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Risk of hospitalization and hip fracture associated with psychotropic polypharmacy in patients with dementia: a nationwide register-based study

Johanne Købstrup Zakarias[a,b], Ane Nørgaard[a], Christina Jensen-Dahm[a], Christiane Gasse[c,d], Thomas Munk Laursen[e], Henrik Palm[f], René Ernst Nielsen[b,g], Gunhild Waldemar[a]

a. Danish Dementia Research Centre, Department of Neurology, Rigshospitalet, Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark
b. Department of Clinical Medicine, Aalborg University, Aalborg, Denmark
c. Department of Depression and Anxiety/Psychosis Research Unit, Aarhus University Hospital Psychiatry, Aarhus, Denmark
d. Department of Clinical Medicine, Aarhus University, Aarhus, Denmark
e. National Centre for Register-based Research, Aarhus University, Aarhus, Denmark
f. Department of Orthopedic Surgery, Copenhagen University Hospital Bispebjerg, Copenhagen, Denmark
g. Aalborg University Hospital - Psychiatry, Aalborg, Denmark

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Correspondence to:

Johanne Købstrup Zakarias, M.D.
Danish Dementia Research Centre
Department of Neurology, Neuroscience Centre
Rigshospitalet, University of Copenhagen
Blegdamsvej 9, #6991
2100 Copenhagen Ø, Denmark
Office phone: +45 3112 2789
Email: johanne.koebstrup.zakarias@regionh.dk

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Data availability statement

The data related to this paper are obtained from access to national health registries via Statistics Denmark and the authors cannot be authorized to transfer data to other researchers.

Conflict of Interest

All authors do have any conflicts of interest to declare. The authors do not have any affiliations or financial involvement with any organization or entity with financial interest in, or in financial competition with, the subject matter or materials discussed in the submitted work.

Abstract

Objective: To investigate the association of benzodiazepines and antidepressants on the risk of hospitalization and hip fracture in patients with dementia initiating antipsychotic drug treatment.

Methods: A register-based retrospective cohort study using data on all incident dementia cases (≥ 65 years) initiating antipsychotic treatment as monotherapy or in combination with benzodiazepines and/or antidepressants in Denmark from 2000 to 2015. The outcomes of interest were all-cause hospitalization and hip fracture. Cox proportional hazards models with adjustment for multiple variables were used to investigate risk of hospitalization and hip fracture within 180 days.

Results: The risk of all-cause hospitalization during 180-day follow-up was significantly increased by 55% (adjusted HR: 1.55, 95% CI: 1.29-1.86, p<0.0001), when antipsychotic use was combined with benzodiazepines, when compared to antipsychotic monotherapy. The association between the combination of antipsychotics and benzodiazepines with the risk of hip fracture did not reach statistical significance (adjusted HR: 1.50, 95% CI: 0.99-2.26, p=0.0534).

Conclusions: The observed increased risk of all-cause hospitalization and hip fracture may indicate increased drug-related adverse events. Thus, careful and regular monitoring is needed to assess response to treatment and decrease the risk of adverse events, when antipsychotics are combined with BZDs, albeit confounding cannot be fully excluded within the current design.

Key points

- Psychotropic drugs are widely used to treat neuropsychiatric symptoms in patients with dementia.
- Treatment with benzodiazepines in combination with antipsychotics was associated with a 55% increased risk of hospitalization and a trend for increased risk of hip fracture.
- The combination of antidepressants with antipsychotics was associated with a trend for increased risk of hospitalization, but not for hip fracture.
- Clinicians need to be aware of the potential increased risk of hospitalization and hip fracture for patients with dementia when planning psychopharmacological treatments.

Introduction

Neuropsychiatric symptoms in patients with dementia are common (1). Antipsychotic drugs are widely used to treat behavioral disturbances, aggression, and psychotic symptoms albeit the efficacy is questionable and non-pharmacological interventions are recommended as first-line approach (2,3). The use of antipsychotics in elderly patients with dementia is cause for safety concerns due to increased risk of hospitalization (4), cerebrovascular adverse events (3,5), cardiovascular adverse events (6,7,8), fall injuries (4), hip fractures (9), and increased rates of death (7,10,11). Furthermore, patients with dementia are more susceptible to side effects of other psychotropic drugs (12).

Psychotropic polypharmacy is found to be prevalent in previous observational studies among patients with dementia (13,14,15,16). A registry-based Swedish study in the general population indicated increased risk of hospitalization, injurious falls, and mortality among older adults who used psychotropic polypharmacy (4). However, no studies have addressed whether psychotropic polypharmacy may increase the risks already known to be associated with antipsychotic drug treatment in patients with dementia. In a previous study, we found that the combination of antipsychotics and benzodiazepines and related drugs (BZDs) was associated with increased mortality in elderly patients with dementia (17).
However, it is unknown to which extent the increased risk of hospitalization and falls also applies in patients with dementia.

Hospitalization is a serious adverse event and may be used as a surrogate marker for overall drug safety. Likewise, hip fracture is a potentially disabling or fatal adverse event in elderly people (18) and may be related to sedation or to impaired gait and balance due to pharmacological side effects. Generally, hospitalization and hip fracture are serious negative outcomes, particularly in vulnerable patients with dementia. It remains unclear whether concomitant treatment with either BZDs or antidepressants, when compared to antipsychotic monotherapy, are associated with an increased risk of hospitalization and hip fracture among patients with dementia. Observational studies are crucial to investigate potential negative health outcomes in patients with dementia treated with multiple psychotropic drug classes. Danish registries are unique with respect to capturing

prescription patterns utilizing a national cohort of dementia patients with complete follow-up. Thus, we aimed to investigate the risk of hospitalization and hip fractures among incident users of antipsychotics, also being treated with BZDs and/or antidepressant and to compare this with the risk among patients with dementia treated with antipsychotic monotherapy.

Methods

Study design

An observational cohort study using data from nationwide Danish registries.

Registry data sources

All permanent Danish residents are assigned a civil personal registration number (CPR number) at the time of birth or immigration (19), which allows for retrieval of demographic and health-care data at an individual level in the nationwide registers (20). The entire Danish population's contacts within the secondary health care system have been recorded in the two national hospital registers; The Psychiatric Central Research Register for psychiatric contacts since 1969 and the National Patient Register for somatic contacts since 1977 (21,22). Information comprises dates and discharge diagnosis (and outpatient contacts since 1995), which are registered according to World Health Organization's (WHO) International Classification of Diseases (ICD) codes. ICD-8 was used from 1970 to 1993 and ICD-10 from 1994 and onwards. Data on all dispensed prescription drugs have been registered in the Danish National Prescription Registry since 1994 (23). The drugs are registered according to the Anatomical Therapeutic Chemical (ATC) classification system with information on the date of dispensing, package size and strength. Statistics Denmark provided demographic data on sex and date of death.

Study population

Among all Danish residents aged 65 and older, we identified patients with incident dementia. Incident cases of dementia comprised individuals registered with a first-time diagnosis of dementia (see Table 1 for diagnostic codes) from a Danish hospital or at an outpatient visit, and/or individuals who had filled at least one prescription for an anti-dementia drug (ATC: N06D) between January 1st, 2000 and December 31st, 2015. Patients previously given an ICD-8 diagnosis of dementia from January 1st, 1980, through 1993 or an ICD-10 diagnosis of dementia from January 1st, 1994, through 1999 were excluded from the study population to ensure inclusion of incident patients only. Patients treated with anti-dementia drugs before January 1st, 2000 were also excluded.

Patients 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 1st, 2000 and December 31st, 2015.

The validity of the dementia diagnosis in the Danish registries has been shown to be low in patients diagnosed earlier than the age of 60 (24), and high in patients diagnosed at 65 years or older (25), thus the study population included those aged 65 and older.

Firstly, we excluded patients who used antipsychotics for 180 days washout period before first antipsychotic prescription after dementia diagnosis (index date) to avoid prevalent user bias. Secondly, we excluded patients who were admitted to a hospital for >30 consecutive days preceding the index date because information about drug use during hospitalization was not available in the national registries.

Psychotropic drug exposure

Psychotropic drug exposure was defined as use of antipsychotics (N05A, except lithium), BZDs (N05B, N05C), and/or antidepressants (N06A). Psychotropic polypharmacy was defined as concomitant use of psychotropic drugs from two or more drug classes. The treatment duration of each prescription was used to identify patients using psychotropic polypharmacy (26). 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 (27). 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. Antipsychotic treatment was the underlying exposure, and 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.

Outcomes

The outcomes of interest were all-cause hospitalization and hip fracture 180 days following index date. All-cause hospitalization was defined as an in-patient contact for any diagnosis. When counting the number of hospitalizations, a new hospitalization was defined as at least seven days apart from previous hospitalizations to exclude patients who were transferred from one department to another during the same hospitalization. International Classification of Diseases (ICD-10) codes for primary diagnosis at discharge from hospital were used to define hip fracture as fracture of the femur (S72.0), pertrochanteric fracture (S72.1), and subtrochanteric fracture (S72.2).

Covariates

Time since dementia diagnosis at index date was used as a marker of dementia severity. Somatic comorbidity (Charlson Comorbidity Index score) was assessed through registered diagnoses at discharge or at an outpatient visit before any time the index date (28,29). Psychiatric comorbidity was assessed using registered psychiatric contacts before first dementia diagnosis as well as antipsychotic drug use 10 years before the time of dementia diagnosis to detect chronic psychiatric illness. To assess comorbidity beyond registered diagnoses in hospital registries, we used data on the total number of drugs used other than psychotropic drugs (30). The total number of 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.

Data analysis

Individuals were followed from the date of the first antipsychotic filled prescription (index date) until emigration, death, occurrence of a hospitalization, a hip fracture or completion of 180 days of follow-up, whichever came first. As a primary model, an extended Cox regression model was performed to calculate hazard ratios (HR) for the 180-day risk of adverse events with the exposure of 1) antipsychotics only, 2) antipsychotics and antidepressants, 3) antipsychotics and BZDs and 4) antipsychotics, antidepressants and BZDs. The time since index date (initiation of antipsychotic drug use) was used as the underlying time scale. The full model included the following covariates (defined at index date): age, sex, calendar year, time since dementia diagnosis at index date, Charlson Comorbidity Index score, and prior psychiatric disease. In addition, the cumulative days with

antipsychotic treatment and total number of drugs used within the last three months were included in the full model as time dependent variables.

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 adverse events. 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. Furthermore, a sensitivity analysis on hospitalization was performed by calculating the outcome without excluding hospital contacts within seven days of the previous hospitalization. Data analysis was performed using SAS statistical software, version 9.4 (SAS Institute Inc., Cary, NC, USA).

Ethical Approval

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

Results

Study population

We identified 116,562 patients with incident dementia aged 65 or older between 2000 and 2015, of whom 34,536 (29.6%) initiated antipsychotic drug treatment after their dementia diagnosis, and thus were included in the study. We excluded 362 individuals due to hospital admissions exceeding 30 consecutive days prior to the index date. Another 5,293 individuals were excluded due to antipsychotic drug use within 180 days prior to the first antipsychotic prescription after diagnosis. This resulted in 28,879 individuals with complete follow-up information (see Figure 1 for population). Table 2 presents characteristics of the study cohort. The median time from dementia diagnosis to first antipsychotic prescription was 373 days (interquartile range: 80-957). During the initial 180 days after the first antipsychotic prescription, 9275 (32.1%) died.

Risk of all-cause hospitalization

During the initial 180 days after antipsychotic treatment, 1,011 (3.5%) hospitalizations occurred. Table 3A presents 180 days risk and rates of hospitalization for antipsychotic monotherapy and specific combinations of antipsychotics with other psychotropic drug classes in specific treatment groups. In comparison with antipsychotic monotherapy, use of antipsychotics in combination with BZDs was associated with a 55% significant increase in the risk of hospitalization (adjusted HR: 1.55, 95% CI: 1.29-1.86, p<0.0001). Use of antipsychotics in combination with antidepressant showed a trend for risk of hospitalization with a 14% increase which approached statistical significance (adjusted HR: 1.14, 95% CI: 0.98-1.33, p=0.0851). Furthermore, a 26% significant increase was observed with antipsychotics in combination with BZDs and antidepressants (adjusted HR: 1.26, 95% CI: 1.04-1.54, p=0.0210).

Risk of hip fracture

In total, 173 (0.6%) hip fractures occurred in 180 days following antipsychotic treatment (see Table 3B). Use of antipsychotics in combination with BZDs resulted in a numerically increased HR of 1.50 95% CI: 0.99-2.26 for hip fracture, albeit statistically non-significant (p=0.053). However, treatment periods with the combination of antipsychotics and antidepressants showed no association with hip fractures in comparison to antipsychotics alone (adjusted HR: 0.83, 95% CI: 0.57-1.21, p=0.3398).

Likewise, treatment combinations of antipsychotics, antidepressants, and BZDs showed no association with hip fracture (adjusted HR: 0.93, 95% CI: 0.58-1.49, p=0.7524).

Sensitivity analyses

In sensitivity analyses of 0.25 DDD per day of antipsychotic treatment, HRs were slightly higher in treatment with antipsychotics and BZDs as well as combinations of antipsychotics, antidepressants, and BZDs regarding hospitalization (data not shown). When we assumed an intake of 1.0 DDD per day, the HRs were slightly higher in treatment combinations of antipsychotics, antidepressants, and BZDs regarding hospitalizations and in combinations of antipsychotics and BZDs regarding hip fractures. Overall, the conclusion from the main analysis did not change.

Discussion

In this nationwide study of 28,879 patients with dementia initiating antipsychotic treatment, the risk of all-cause hospitalization during 180-day follow-up was significantly increased markedly by 55%, when antipsychotic use was combined with BZDs, as well as when patients were exposed to antipsychotics, antidepressants and BZDs in combination. A similar association between psychotropic drug treatment and hip fracture did not reach statistical significance in the current study, which might be a result of lack of power.

To our knowledge, this is the first study describing risk of hospitalization and hip fracture associated with use of psychotropic polypharmacy in patients with dementia.

However, a Swedish register-based case-control study in the general elderly population investigated risk of fall injuries, hospitalization, and mortality with psychotropic drugs (4), and found that treatment with four psychotropic drugs was associated with a 27% significantly increased risk of hospitalizations compared to no use. Similarly, our study found a significantly increased risk of 55% in hospitalizations when patients with dementia were treated with antipsychotics and BZDs compared to antipsychotic monotherapy. The Swedish study analyzed a subgroup of patients with dementia and found a slight (7%), but significant decrease in the risk of hospitalizations with antidepressant monotherapy compared to no use. The current study did not investigate antidepressant monotherapy. However, we found a trend for a 14% increased risk of hospitalizations with the combination of antipsychotic and antidepressant use when compared to antipsychotic treatment alone, as our finding only approached statistical significance in the adjusted model.

Concerning the risk of hip fracture, our study observed a significant increase of 58% associated with combinations of antipsychotics and BZDs as compared to antipsychotics alone when using a crude analysis, though the increase was 50% and only approached statistical significance after adjusting for potential confounders. The previously mentioned Swedish study in the general elderly population found an increase of 53% in hip fractures due to falls, when the older population was treated with four psychotropic drugs compared to no use. However, the Swedish study found no association between number of psychotropic drugs and hip fractures in a subpopulation of patients

with dementia. On the contrary, a Finnish register-based study reported a 43% increase in the risk of hip fracture associated with monotherapy of BZDs in community-dwelling patients with Alzheimer's disease when compared to community-dwelling patients without Alzheimer's disease (31). This is in line with our findings in a much broader population of patients with dementia, which indicated a trend for increase in the risk of hip fracture when treated with antipsychotics and BZDs compared to monotherapy with antipsychotics. It is worth noticing that the mortality during the 180-day follow-up was high (32%) as described in a previous study (17), which also found a significant increase in risk of mortality in patients with dementia treated with combinations of antipsychotics and BZDs.

Two other register-based studies have demonstrated an increased risk of hip fracture in patients on antidepressant treatment. A Finnish register-based study found that monotherapy with antidepressants was associated with a 61% increase in risk of hip fracture among community-dwelling patients with Alzheimer's disease when compared to those without Alzheimer's disease (32). These results are not directly comparable to our findings, due to differences in exposure and comparison group, in which we found no association between hip fracture and treatment combinations of antipsychotic and antidepressant use as compared to antipsychotic treatment alone. A US cohort study investigated risk of fracture (pelvic fracture, upper femur fracture, lower femur fracture, and pathological fracture) with antidepressant monotherapy compared to antipsychotic monotherapy in patients with dementia living in nursing homes (33), and found a 35% increased risk in pelvic and hip fracture among patients treated with antidepressant monotherapy. However, the study used data from private health insurance, thus investigating a selected population compared to our study.

In our study, when antipsychotics were combined with BZDs regardless of antidepressant use, it was associated with a significantly and markedly increased risk of hospitalization and with a trend for increased risk of hip fracture compared with antipsychotic monotherapy. Use of antipsychotics can lead to impaired gait due to extrapyramidal symptoms, hypotension or sedation and combined with use of BZDs pharmacodynamic interactions may result in increased side effects via synergistic effects. It could be hypothesized that the sedative effects increase the risk of serious infections such

as pneumonia as well as risk of serious falls potentially leading to hip fracture. Vulnerable elderly patients with dementia have difficulties breaking a fall and run a higher risk of hip fracture.
Our study observed that concomitant treatment with antipsychotics and antidepressants was not associated with any increase in neither hospitalization nor hip fracture as compared to treatment with antipsychotics alone. Clinicians may have chosen to combine antipsychotics and antidepressant to reduce the dose of antipsychotics, thus leading to a lower risk profile for these patients but our data does not contain information on the dose of antipsychotics. Antidepressants are often administered for a longer treatment period, and thus it may be hypothesized that our population represents patients who have used antidepressant drugs for a long time and consequently better tolerate potential adverse events of the drugs.

The significantly increased risk of hospitalization may reflect a wide range of potential serious adverse events related to psychotropic polypharmacy, particularly in vulnerable patients with dementia, such as falls, infections, or delirium. Furthermore, patients with dementia are also at high risk of delirium following hospitalization which may lead to further complications.
Healthcare professionals need to be aware of the potential increased risk of hospitalization and possibly also hip fracture for patients with dementia when planning pharmacological treatments.

Despite the strengths in a long follow-up period and a large sample, with no loss to follow-up, the study has limitations. The register data did not provide information on severity of dementia or details on neuropsychiatric symptoms. Moreover, we had no information on the indications for use of psychotropic polypharmacy, and this enlists a risk of confounding by indication, where severely ill patients are treated with psychotic polypharmacy, and thus becomes a proxy for disease, either dementia or other somatic, more so than a causal association between risk of hospitalization and drug exposure thus were not able to adjust for neuropsychiatric symptoms. Furthermore, all-cause hospitalization was used as a surrogate marker for severe adverse events or uncontrolled disease, however not all adverse events result in hospitalization as some adverse events may be managed by the primary care physicians. Another important limitation is that our observational study indicates an association between exposure and outcome, but causality cannot be established, and

it is possible that residual confounding remains (34). Thus, as a result of design and data availability, we cannot exclude that our findings could also be influenced by confounding by indication.

One of the strengths of this study is its nationwide registry data with complete prescription data and diagnoses from the secondary health care sector, thus avoiding problems of selection bias. It was possible to assess real-life prescription patterns due to the detailed longitudinal data, which is not possible in a range of other studies as these only have information about initiation of treatment. The longitudinal follow-up design in our study is of great importance as patients may change treatment during the 180-day follow-up. Moreover, Denmark has free access to public health care services, thus removing a potential confounder compared to studies conducted in countries where private health insurance is needed to access adequate treatment.

Conclusion

In patients with dementia, concomitant use of antipsychotics and BZDs was associated with a significantly increased risk of all-cause hospitalization and a trend for increased risk of hip fracture when compared to antipsychotic treatment alone. These are serious drug-related adverse events and thus careful and regular monitoring is needed to assess response to treatment and lower the risk of adverse events. Our results lend further support to the general guideline already issued by several authorities that non-pharmacological treatments should be considered prior to antipsychotic treatment and combination of antipsychotics and BZDs should be limited and closely monitored.

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Table 1. ICD-8 and ICD-10 codes for dementia

Dementia diagnoses	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

Figure 1: Selection of the study cohort

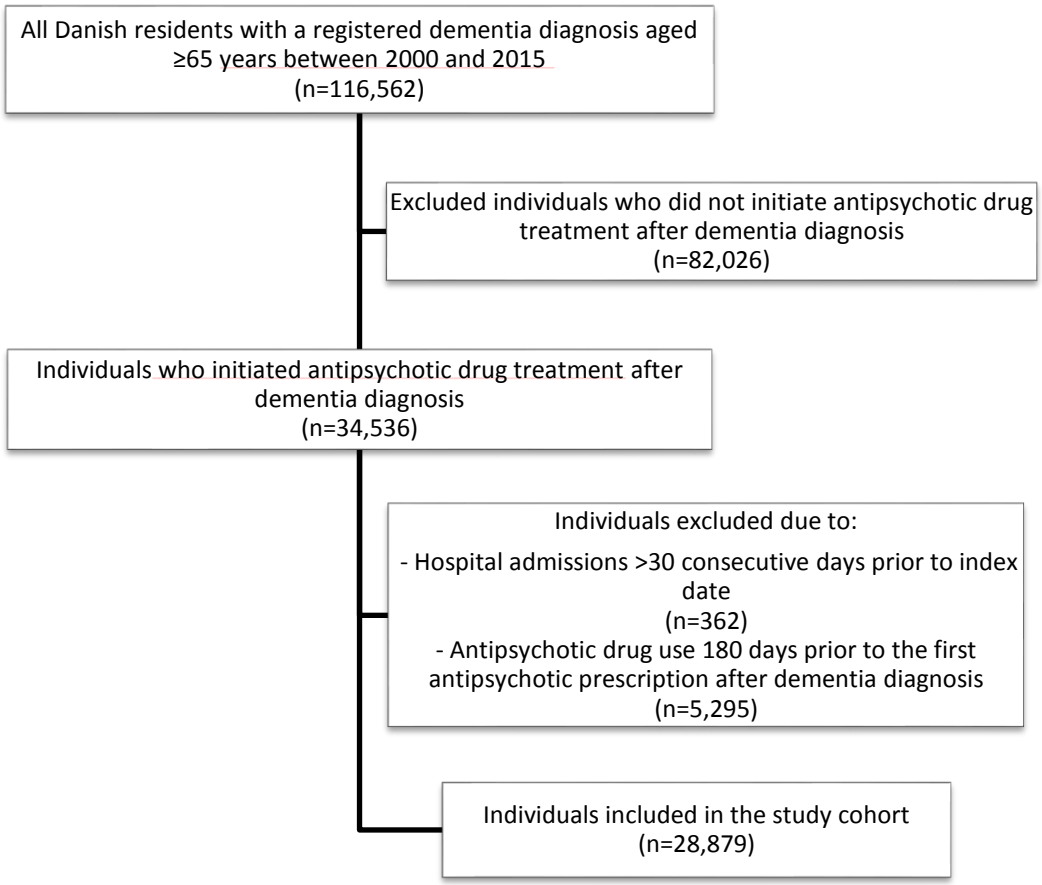

Table 2. Baseline characteristics of the study cohort

Characteristic	n= 28,879
Age (y) at time of dementia diagnosis, mean (SD)	81.6 (6.6)
Age (y) at index date, mean (SD)	83.3 (6.4)
Female sex, No. (%)	17,338 (60.0%)
Time (d) from first dementia diagnosis to first antipsychotic prescription, median (IQR)	373 (80-957)
No. of drugs other than psychotropic drugs (at index date), median (IQR)	5 (5-8)
Charlson Comorbidity Index score (excluding dementia), No. (%)	
0	4,957 (17.1)
1	7,984 (27.7)
≥2	15,938 (55.2)
Psychiatric diagnosis prior to dementia diagnosis, No. (%)	4,252 (14.7)
Prior antipsychotic use, No. (%) [a]	4,578 (15.9)

Abbreviations: IQR, Interquartile range; SD, standard deviation.
[a]Use of antipsychotic drugs 10 years prior to index date.

Table 3A. 180-Day Rates and Risk of Hospitalization for Specific Combinations of Antipsychotics with other Psychotropic Drugs versus Antipsychotic Treatment Alone

	No. hospitalization within 180 days	Person-years	Rate of hospitalization per 100 person-years (95% CI)	Crude hazard ratio (95% CI)	p-value	Adjusted hazard ratio[a] (95% CI)	p-value
Antipsychotic	369	3090.44	11.94 (10.78-13.22)	1 [Reference]		1 [Reference]	
Antipsychotic + BZDs	180	654.74	27.49 (23.76-31.82)	2.32 (1.94-2.78)	<.0001	1.55 (1.29-1.86)	<.0001
Antipsychotic + Antidepressant	323	1770.57	18.24 (16.36-20.34)	1.51 (1.30-1.75)	<.0001	1.14 (0.98-1.33)	0.0851
Antipsychotic + Antidepressant + BZDs	139	588.42	23.62 (20.00-27.89)	2.00 (1.65-2.44)	<.0001	1.26 (1.04-1.54)	0.0210
Total	1,011	6,104.17					

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), and total number of days on antipsychotic treatment.

Table 3B. 180-Day Rates and Risk of Hip Fracture for Specific Combinations of Antipsychotics with other Psychotropic Drugs versus Antipsychotic Treatment Alone

	No. hip fracture within 180 days	Person-years	Rate of femur fracture per 100 person-years (95% CI)	Crude hazard ratio (95% CI)	p-value	Adjusted hazard ratio[a] (95% CI)	p-value
Antipsychotic	68	1,842.14	3.69 (2.91-4.68)	1 [Reference]		1 [Reference]	
Antipsychotic + BZDs	36	654.34	5.50 (3.97-7.63)	1.58 (1.10-2.37)	0.0266	1.50 (0.99-2.26)	0.0534
Antipsychotic + Antidepressant	46	1,766.05	2.60 (1.95-3.48)	0.70 (0.48-1.02)	0.0663	0.83 (0.57-1.21)	0.3398
Antipsychotic + Antidepressant + BZDs	23	581.02	3.96 (2.63-5.96)	1.15 (0.72-1.81)	0.5698	0.93 (0.58-1.49)	0.7524
Total	173	4,843.55					

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), and total number of days on antipsychotic treatment.