Effects of Antipsychotics on Secular Mortality Trends in Patients With Alzheimer's Disease

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ABSTRACT

Objective: To investigate secular changes in mortality rates between patients with Alzheimer's disease (AD) and the general population as well as changes in antipsychotic drug treatment and the association between drug treatment and mortality in patients with AD in Denmark during a 12-year study period.

Methods: This nationwide, retrospective cohort study identified all-cause mortality in all Danish patients with incident *ICD-10*–defined AD from 2000 through 2011. The cumulative antipsychotic dosages from dementia diagnosis until end of study for each participant were calculated and categorized in 1 of 5 groups per the World Health Organization Defined Daily Doses (DDDs). Data were obtained from relevant Danish national registers.

Results: The study included 32,001 patients (11,194 male and 20,807 female). During the study period, an increasing trend was found in median survival time, but no decline was seen in standardized mortality ratios, which spanned from 1.19 (95% CI, 0.98–1.46) in 2001 to 1.52 (95% CI, 1.38–1.68) in 2011. The findings showed a decline in proportion of patients with incident AD exposed to antipsychotic drugs as well as decline in mean annual cumulative DDDs. Adjusted Cox regression analyses revealed that current exposure to antipsychotic drugs was associated with increased mortality, although hazard ratios declined during the study period from 2.24 (95% CI, 2.07–2.43) in 2000–2002 to 1.24 (95% CI, 1.09–1.41) in 2009–2011, with *P* values < .001.

Conclusions: These findings appear to underscore the current guideline recommendations for using antipsychotic drugs at only the lowest effective dose and only in patients for whom all non-pharmacologic options have been exhausted. Furthermore, these results seem to indicate that the reduced use of antipsychotic drugs has no impact on relative mortality, suggesting that the AD population has gained less from improvements in care of other diseases that impact mortality rates in patients with AD as well as in the general population.

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Neuropsychiatric symptoms in patients diagnosed with Alzheimer's disease (AD) are common.[1] The European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) have never approved a specific pharmacotherapy for this indication.[2] Risperidone has been approved by EMA for only short-term treatment of persistent aggression in patients with moderate to severe AD not responding to other non-pharmacologic treatments.[2] Despite the lack of approved treatments, the off-label pharmacologic treatment of neuropsychiatric symptoms associated with AD is common.[3] In 2005, the FDA and European agencies issued warnings against the use of antipsychotic drugs, and guidelines have since suggested restricting the use of this drug class in patients diagnosed with dementia due to an increased risk of cerebrovascular events and increased mortality.[4,5] These findings were questioned by pharmacoepidemiologic studies,[6,7] but later underscored by long-term randomized controlled trials.[8] Several epidemiologic studies have shown a decrease in the use of antipsychotic drugs in AD over time that complies with guidelines,[9–12] although not all studies have shown this trend.[13] We have previously shown an association between lifetime cumulative antipsychotic drug dosages and all-cause mortality in patients with incident AD[14] independent of current antipsychotic exposure and investigated the association between cumulative antipsychotic drug dosages and specific causes of death.[15] Currently, there is a lack of nationwide epidemiologic studies investigating the effects of reducing antipsychotic drug treatment on mortality in patients diagnosed with AD.

In this study, we investigate secular changes in mortality rates between patients with incident AD and the general population as well as the secular changes in antipsychotic drug treatment and the association between drug treatment and mortality in a model including all patients with newly diagnosed AD in Denmark during a 12-year study period.

METHODS

Design

This was a nationwide, population-based, retrospective cohort study of all-cause mortality in patients diagnosed for the first time with dementia in AD during the study period from 2000 to the end of 2011. Every patient was followed from date of diagnosis until death or end of study (whichever came first). We compared patients diagnosed in the time periods of 2000 to end of 2002, 2003 to end of 2005, 2006 to end of 2008, and 2009 to end of 2011 to each other as well as to the overall Danish population.

Clinical Points

- Previous studies have shown an increased risk of mortality in patients with dementia who have been exposed to antipsychotic drugs. Guidelines have suggested reducing use of these agents, but studies evaluating the effects on mortality of changes in prescription patterns have not been conducted.
- This study found that a reduction in antipsychotic drug use over the study period did not result in a lowered relative mortality for patients with AD dementia as compared to the background population.
- The study supports the general recommendation to minimize antipsychotic drug treatment in the current population, but also suggests that AD dementia patients might not have gained as much from improvements in care of physical diseases as compared to the background population.

Sample

We formed a cohort of patients from the total Danish population with incident AD defined as receiving an *ICD-10* diagnosis of either F00x (dementia in Alzheimer's disease) or G30x (Alzheimer´s disease) from January 1, 2000, to December 31, 2011. Persons previously given an *ICD-8* dementia diagnosis from January 1, 1980, through 1993 or an *ICD-10* diagnosis of dementia (F00x, F01x, F02x, F03x, G30x, or G31x) from January 1, 1994, through 1999 were excluded from the analysis. Patients treated with antidementia drugs (ATC N06D), as defined by picking up a prescription in the period January 1, 1998, to first AD diagnosis, were also excluded to ensure inclusion of incident patients only.

Medication Measures

All medication variables were coded as time-dependent variables, with patients being coded as nonexposed until first prescription.

Antipsychotics were defined via Anatomical Therapeutic Chemical (ATC) classification as ATC N05A, which includes all typical and atypical antipsychotic drugs, excluding lithium (ATC N05AN).[16]

The current exposure variable was based on the use of antipsychotics over the previous year and was grouped as present or absent with index defined as a prescription for an antipsychotic drug. The cumulative antipsychotic dosages from dementia diagnosis until end of study for each participant were calculated and categorized in 1 of 5 groups per the World Health Organization Defined Daily Doses (DDDs).[16] The following groups were defined: (1) baseline: no antipsychotic treatment at all; (2) $0 < \text{DDDs} < 90$; (3) $90 \leq \text{DDDs} < 365$; (4) $365 \leq \text{DDDs} < 730$; and (5) ≥ 730 DDDs). Because of the definitions, no patients currently exposed to antipsychotics could be in the baseline cumulative exposure group. The groups were defined arbitrarily, but the definition has been utilized before in a similar study.[14]

Explanatory Variables for the Adjusted Model

Severity of neuropsychiatric symptoms. The current Danish registers do not include data on severity of neuropsychiatric symptoms of AD. Therefore, we used number of psychiatric bed days and number of psychiatric outpatient contacts after incident dementia diagnosis as proxy markers of neuropsychiatric symptom severity.

Psychiatric comorbid disorder. Psychiatric comorbidity was scored from 0 to 5, with a point given for a diagnosis in each of the following groups: psychosis, affective disorders, substance misuse, other psychiatric diagnosis, and intentional self-harm. This score has previously been utilized in a similar study.[14,15]

Somatic comorbid disease. We divided somatic diseases into the following groups: cardiovascular disease, cancer, infection, diabetes, epilepsy, lower respiratory disease, and other somatic diseases (excluding AD). One point was added for a diagnosis in each of the groups unless the diagnosis occurred before the age of 51 years for men or 56 years for women, for whom 2 points were added instead due to an increased risk associated with early onset of disease. This score has previously been utilized in a similar study.[14,15]

Cardiovascular risk factors. The current Danish registers do not include data on blood pressure or blood test results, such as lipid and glucose levels. Most cases of hypertension, increased cholesterol, and type 2 diabetes are treated by general practitioners, who do not report diagnoses to the Danish registers. As proxy measures of arterial hypertension, increased cholesterol, and diabetes, we used—in addition to the actual diagnoses (as described in the previous paragraph)—data on the prescription of antihypertensive drugs (ATC C02), drugs used to lower lipids (ATC C10), and drugs for treatment of diabetes (blood glucose–lowering drugs [excluding insulins]: ATC A10B, A10XA; insulins: ATC A10A). All medication variables were coded as time-dependent variables, with patients being coded as nonexposed until first prescription.

Registers Used in the Study

Data on psychiatric contacts and psychiatric disorders were retrieved from the Danish Psychiatric Central Research Register (DPCRR).[17] Data on hospital contacts and somatic diseases were retrieved from the Danish National Patient Register (NPR).[18] Data on deaths were retrieved from the Danish Register of Causes of Death.[19] Data on prescription of medication are available from January 1, 1995, in the Danish National Prescription Registry (DNPR).[20] Data on inpatients' medication use linked to the individual patients are not available.

All register data are linked to each individual patient via the unique personal identification number assigned to all residents at birth or upon immigration.

Data are not accessible to the public, and access is given after approval by the Danish Data Protection Agency, the Danish Health Authority, and Statistics Denmark.

Statistical Analysis

Simple descriptive analyses of demographics and crude risks of mortality were conducted initially. Analyses of trends in changes in median age at death for patients

diagnosed in each time period were conducted second. Third, we calculated the standardized mortality ratios (SMRs) for each year in the study period, defined as the ratio of observed deaths in patients diagnosed with AD dementia in the previous year as compared to number of deaths in the Danish population in the same age and sex strata.[21] Cox regression analysis of all-cause mortality, investigating effects of antipsychotic treatment on all-cause mortality, was conducted last. The first model included both current exposure and cumulative exposure, as described previously in the Methods section, whereas the second model included only cumulative exposure. Both models adjusted for severity of NPS, psychiatric comorbidity, somatic comorbidity, and cardiovascular risk factors for each defined time period.

The Cox regression analyses were conducted with entry time defined as time of birth, and all variables were coded as time-dependent to avoid misclassification of time and to avoid immortal time biases.[22] Most covariates were coded as discrete rather than continuous variables, as assumptions of linearity otherwise could not be met.

The 2 models were computed to investigate if current exposure interfered with the effects of cumulative antipsychotic drug dosages, an interaction termed *effect modification*. Effect modification is when the magnitude of an association between a variable and an outcome differs depending on a third variable, in this case the current exposure. With the current models of analysis, we were able to investigate the effects of cumulative antipsychotic exposure with and without current exposure, making results easier to interpret.

P values < .05 were considered statistically significant. Statistical analyses were performed with STATA 13[23] via remote access to the Statistics Denmark server.

RESULTS

We included 32,001 patients (11,194 men and 20,807 women) with a mean ± SD age at diagnosis of 80.25 ± 7.99 years (men: 78.94 ± 8.30 years, women: 80.95 ± 7.73 years) during the total study period from January 1, 2000, to December 31, 2011. Demographics from each study period are shown in Table 1.

During the study period, we saw an increasing trend in median survival time for patients who had been diagnosed with AD for the first time. For patients diagnosed in the period from January 1, 2000, to December 31, 2002, the median (95% confidence interval [CI]) age at death was 85.26 (85.03–85.57) years. The median (95% CI) age at death increased for patients diagnosed in each of the other 3 time periods: 2003–2005: 86.55 (86.38–86.75) years; 2006–2008: 88.00 (87.82–88.18) years; and 2009–2011: 90.97 (90.75–91.16), *P* < .001. Similarly, we investigated SMR in the calendar year after diagnosis; as shown in Table 2,

Table 1. Demographics of the Study Population

	2000–2002			2003–2005			2006–2008			2009–2011		
Variable	Total	Men	Women	Total	Men	Women	Total	Men	Women	Total	Men	Women
Patients, n (%)	4,794	1,696 (35)	3,098 (65)	7,839	2,623 (33)	5,216 (67)	8,890	3,093 (35)	5,797 (65)	10,478	3,782 (36)	6,696 (64)
Deaths, n (%)	4,407 (92)	1,588 (94)	2,819 (91)	6,411 (82)	2,259 (86)	4,152 (80)	5,380 (61)	2,028 (66)	3,352 (58)	3,001 (29)	1,208 (31.94)	1,793 (26.78)
Survival, median (95% CI), y	85.26 (85.03–85.57)	83.60 (83.21–84.00)	86.29 (85.99–86.66)	86.55 (86.38–86.75)	84.97 (84.59–85.23)	87.43 (87.19–87.65)	88.00 (87.82–88.18)	85.94 (85.69–86.23)	88.95 (88.70–89.16)	90.97 (90.75–91.16)	89.18 (88.79–89.50)	81.73 (91.41–92.13)
Age at diagnosis, mean (95% CI), y	78.96 (78.73–79.19)	77.76 (77.36–78.17)	79.62 (79.35–79.89)	80.00 (79.83–80.17)	78.89 (78.59–79.20)	80.56 (80.35–80.76)	80.27 (80.10–80.44)	78.86 (78.59–79.15)	81.03 (80.83–81.23)	81.00 (80.85–81.15)	79.56 (79.30–79.82)	81.82 (81.63–82.00)
Exposed to antidementia, n (%)	4,070 (85)	1,431 (84)	2,639 (85)	6,869 (88)	2,274 (87)	4,595 (88)	7,755 (87)	2,669 (86)	5,086 (88)	8,548 (82)	3,066 (81)	5,482 (82)
Cardiac risk factors, n (%)	3,165 (66)	1,186 (70)	1,979 (64)	5,703 (73)	1,998 (76)	3,705 (71)	6,848 (77)	2,427 (78)	4,421 (76)	8,265 (79)	3,050 (81)	5,215 (78)
Somatic comorbidity, n (%)	4,756 (99)	1,681 (99)	3,075 (99)	7,793 (99)	2,612 (100)	5,181 (99)	8,847 (100)	3,077 (99)	5,770 (100)	10,392 (99)	3,761 (99)	6,631 (99)
Psychiatric comorbidity, n (%)	3,375 (70)	1,160 (68)	2,215 (72)	5,693 (73)	1,939 (74)	3,754 (72)	6,089 (68)	2,153 (70)	3,936 (68)	6,027 (58)	2,181 (58)	3,846 (57)
No. of bed days per year, mean (95% CI)	2.59 (2.18–3.01)	3.18 (2.47–3.89)	2.28 (1.77–2.78)	1.66 (1.39–1.92)	2.60 (1.97–3.23)	1.19 (0.94–1.43)	1.73 (1.45–2.01)	2.26 (1.72–2.80)	1.45 (1.13–1.77)	1.95 (1.41–2.49)	2.02 (1.36–2.69)	1.91 (1.15–2.67)
No. of outpatient contacts per year, mean (95% CI)	1.04 (1.00–1.09)	1.15 (1.07–1.24)	0.98 (0.94–1.03)	0.95 (0.92–.098)	1.06 (1.00–1.12)	0.89 (0.86–.093)	0.87 (0.82–0.92)	0.98 (0.85–1.11)	0.81 (0.78–0.84)	1.28 (1.21–1.36)	1.37 (1.21–1.54)	1.23 (1.16–1.30)
Exposed to antipsychotics, n (%)	2,226 (46)	831 (49)	1,395 (45)	3,001 (38)	1,065 (41)	1,936 (37)	2,736 (31)	1,048 (34)	1,688 (29)	1,787 (17)	689 (18)	1,098 (16)
Annual cumulative DDD, mean (95% CI)	31.38 (29.32–33.45)	33.16 (28.73–37.58)	30.41 (28.33–32.50)	25.28 (23.95–26.60)	28.01 (25.43–30.59)	23.90 (22.39–25.41)	20.91 (19.65–22.17)	22.46 (20.32–24.61)	20.08 (18.51–21.64)	10.58 (9.73–11.42)	11.24 (9.81–12.66)	10.20 (9.15–11.26)

Abbreviations: CI = confidence interval, DDD = Defined Daily Dose.

Table 2. Standardized Mortality Ratio (SMR) in the Total Population and by Sex for Each Calendar Year After Diagnosis for Incident Patients With Alzheimer's Disease

	Total		Men		Women	
Year	SMR	95% CI	SMR	95% CI	SMR	95% CI
2001	1.19	0.98–1.46	1.30	0.96–1.77	1.12	0.86–1.46
2002	1.48	1.28–1.73	1.80	1.45–2.24	1.27	1.02–1.57
2003	1.34	1.17–1.53	1.38	1.12–1.70	1.31	1.10–1.56
2004	1.28	1.12–1.45	1.53	1.27–1.85	1.11	0.93–1.33
2005	1.32	1.16–1.49	1.38	1.13–1.68	1.28	1.09–1.50
2006	1.39	1.23–1.56	1.58	1.32–1.89	1.27	1.09–1.48
2007	1.37	1.22–1.54	1.62	1.37–1.92	1.23	1.05–1.43
2008	1.23	1.10–1.39	1.50	1.27–1.78	1.06	0.90–1.25
2009	1.38	1.23–1.54	1.66	1.40–1.97	1.23	1.06–1.42
2010	1.42	1.28–1.56	1.69	1.46–1.96	1.26	1.10–1.43
2011	1.52	1.38–1.68	1.59	1.36–1.86	1.48	1.31–1.68

we did not find a comparable trend in decreasing SMRs over time. Analyses that included a 3-year period after incident diagnosis showed similar results (data not shown).

We found a decline in the proportion of patients with incident AD exposed to antipsychotic drugs and a decline in mean annual cumulative DDDs. In the period from 2000 to 2002, 2,226 (46%) of the 4,794 incident AD patients were exposed to antipsychotic treatment. From 2003 to 2005, 3,001 (38%) of the 7,839 incident AD patients were exposed to antipsychotic treatment, whereas only 2,736 (31%) of the 8,890 incident AD patients diagnosed from 2006 to 2008 and 1,787 (17%) of the 10,478 patients diagnosed in the last period from 2009 to 2011 were exposed. Similarly, we found a decline in mean annual cumulative DDDs across the 4 time periods, with a mean (95% CI) annual DDD of 31.38 (29.32–33.45) per year from 2000 to 2002, 25.28 (23.95–26.60) from 2003 to 2005, 20.91 (19.65–22.17) from 2006 to 2008, and 10.58 (9.73–11.42) from 2009 to 2011. Results separated by sex are shown in Table 1.

In the adjusted Cox regression analyses, we found that current exposure to antipsychotic drugs was associated with an increased mortality in all 4 investigated time periods (data shown as hazard ratio [HR] [95% CI]; 2000–2002: 2.24 [2.07–2.43], $P < .001$; 2003–2005: 2.02 [1.88–2.17], $P < .001$; 2006–2008: 1.71 [1.57–1.85], $P < .001$; and 2009–2011: 1.24 [1.09–1.41], $P < .001$).

Cumulative dosages of antipsychotic treatment increased the rate of mortality, as shown in Table 3. Associations of explanatory variables with all-cause mortality in the regression analysis are also shown in Table 3.

Because current exposure and cumulative dosages of antipsychotic medication were associated, we conducted a secondary analysis without current exposure, which showed that all-cause mortality increased in each successive dosage group except for cumulative DDDs >730, with adjustment made for remaining explanatory variables, as shown in Table 4.

DISCUSSION

In this study of 32,001 patients, we observed 19,199 deaths during the 12-year study period. We saw an increased mean age at time of diagnosis as well as an increase in median age at death for each consecutive study period, most likely as a result of an overall increased mean age at death for the general population. When investigating SMRs of patients with AD as compared to the general population, we found no changes over the consecutive study periods investigated.

In the Cox regression analysis, we saw a decrease in hazard ratio for current exposure, which could correspond to the lowered mean antipsychotic dose prescribed, suggesting a dose-response relationship, which has been investigated only scarcely before now[24] but is in line with the recommendation of using the lowest effective dosage.[25] The association between cumulative antipsychotic drug dosages and mortality seemed to be unaffected by the changes in prescription patterns, but these variables are also defined to incorporate changes in dosage used.

Previous studies have investigated changes in drug use among patients diagnosed with dementia before and after the black box warnings were issued regarding antipsychotic drug use.[4,25] Studies in Denmark,[9] but also in other European countries,[12,26–29] Asia,[30] and North America,[31–33] have mostly shown a decrease in use, although in the current study we show a decreased exposure to antipsychotics between the first 2 time periods, which should have been minimally affected by the warnings issued in 2005.

Studies so far have not investigated the effects on mortality associated with decreased drug utilization. We showed a decreased relative risk associated with current exposure in that the mean current exposure had diminished over time with an unchanged effect of cumulative dosages, which are adjusted for dose given. Simultaneously, as the proportion of patients who were exposed decreased and drug dose diminished, we saw a trend toward increasing median age at death for patients with AD. Despite the lowered use and dose of antipsychotic drugs in AD patients, we did not find a lowered relative mortality rate in AD patients as compared to the background population, as shown by an unchanged or increasing SMR over time, a finding similar to those in other countries.[34–37] As SMRs were unchanged over time, our data suggest that the impact of antipsychotic drug use on mortality in incident AD patients is negligible, which would be in opposition to the findings from our Cox regression analyses as well as multiple previous studies.[25] Therefore, we find it more likely that the mortality rates are defined by multiple factors,[38] including antipsychotic drugs. If one risk factor, antipsychotic drugs, is decreasing but relative mortality as compared to the background population is unchanged or even increasing, data suggest that the AD population has gained less from possible improvements in care of other physical diseases that may be factors that define mortality rates as compared to the background population.[39]

In our all-cause mortality study,[14] we showed an apparent association between increasing cumulative antipsychotic drug dosages and decreased all-cause mortality. In the current study, we found a similar association, at least for the 2000–2002 and 2003–2005 study periods. When conducting

Table 3. Cox Regression Analysis With All-Cause Mortality as Outcome[a]

	Study Period 2000–2002			Study Period 2003–2005			Study Period 2006–2008			Study Period 2009–2011		
Variable	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Antipsychotic Medication												
Current Exposure												
Exposed within calendar year	2.24	2.07–2.43	<.001	2.02	1.88–2.17	<.001	1.71	1.57–1.85	<.001	1.24	1.09–1.41	0.001
Cumulative Exposure												
0 DDDs		Reference			Reference			Reference			Reference	
0 < DDDs ≤ 90	1.36	1.25–1.49	<.001	1.49	1.39–1.61	<.001	1.56	1.43–1.69	<.001	1.77	1.55–2.02	<.001
90 < DDDs ≤ 365	1.08	0.97–1.20	.162	1.17	1.06–1.29	<.01	1.09	0.97–1.23	.163	1.47	1.18–1.82	<.001
365 < DDDs ≤ 730	0.75	0.64–0.88	<.01	1.02	0.87–1.20	.828	1.19	0.96–1.49	.113	1.48	0.87–2.54	.149
730 < DDDs	0.51	0.40–0.65	<.001	0.79	0.62–1.00	<.05	0.82	0.58–1.15	.250	1.27	0.51–3.13	.608
Explanatory Variables												
Demographic Factors												
Female	0.71	0.67–0.76	<.001	0.67	0.64–0.71	<.001	0.66	0.63–0.70	<.001	0.62	0.58–0.67	<.001
Age at diagnosis	0.80	0.79–0.81	<.001	0.74	0.73–0.75	<.001	0.61	0.60–0.62	<.001	0.44	0.43–0.45	<.001
Other Medication												
Cardiac risk factors	1.03	0.95–1.11	.442	1.04	0.97–1.11	.249	1.04	0.97–1.12	.294	1.06	0.94–1.18	.335
Proxy Markers of NPS Severity												
Psychiatric bed days = 0		Reference			Reference			Reference			Reference	
Psychiatric bed days = 1–9	1.11	1.00–1.22	.054	1.02	0.93–1.13	.650	1.28	1.15–1.43	<.001	0.84	0.71–1.01	.059
Psychiatric bed days ≥ 10	0.89	0.59–1.32	.555	1.04	0.67–1.61	.875	0.99	0.69–1.43	.964	1.32	0.62–2.78	.468
Psychiatric outpatient contacts = 0		Reference			Reference			Reference			Reference	
Psychiatric outpatient contacts = 1–5	1.35	1.24–1.47	<.001	1.34	1.25–1.42	<.001	1.34	1.25–1.43	<.001	1.38	1.27–1.50	<.001
Psychiatric outpatient contacts = 6–10	1.24	1.14–1.36	<.001	1.25	1.16–1.34	<0001	1.23	1.14–1.34	<.001	1.20	1.05–1.35	<.01
Psychiatric outpatient contacts > 10	1.11	1.02–1.21	<.05	1.04	0.96–1.12	.395	1.00	0.90–1.11	.947	1.26	1.01–1.58	<.05
Comorbidity												
Psychiatric comorbid score	1.11	1.06–1.15	<.001	1.13	1.10–1.17	<.001	1.08	1.04–1.12	<.001	1.26	1.20–1.32	<.001
Somatic comorbid score	1.32	1.28–1.36	<.001	1.30	1.27–1.33	<.001	1.31	1.28–1.34	<.001	1.36	1.32–1.40	<.001

[a]N = 32,001 with 19,199 deaths.
Abbreviations: DDD = Defined Daily Dose, HR = hazard ratio, NPS = neuropsychiatric symptom.

Table 4. Cox Regression Analysis Without Current Exposure With All-Cause Mortality as Outcome[a]

	Study Period 2000–2002			Study Period 2003–2005			Study Period 2006–2008			Study Period 2009–2011		
Variable	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Antipsychotic Medication												
Cumulative Exposure												
0 DDDs		Reference			Reference			Reference			Reference	
0 < DDDs ≤ 90	1.95	1.81–2.10	<.001	2.13	2.01–2.27	<.001	2.08	1.94–2.23	<.001	2.04	1.85–2.25	<.001
90 < DDDs ≤ 365	1.81	1.65–1.98	<.001	1.90	1.75–2.07	<.001	1.66	1.50–1.85	<.001	1.77	1.48–2.12	<.001
365 < DDDs ≤ 730	1.37	1.18–1.58	<.001	1.76	1.51–2.05	<.001	1.89	1.53–2.32	<.001	1.81	1.07–3.05	<.05
730 < DDDs	1.01	0.81–1.27	0.923	1.50	1.19–1.89	<.001	1.33	0.95–1.86	.092	1.51	0.61–3.73	.376
Explanatory Variables												
Demographic Factors												
Female	0.68	0.64–0.73	<.001	0.66	0.62–0.69	<.001	0.65	0.61–0.69	<.001	0.62	0.57–0.67	<.001
Age at diagnosis	0.81	0.80–0.81	<.001	0.74	0.73–0.75	<.001	0.61	0.60–0.62	<.001	0.44	0.43–0.44	<.001
Other Medication												
Cardiac risk factors	1.04	0.96–1.13	0.299	1.04	0.98–1.11	0.212	1.02	0.96–1.09	.525	1.06	0.95–1.18	.331
Proxy Markers of NPS Severity												
Psychiatric bed days = 0		Reference			Reference			Reference			Reference	
Psychiatric bed days = 1–9	1.10	0.99–1.22	.074	0.99	0.90–1.09	.800	1.28	1.15–1.43	<.001	0.84	0.71–1.00	.057
Psychiatric bed days ≥ 10	0.92	0.61–1.36	.663	0.93	0.60–1.44	.740	0.93	0.64–1.33	.674	1.30	0.61–2.75	.496
Psychiatric outpatient contacts = 0		Reference			Reference			Reference			Reference	
Psychiatric outpatient contacts = 1–5	1.38	1.27–1.50	<.001	1.35	1.27–1.44	<.001	1.35	1.27–1.44	<.001	1.38	1.28–1.50	<.001
Psychiatric outpatient contacts = 6–10	1.28	1.17–1.41	<.001	1.24	1.15–1.33	<.001	1.23	1.13–1.33	<.001	1.19	1.05–1.35	<.01
Psychiatric outpatient contacts > 10	1.13	1.03–1.23	<.01	1.02	0.94–1.10	.674	1.00	0.90–1.11	.978	1.25	1.00–1.57	<.05
Comorbidity												
Psychiatric comorbid score	1.12	1.07–1.16	<.001	1.13	1.10–1.17	<.001	1.07	1.04–1.11	<0.001	1.26	1.20–1.32	<.001
Somatic comorbid score	1.33	1.29–1.36	<.001	1.31	1.28–1.34	<.001	1.31	1.28–1.34	<0.001	1.37	1.33–1.41	<.001

[a]N = 32,001 with 19,199 deaths. Data on current exposure were omitted to illustrate collider bias as is discussed in the Methods section.
Abbreviations: DDD = defined daily dose, HR = hazard ratio, NPS = neuropsychiatric symptom.

multivariate regression analyses, there is a risk that one variable may interfere with how other variables correlate with an outcome so that the true correlations are obscured. This phenomenon is referred to as *effect modification*. To investigate if current exposure interfered with the effects of cumulative antipsychotic drug dosages, we conducted analyses without current exposure as a variable and observed that the finding of decreased mortality associated with long-term treatment disappeared. We believe that the initial finding is most likely a result of effect modification with current exposure, as none of the cumulative dosages were associated with lowered all-cause mortality in the latter analysis. This interpretation is supported by Ballard et al,[8] who showed an increased mortality after 12 and 24 months in patients with dementia who were randomized to continue antipsychotic treatment as compared to discontinuation. A non-randomized study by Langballe et al[40] showed an increased mortality within 30 days, but also in the period from 730 to 2,400 days after administration of antipsychotic medication, although with a decreasing HR over time. Lastly, Simoni-Wastila et al[24] showed a lower mortality rate in patients exposed to antipsychotic drugs for longer time periods as compared to short-term use, which is similar to the results from the current study, in which mortality ratios decrease with increasing cumulative dosages. The findings of decreasing mortality ratios with increasing exposure in the non-randomized studies by Simoni-Wastila et al,[24] Langballe et al,[40] and the current study could partly be a result of survival bias, in which patients need to survive to be able to be exposed to antipsychotic drugs again, with the result that time, as well as dose per administration, is a factor responsible for which cumulative drug dosage group patients end up in.[41,42]

Previous studies have not adjusted for or allowed inclusion of patients with known psychiatric disorders, although research has shown that developing psychiatric symptoms after AD dementia diagnosis worsens outcome.[43] We showed that both somatic and psychiatric comorbidity increased the rate of mortality when adjusting for remaining covariates. This finding is not surprising, as patients with psychiatric comorbidity in general have an increased mortality rate,[44–46] although patients who survive up to an age in which dementia occurs could be generally less somatically ill than the remaining psychiatric population, which could have resulted in a lowered hazard ratio due to survival bias, as discussed previously. Similarly, patients with somatic illnesses would be expected to have an increased mortality rate as compared to non-ill or less physically ill individuals.[47]

As was the case for previous studies of all-cause and specific-cause mortality,[14,15] this study has limitations, the most important one being the lack of randomization in register-based studies, which increases the risk of systematic biases between the exposed and nonexposed groups. Although we added explanatory variables to minimize the bias in psychiatric and somatic comorbidities and in severity of the disorder, there are unmeasured differences between the exposed and unexposed groups that may have affected the results. With no access to data on cognitive function or level of activities of daily living, we are unable to assess the severity of AD directly. The proxy markers used in this study, such as number of admissions, number of days admitted, and number of outpatient treatments, are the sum of different factors that vary from patient to patient; eg, admission to hospital may be dependent on living conditions such as living alone or with family capable of helping the patient. However, the proxy markers indicate a broad and general severity level of each patient's condition, especially regarding neuropsychiatric symptoms, that may pertain to the rate of death.

Despite these limitations, the main strengths of the study are the long follow-up time and the capture of all eligible patients in a nationwide sample in which the current data were systematically gathered and no patients were lost to follow-up. Primary and secondary care in Denmark is free, and thus no private health insurance is needed to receive adequate treatment of physical or mental disorders, removing a potential confounder compared to studies conducted in countries where free health care is less available. The use of all-cause mortality as an outcome measure compensates for a possibly low diagnostic validity of specific causes of death in the register.

In conclusion, we showed a decreasing use of antipsychotic drugs and an increased median age at death, but also an unchanged SMR in subsequent time periods investigated. In the Cox regression analyses, we showed a declining HR for all-cause mortality over time, whereas the effects of dose-adjusted cumulative dosages were unchanged. We believe that these findings underscore the current guideline recommendations regarding using antipsychotic drugs in patients only when all non-pharmacologic options have been exhausted and only in the lowest effective dose. Furthermore, data suggest that the reduced use of antipsychotic drugs has no impact on relative mortality as shown by our SMR analyses, suggesting that the AD population has gained less from possible improvements in care of other physical diseases and that differences in treatment between AD patients and nondemented persons should be targets for future research.

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