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Original Study

Associations of Neuropsychiatric Symptoms and Antidepressant Prescription with Survival in Alzheimer's Disease

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A B S T R A C T

Objective: Depression is associated with increased mortality in community samples. The use of antidepressant medication may also increase mortality, however, it is still unclear whether taking antidepressants before or after a diagnosis of dementia influences survival.
Design: Retrospective.
Setting: A cohort with a diagnosis of Alzheimer disease (AD) from a large mental health and dementia care database in South London, linked to hospitalization and mortality data.
Participants: Mild dementia (Mini-Mental State Examination ≥18/30) at the point of diagnosis.
Measurements: We ascertained antidepressant prescription, either in the 6 months before or after dementia diagnosis, and used the HoNOS65+, a standard clinician-rated measure of patient well-being, to determine depression severity and other neuropsychiatric, physical health, and functional difficulties. We conducted a survival analysis, adjusted for potential confounders and addressed possible confounding by indication through adjusting for a propensity score.
Results: Of 5473 patients with AD, 22.8% were prescribed an antidepressant in a 1-year window around dementia diagnosis. Of these, 2415 (44.1%) died in the follow-up period [mean (standard deviation) 3.5 (2.4) years]. Prescription of an antidepressant, both before and after dementia diagnosis, was significantly associated with higher mortality after adjusting for a broad range of potential confounders including symptom severity, functional status, and physical illness (hazard ratio 1.22; 95% confidence interval 1.08−1.37 for prescription prior to dementia diagnosis; 95% confidence interval 1.04−1.45 for prescription post dementia diagnosis). In stratified analyses, risks remained significant in those without neuropsychiatric symptoms.
Conclusions: The prescription of antidepressants around the time of dementia diagnosis may be a risk factor for mortality.

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There is increasing recognition that psychiatric comorbidities are a common and distressing feature among people with Alzheimer disease (AD),[1] of which depression is one of the most prevalent and troubling.[2] Previous meta-analyses have concluded that depression is associated with increased risk of a person developing AD, potentially because of inflammatory processes, stress or reduced cognitive reserve.[3] Furthermore, the prevalence of depression among people with AD may be as high as 80%,[4,5] and probably associated with higher mortality,[6] greater medical comorbidity and poorer quality of life for the individual and caregivers.[7]

Antidepressant medications are a commonly used treatment for depression in the general population[8] and are also used in people with AD,[9] although there is uncertainty as to the benefits in people affected by dementia and/or AD. Some trials support a beneficial effect,[10–12] but more recent studies report that antidepressants are not effective[13,14] as indicated by a Cochrane review.[15]

In addition, there is a contentious debate about the potential association between antidepressant medication and higher mortality among people with AD. In the general population, there have been mixed results for this association, including lower mortality,[16] no association,[17] and higher mortality.[18] However, information on people with AD remains sparse. One previous study among people with dementia, found that antidepressant medication was associated with a significantly higher mortality risk of 36%,[19] but another study found 18% lower mortality in people taking antidepressant medications for 3 years before an AD diagnosis.[20]

Given the high comorbidity of depression among people with AD, the common use of antidepressants, but paucity of studies on the relationship with mortality in this population, we aimed to investigate the association between the use of antidepressants and mortality in a large cohort of people with diagnosed AD.

Methods

Data Source and Setting

We obtained the data for this study using the South London and Maudsley NHS Foundation Trust (SLaM) Clinical Record Interactive Search (CRIS) application. CRIS has ethical approval (Oxford Research Ethics Committee C, reference 08/H0606/71+5) as an anonymized data source within a robust governance framework. It provides research access to anonymized copies of SLaM's electronic health records.[21,22] SLaM is one of Europe's largest providers for dementia and mental healthcare and serves a geographic catchment of 4 South London boroughs (Lambeth, Lewisham, Southwark, and Croydon) with a population of over 1.2 million residents. Its electronic health records contain data on more than 270,000 cases across all age groups and mental health services, and secure linkages have been established to national data on hospitalization (Hospital Episode Statistics) and mortality. Data are extracted from routinely completed compulsory fields and supplemented by a range of natural language processing algorithms using the General Architecture for Text Engineering software to interrogate free text clinical records and correspondence.[21,23]

Participants

We used CRIS to identify patients who received a first diagnosis of dementia according to the *International Classification of Diseases, Tenth Revision* codes[24] from SLaM outpatient services within between January 1, 2006 and July 28, 2016. To be included, patients needed to have a diagnosis of AD (etiher at first diagnosis or during the follow-up period), and be diagnosed with dementia in the mild stage defined as an Mini Mental State Examination (MMSE) score of 18 or higher.[25]

Variables

To distinguish longstanding antidepressant use from use associated with the diagnosis of dementia we defined 2 exposure groups. Patients were classified as prescribed antidepressants before dementia diagnosis if any antidepressant was mentioned in their case record in the 6 months before dementia diagnosis. If the antidepressant was continued after dementia diagnosis, patients were also classified in this group. The second exposure group consisted of those prescribed an antidepressant in the 6 months after dementia diagnosis (but not before). Patients with AD who were not prescribed an antidepressant in the 1-year window around dementia diagnosis served as control group.

Baseline covariates recorded were age, sex, ethnicity, marital status, a neighborhood-level index of multiple deprivation,[26] and MMSE score closest to dementia diagnosis. To account for cerebrovascular comorbidity we ascertained if an *International Classification of Diseases, Tenth Revision* diagnosis of vascular dementia (F01) or mixed-type AD (F00.2) was mentioned in the follow-up period. General physical health and multimorbidty was described through the "physical illness and disability problems" subscale of the Health of the Nation Outcome Scales (HoNOS65+) instrument. The HoNOS65+ is a standard measure of patient well-being used in United Kingdom mental health and dementia services, and subscales are each rated 0 (no problem) to 4 (severe or very severe problem).[27,28] In addition to the physical illness subscale, we also ascertained subscales relating to mental health symptoms and functional abilities. To facilitate interpretation, we dichotomized these to "minor or no problem" (scores of 0 and 1) and "mild to severe problems" (scores 2 to 4). Further, HoNOS65+ mental health problems scores were used to define subgroups of patients according to their neuropsychiatric symptom profile.

Statistical Analysis

Analyses were conducted using STATA 13 software (Stata Corp LP, College Station, TX). Patients prescribed antidepressants were compared with the remainder with respect to other covariates. Patients were followed-up until their death or a census date on December 10, 2016. We used log-rank tests to compare survival between exposure groups and then applied Cox regression models to investigate associations between antidepressant prescription and survival. To reduce impact of confounding by indication, propensity scores were calculated.[29] These represent the probability of being treated with an antidepressant based on a regression model that included all the above-mentioned covariates and we included the propensity score in a Cox model.

Results

Population Characteristics

Among the 10,011 patients diagnosed with AD initially identified, 8695 had an MMSE score recorded at diagnosis. Of these a total for 5473 patients fulfilled inclusion criteria. 2415 (44.1%) patients with AD died in the follow-up period, and mean [standard deviation (SD)] follow-up time to death or the end of the observation period was 3.5 (2.4) years. Nine hundred one (901; 16.5%) patients were prescribed an antidepressant prior to dementia diagnosis, of which 472 (8.6%) remained on the medication after diagnosis. Three hundred forty-seven (6.3%) patients were prescribed an antidepressant solely after dementia diagnosis.

Characteristics of antidepressant non-receivers and the 2 exposure groups are compared in Table 1. Antidepressant receivers were younger, more likely to be female, from a White ethnic background, and from more deprived areas. Those receiving antidepressants after dementia diagnosis had lower cognitive scores than those without or prior antidepressant prescription. Further, patients prescribed antidepressants

Table 1
Sociodemographic and Clinical Characteristics of the Sample, by Antidepressant Status

Risk Factors	Antidepressant non-receipt (n = 4225)	Antidepressant receipt prior to (and post) dementia diagnosis (n = 901)	Antidepressant receipt post dementia diagnosis (n = 347)	*P* Value*
Sociodemographic status and cognitive function†				
Mean age at dementia diagnosis, y (SD)	81.3 (7.3)	79.9 (8.7)	80.8 (8.4)	<.01
Female sex (%)	62.0%	71.1%	70.3%	<.01
Non-White ethnicity (%)	22.0%	19.1%	17.2%	.03
Married or cohabiting status (%)	38.0%	34.9%	33.4%	.08
Mean index of deprivation (SD)	25.2 (11.3)	26.7 (10.8)	26.4 (11.1)	<.01
Mean MMSE score at diagnosis (SD)	22.8 (3.2)	23.0 (3.3)	22.3 (3.1)	<.01
HoNOS65+ problems because of mental health symptoms (% with subscale scores 2–4)†				
Agitated behavior	7.7%	16.2%	20.1%	<.01
Nonaccidental self-injury	0.6%	3.4%	2.1%	<.01
Problem-drinking or drug taking	2.8%	2.6%	2.1%	.84
Hallucinations or delusions	7.7%	12.3%	13.0%	<.01
Depressed mood	6.7%	33.6%	26.3%	<.01
HoNOS65+ functional problems (% with subscale scores 2–4)†				
Activities of daily living	40.5%	49.4%	48.1%	<.01
Living conditions	8.2%	7.5%	10.2%	.37
Occupational and recreational activities	21.6%	30.8%	32.1%	<.01
Social relationships	9.2%	17.7%	19.8%	<.01
HoNOS65+ "physical illness or disability problems" scale†				<.01
0–1 (no or minor problem)	62.9%%	51.6%	52.2%	
2 (mild problem)	22.9%%	26.4%	26.3%	
3 (moderately severe problem)	12.4%	18.2%	18.0%	
4 (severe to very severe problem)	1.8%	3.8%	3.5%	
Cerebrovascular comorbidity	35.1%	35.6%	39.5%	.26

*Analysis of variance, Kruskal-Wallis rank test or χ^2 test.
†At the time of AD diagnosis.

had worse scores on HONOS65+ subscales for agitated behavior, non-accidental self injury, hallucinations or delusions, depressed mood, physical illness, and functional scales (activities of daily living, occupational and recreational activities, social relationships). No signifcant difference in cerebrovascular comorbidty was detected between groups.

Table 2
Unadjusted and Adjusted Analyses of Associations between Covariates and Mortality after AD Diagnosis

Covariate Status at/around Diagnosis	Association with Mortality – Hazard Ratio (95% CI)	
	Unadjusted	Adjusted for Demographics* and MMSE
Age (per y increment)†	1.08 (1.08–1.09)‡	1.08 (1.08–1.09)‡
Female sex	0.82 (0.76–0.89)‡	0.69 (0.64–0.75)‡
Non-White ethnicity	0.52 (0.45–0.58)‡	0.61 (0.53–0.69)‡
Married or cohabiting status†	0.85 (0.78–0.93)‡	0.97 (0.88–1.06)
Deprivation score above sample mean†	1.09 (1.01–1.18)‡	1.18 (1.08–1.28)‡
MMSE score (per unit increment)†	0.94 (0.93–0.95)‡	0.95 (0.94–0.97)‡
HoNOS65+ problem because of mental health symptom†		
Agitated behavior	1.31 (1.16–1.49)‡	1.30 (1.14–1.47)‡
Nonaccidental self-injury	1.08 (0.76–1.53)	1.12 (0.79–1.60)
Problem-drinking or drug taking	1.03 (0.80–1.32)	1.21 (0.94–1.57)
Hallucinations or delusions	1.32 (1.16–1.50)‡	1.33 (1.16–1.52)‡
Depressed mood	1.01 (0.89–1.14)	1.17 (1.03–1.34)‡
HoNOS65+ functional problem†		
Activities of daily living (ADLs)	1.73 (1.60-1.88)‡	1.49 (1.37–1.63)‡
Living conditions	1.61 (1.41–1.85)‡	1.51 (1.31–1.74)‡
Occupational and recreational activities	1.42 (1.30–1.56)‡	1.30 (1.18–1.43)‡
Social relationships	1.14 (1.02–1.29)‡	1.17 (1.03–1.32)‡
HoNOS65+ "physical illness or disability problem"†	1.76 (1.62–1.91)‡	1.57 (1.44–1.71)‡
Cerebrovascular comorbidity	1.07 (0.97–1.19)	1.08 (1.00–1.18)

CI, confidence interval.
*Includes age, sex, ethnicity, marital status, deprivation score at dementia diagnosis.
†At/around the time of AD diagnosis.
‡$P < .05$.

Predictors of Mortality

Adjusted and unadjusted multivariate Cox regression models are presented in Table 2. In models adjusted for demographics and cognition the following factors were asscciated with higher mortality in the study cohort: higher age, being male, White ethnicity background, being from more deprived areas, and having a lower MMSE. In addition, poorer physical health and functional status, as well as the following neuropsychiatric symptoms were associated with increased mortality: agitated behavior, hallucinations or delusions, and depressed mood. Of note, 2 factors associated with antidepressant prescribing (lower age and female sex) were linked to better survival.

Antidepressant Receipt and Survival

A log-rank test demonstrated significant differences in survival function between antidepressant non-receivers and those prescribed antidepressants before or after dementia diagnosis ($\chi^2 = 14.0, P < .01$). Cox regression models also showed significant associations between antidepressant prescription and an increased risk for all-cause mortality. Associations did not seem to differ significantly between those prescribed antidepressant before and after dementia diagnosis and remained significant after including a broad range of confounders into the models (Table 3). We created standard propensity scores from all available variables and included those as covariates in Cox regression models. In propensity score adjusted models both exposure groups differed in 95% confidence intervals, but equal hazard ratios of 1.22 compared with nonpescription were detected.

Stratified Analyses According to Neuropsychiatric Symptom Profiles

We assessed the effect of antidepressant prescription in patients with depressed mood (n = 483), with depressed mood and other comorbid neuropsychiatric symptoms (agitated behavior and/or psychosis symptoms; n = 170), with agitated behavior and/or psychosis, but no depressed mood (n = 653), and in patients without any of the

Table 3
Multivariate Cox Regression Analyses of Association between Receiving Antidepressant Treatment and Mortality

Multivariate Cox Regression Models	Antidepressant receipt prior to (and) post dementia diagnosis	Antidepressant receipt post dementia diagnosis only
	Hazard Ratio (95% CI)	Hazard Ratio (95% CI)
Unadjusted	1.15 (1.04–1.29)*	1.26 (1.08–1.46)*
Adjusted for demographics† and cognitive scores	1.29 (1.16–1.44)*	1.32 (1.13–1.55)*
Adjusted for demographics†, cognitive scores and all mental health and functional problems HoNOS65+ subscales	1.24 (1.10–1.39)*	1.28 (1.09–1.51)*
Adjusted for demographics†, cognitive scores and hospitalization, HoNOS65+ physical illness subscale, and vascular comorbidity	1.22 (1.09–1.36)*	1.26 (1.08–1.48)*
Fully adjusted (for demographics†, cognitive scores, and all HoNOS65+ subscales, and vascular comorbidity)	1.20 (1.06–1.35)*	1.25 (1.06–1.48)*
Adjusted using propensity score as covariate	1.22 (1.08–1.37)*	1.22 (1.04–1.45)*

CI, confidence interval.
*$P < .05$.
†Includes age, sex, ethinicity, marital status, and deprivation score at dementia diagnosis.

aforementioned neuropsychiatric problems (n = 3975) (Table 4). In patients with depressed mood antidepressant prescription before, but not after dementia diagnosis, was significantly associated with an increased mortality risk. In patients with agitated behavior and/or psychotic symptoms antidepressant prescription did not lead to a significantly increased risk of death. Only in the group suffering from depressed mood and comorbid agitated behavior/psychosis, a trend toward increased mortality was detected in those prescribed an antidepressant after dementia diagnosis in a fully adjusted Cox regression model (HR 1.91; 95% confidence interval 0.89–4.11; $P = .08$). Most notably, in the group without depression, agitated behavior or psychosis, both antidepressant prescription before and after dementia diagnosis resulted in an increased hazard for all-cause mortality.

Differences in Survival Times

In those who died in the follow-up period (n = 2415), mean (SD) survival time from dementia diagnosis to death was 3.3 (2.3) years. Mean (SD) survival time for patients not prescribed antidepressants was 3.4 (2.3) years, and for patients taking antidepressants before dementia diagnosis 3.1 (2.1) years and after dementia diagnosis 3.0 (2.3) years ($P = .01$). This indicates a mean difference of 3–4 months of survival between antidepressant receivers and nonreceivers.

Survival time was significantly ($P < .01$) shorter for patients with depressed mode [2.9 (SD 2.3) years] than those presenting without [3.4 (SD 2.3) years]. In those who suffered from depressed mode and died in the follow-up period (n = 266), no significant differences in survival time were detected between antidepressant receivers and nonreceivers ($P = .77$).

Discussion

In this study of 5473 patients with clinically diagnosed AD, we found that people who took antidepressant medications in the year encompassing the dementia diagnosis were more likely to die during the follow-up period. This association was similar in those with predementia antidepressant prescription and those receiving the medication after dementia diagnosis and remained robust after adjustment for potential confounders and in analyses including a propensity score representing the risk of being treated. Moreover, the presence of neuropsychiatric, functional, and physical health problems and socioeconomic deprivation were associated with a higher mortality risk in this cohort of patients with AD.

Approximately 23% of the sample with AD were prescibed at least 1 antidepressant medication, and almost three-quarters of those already before dementia diagnosis. Compared with those not taking antidepressants, participants taking such medication had a higher presence of neuropsychiatric symptoms, had worse functioning according to HONOS65+ scores, and worse physical health. Altogether, these findings suggest that participants taking antidepressant medications had a higher presence of risk factors for mortality, which may partly explain our findings. However, the association of interest remained robust, although relatively small, after adjustment for these confounders.

There are a number of potential mechanisms by which antidepressant medication may influence mortality in people with AD. First, antidepressant medications are associated with a higher risk of several medical conditions also associated with higher mortality risk; these include falls,[19,30,31] poor bone health,[32] fractures,[33] and potentially cardiovascular disease.[34] Second, antidpressants may interact with other medications taken by people affected by AD and increase the likelihood of adverse effects. For example, the use of some antidepressants could lead to a prolongation of QT intervals, especially if coprescribed with other medications commonly used in people affected by AD, such as antipsychotics.[35] Finally, some antidepressants (like tricyclic medications) may have a role on basal heart rate and heart rate variability,[36] 2 important factors for mortality.[37]

Previous literature considering the relationship between antidepressant use and mortality among people with AD is equivocal, and our findings add to a growing picture of a complex relationship. A large study including 20,050 participants affected by various types of dementia[20] reported that the use of antidepressant medications is associated with a significant lower risk of mortality. However, other large studies have reported an association with increased mortality.[19] Several reasons could explain these conflicting findings in the literature and our own data. First, factors as cognitive function, diagnostic criteria for AD, and the presence of diseases at higher risk of mortality could explain the differences. Second, the authors of the first study found that only a prolonged use of antidepressants (more than 3 years) was associated with a lower risk of mortality, whereas using antidepressants at the time of diagnosis or less than 3 years was not associated with any decreased risk.[20] Finally, our study had a considerably longer follow-up time than Enache et al,[20] who only observed their patients for 2 years after dementia diagnosis. It is conceivable that the hazardous effects of antidepressants only become apparent later in the dementia disease course.

The findings of our study should be interpreted within its limitations. First, it is an observational study, and therefore, we cannot exclude that some potential confounders not considered in our analysis could play a role in the association between antidepressants and mortality. Second, we did not have any information regarding the causes of mortality. Third, the type of antidepressant was not ascertained, and therefore, we are not able to conclude if a particular medication or class is responsible for the increased mortality found.

Table 4
Adjusted Hazard Ratios (95% CIs) of Antidepressant Use Using Multivariate Cox Regression Models

	Patients with Depressed Mood* (n = 483)			Patients with Depressed Mood and Agitated Behavior/Psychosis* (n = 170)			Patients with Agitated Behavior/Psychosis, but Not Depressed Mood* (n = 653)			Patients without Neuropsychiatric Symptoms* (n = 3975)		
	N Prescribed Antidepressant (%)	Model 1	Model 2	N Prescribed Antide-pressant (%)	Model 1	Model 2	N Prescribed Antide-pressant (%)	Model 1	Model 2	N Prescribed Antide-pressant (%)	Model 1	Model 2
Antidepressant receipt prior to (and post) dementia diagnosis	208 (43.1%)	**1.42 (1.03–1.97)**†	**1.56 (1.12–2.17)**‡	85 (50.0%)	0.85 (0.51–1.43)	0.97 (0.54–1.74)	117 (17.9%)	1.24 (0.94–1.63)	1.27 (0.95–1.69)	461 (11.6%)	**1.28 (1.10–1.49)**†	**1.20 (1.03–1.39)**†
Antidepressant receipt post dementia diagnosis	65 (13.5%)	1.13 (0.70–1.82)	1.11 (0.68–1.83)	24 (14.1%)	1.28 (0.67–2.46)	**1.91 (0.89–4.11)**‡	64 (9.8%)	1.25 (0.91–1.72)	1.31 (0.94–1.83)	185 (4.7%)	**1.30 (1.04–1.61)**†	**1.22 (0.97–1.53)**‡

Model 1 = adjusted for demographics (includes age, sex, ethnicity, marital status, deprivation score at dementia diagnosis) and cognitive scores.
Model 2 = Fully adjusted (Table 3).
Bold indicates significance ($P < .05$) or a trend ($P < .10$).
*Using HoNOS65+ mental health problems subscales (a score of 2 or more represents a problem).
†$P < .05$.
‡$P < .10$.

Fourth, we assessed the use of antidepressants only in a window ranging from 6 months before to 6 months after first dementia diagnosis, and this could introduce a bias in our results. Depressive symptoms, such as social withdrawal can be a prodromal feature of AD,[38] rather than representing clinical depression and we are unable to deliniate the clinical phenotype of our study sample. Fifth, we did not have sufficient information to adjust for level of education, although this is a factor partly reflected in the index of neighborhood-level socioeconomic status, and prospective studies have not found any association between educational level and survival in AD.[39] Sixth, comorbidity was primarily ascertained through the HoNOS65+ "physical illness and disability problems" subscale, which although being widely used as routine measure of clinical outcome in dementia services in the United Kingdom, is a relatively brief measure.

Conclusions

Our findings suggest that antidepressants should be used cautiously in older people affected by AD, consistent with a longitudinal study showing that antidepressants are associated with a higher risk of adverse outcomes, including falls, hyponatremia, cardiovascular, and cerebrovascular conditions.[40] Because the benefits of antidepressant medications on mood in dementia may be limited, the prescribing clinician should carefully consider the risks and benefits of doing so. As this is a retrospective observational study, more solid evidence could be achieved through replicating these results in a prospective cohort study or a randomized controlled trial, and future studies are needed to better elucidate the true role of antidepressants in AD.

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