination with other psychotropic drugs).

Figure 2. Population and Study Cohort Selection



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 death. 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.

Table 1. Baseline Characteristics of the Study Cohort

Characteristic	Value[a]
N	7,151
Age at time of dementia diagnosis, median (IQR), y	81.9 (76.4–86.7)
Age at index date, median (IQR), y	83.1 (77.7–87.8)
No. of drugs other than psychotropic drugs (index date), median (IQR)	6 (4–9)
Time from dementia diagnosis to first antipsychotic prescription, median (IQR), d	252.0 (55.0–643.0)
Female	4,061 (56.8)
Nursing home resident	1,767 (24.7)
Charlson Comorbidity Index score (excluding dementia)	
0	2,304 (32.2)
1	1,578 (22.1)
≥2	3,269 (45.7)
Psychiatric disease prior to dementia diagnosis	1,432 (20.0)
Hospital admission 6 mo prior to index date	3,525 (49.3)
Prior antipsychotic use[b]	1,114 (15.6)
Prior antidepressant drug[c]	3,965 (55.4)

[a]Values are shown as n (%) unless otherwise noted.
[b]Use of antipsychotic drugs 10 years prior to index date.
[c]Use of antidepressant drugs 1 year prior to index date.
Abbreviation: IQR = Interquartile range.

Data analysis was performed using SAS statistical software, version 9.4 (Cary, North Carolina; SAS Institute, Inc; 2013).

Ethical Approval

The study was approved by the Danish Data Protection Agency (ID: 2007–58-0015/30–0667), Statistics Denmark, and the Danish Health and Medicines Authority (ID: 6–8011-907/1). Danish law did not require ethics committee approval or informed patient consent.

RESULTS

We identified 41,494 people with incident dementia aged 65 years 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 3,024 individuals were excluded due to antipsychotic drug use 180 days prior to the first antipsychotic prescription after diagnosis.

This resulted in 7,151 individuals with complete follow-up information (see Figure 2 for population and Table 1 for baseline characteristics). Almost half of the individuals in the study had been hospitalized within the 6 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 7 days after a hospitalization. The individual could have at least 1 period with antipsychotic treatment during follow-up, and on average, each individual had 2 to 3 separate treatment periods during the 180-day follow-up. The total follow-up time was 2,912.6 person-years, with follow-up time during current antipsychotic treatment representing 1,146.0 person-years.

During the initial 180 days after the first antipsychotic prescription, 1,787 people died (25.0%), with 831 (46.5%) of the deaths occurring during current antipsychotic treatment periods. Within the first 60 days after index date, 643 people died during current antipsychotic treatment. The median duration of each treatment period that included at least 1 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 (HR = 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 but that was still higher than for antipsychotic treatment alone. Stratifying the analyses for duration of exposure to combination therapy showed that the risk of death 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 (HR = 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 an HR 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.

DISCUSSION

This nationwide study of 7,151 individuals with dementia initiating antipsychotic treatment found an increased risk of death 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 death.

Several international studies[5,19] have shown a greater risk of death for patients with dementia initiating antipsychotic therapy. However, comedication 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

Table 2. Mortality Rates and Risk of Mortality for Specific Combinations of Antipsychotics With Other Psychotropic Drugs Versus Antipsychotic Treatment Alone

Treatment Group	No. of Deaths Within 180 Days	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 [Reference]		1 [Reference]	
Antipsychotic + antidepressant	185	455.30	40.63 (35.18–46.93)	0.66 (0.55–0.79)	<.0001	0.61 (0.50–0.74)	.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					

[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 1 year before index date, nursing home residency, hospital admission 6 months prior to index date, and total number of days on antipsychotic treatment.
Abbreviation: BZDs = benzodiazepines and related drugs.

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 death 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[21,22] found an increased mortality among patients with schizophrenia using psychotropic drug combinations, ie, combinations of antipsychotics with benzodiazepines. 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 BZD regimens.

The more than 2-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, it 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 BZDs are combined with antipsychotics. Alternatively, the differential mortality in the 2 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 themselves are 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 subgroup.[23]

The median number of days from the dementia diagnosis to first antipsychotic prescription was 252. This observation suggests that focusing on non-pharmacologic approaches to prevent and manage neuropsychiatric symptoms may be crucial during this period of time. 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 implication suggests that clinicians should consider the risk and benefits before starting antipsychotics and particularly combination therapy of antipsychotics and BZDs. Further, this finding highlights that patients should be monitored closely during the first 60 days, including careful evaluation of treatment effect, side effects, and potential drug interactions. Interestingly, we found a decreased risk of death during combinations of antipsychotic and antidepressant treatment. There are various potential mechanisms to explain this decreased risk. 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. A randomized controlled trial[24] compared the effect of an SSRI with that of an antipsychotic in treating neuropsychiatric symptoms in hospitalized patients with dementia. The drugs had similar efficacy; however, side effects occurred more frequently among patients treated with an antipsychotic. 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 death with antipsychotic use continues after discontinued treatment. Some studies[11,19] 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. Our results suggest that there may be an extended risk-of-death window even after discontinuation of antipsychotic treatment or treatment breaks (former antipsychotic use). This risk seems to be modified, however, by the initiation or continuation of BZDs or antidepressant treatment. The dementia antipsychotic withdrawal trial (DART-AD)[25] 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. 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.[26] 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 used only 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 enable complete population data but cannot provide information on important confounders such as dementia severity and degree of behavioral symptoms. We addressed this limitation by adding time from dementia diagnosis to antipsychotic prescription. It is not possible to determine, through registry data, the actual amount of drug dosages consumed, but several sensitivity analyses were performed to assess a possible effect on our results. Our study was 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.[26] The specific cause of death was not included in this study, as the Danish Register of Causes of Death is 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 antidementia 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 death, while the combination of antipsychotics with antidepressants reduced the risk of death. 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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Supplementary Material

Article Title: Association of Benzodiazepines and Antidepressants With 180-Day Mortality Among Patients with Dementia Receiving Antipsychotic Pharmacotherapy: A Nationwide Registry-Based Study

Author(s): Ane Nørgaard, MD, PhD; Christina Jensen-Dahm, MD, PhD; Christiane Gasse, RPharm, PhD; Theresa Wimberley, MSc, PhD; Elsebet Steno Hansen, MD, PhD, and Gunhild Waldemar, MD, DMSca

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Supplementary Table 1. Diagnoses Used for Identification of Patients with Dementia

	ICD-10[a]
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

[a] ICD-10 has been used in Denmark since 1994

Supplementary Table 2. ATC Codes of Psychotropic Drugs

Antipsychotics	Sub Group	Generic Name	ATC Code
	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 Code
	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 Code
	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

Supplementary Table 3. Definition of Covariates

Covariate	Time of definition	Continuous versus dichotomous
Nursing home resident	The year before index date	Dichotomous
Charlson Comorbidity Index	All registered diagnoses before index date	Continuous
Psychiatric comorbidity	All registered diagnoses before index date	Dichotomous
Total number of drugs other than psychotropic drugs	Time-varying covariate with count over three months	Continuous
Hospital admission	Six months prior to index date	Dichotomous
Prior antipsychotic use	Ten years prior to index date	Dichotomous
Prior antidepressant use	One year prior to index date	Dichotomous