ORIGINAL RESEARCH

Impact of Antidepressants on Cardiac Events and All-Cause Mortality in Parkinson's Disease: A National Data-Linkage Study

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Purpose: This study investigated the 1-year risk of ischemic heart disease (IHD), all cardiovascular events, and all-cause mortality among newly diagnosed Parkinson's disease (PD) patients who used antidepressants compared to those who did not.

Patients and Methods: Patients with PD aged 40 years or older were identified using data from 2000 through 2016 held within the Welsh Secure Anonymized Information Linkage (SAIL) databank. Antidepressant users were propensity-score matched 1:1 with non-users, adjusting for patients' demographics, socioeconomic status, and multiple comorbidities. Cox proportional hazard regression analyses were performed to calculate the hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between the antidepressants and the study outcomes. The follow-up period was 1 year after the initial prescription of antidepressants.

Results: The study group comprised a total of 3364 participants, with numbers split equally between the antidepressant-user and non-user groups, based on the propensity score-matching process. Overall, the propensity score-adjusted model showed that antidepressant usage in PD patients was not significantly associated with the risk of IHD (HR = 1.05; 95% CI 0.63–1.75) or all cardiovascular events (HR = 1.01; 95% CI 0.71–1.45) compared to non-users. The propensity score-adjusted model also showed that the use of any antidepressant, regardless of its category, was not statistically significantly associated with all-cause mortality (HR = 0.81; 95% CI 0.65–1.02). However, this association reached statistical significance in the multivariate adjusted model (HR = 0.67; 95% CI 0.54–0.84).

Conclusion: There was no evidence that antidepressant use was associated with an increased risk of IHD or all cardiovascular events in newly diagnosed PD patients who suffered from depression. Furthermore, antidepressant use might reduce the mortality rate in PD patients during the first year after initiation.

Keywords: antidepressants, cardiovascular events, depression, ischemic heart disease, Parkinson's disease

Introduction

Depression is a highly prevalent disease and a serious global health concern. According to the World Health Organization (WHO), it currently affects 322 million people worldwide.[1,2] The most widely available treatments for symptoms are tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs).[2] Despite having comparable efficacies, SSRIs have superseded TCAs due to their more benign overall safety profiles.[2] Although numerous studies have demonstrated the efficacy of antidepressants in treating this condition,[3,4] there have been inconsistent findings regarding their cardiovascular safety.

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TCAs are linked to systematic inflammation that might increase cardiovascular risk[5] and, especially, ischemic heart disease (IHD).[6,7] By contrast, SSRIs can have cardioprotective effects due to their thrombolytic activity;[8] however, they also exhibit antiplatelet activity and can constrict arterial vessels, which may increase the risk of other cardiac events such as stroke.[9] Cardiac events, particularly IHD, are not linked only to the use of antidepressants; it has been established that depression itself is a significant risk factor for IHD and other cardiac events.[10] Additionally, comorbidities that coexist with depression and antidepressant use, such as Parkinson's disease (PD), might increase the cardiovascular risk.[11]

It is estimated that the prevalence of depression among PD patients can reach 35%, and antidepressants are commonly used to treat it.[12] The reported prevalence of antidepressant use among PD patients ranges from 1.9% to 43.2%.[13–22] This variation might be explained by differences in the time period under study. For example, studies conducted in the early 1990s have tended to report a lower prevalence of antidepressant use, such as 13.19% in Norway in 1992 (20) and 1.9% in US nursing homes from 1992 to 1996.[19] By contrast, more recent studies have tended to report a greater prevalence of antidepressant use, such as 23% in Denmark in 2007[15] and 29.8% in the USA in 2014.[23] This increase in the use of antidepressants in recent years is attributed to the increased recognition of depression in PD patients.[24]

Cardiac events, particularly IHD, are more prevalent in PD patients compared to non-PD controls.[25–27] Drugs that are commonly used in PD patients and carry a risk of cardiac effects, such as dopamine agonists[28,29] and antipsychotics,[30,31] can have an impact on this phenomenon. Although antidepressants have been associated with IHD and other cardiac events in the general population,[6,7] the correlation remains unclear in PD patients. Additionally, there is conflicting evidence in the literature of an association between antidepressant use and a higher risk of mortality in the general population and in patients with various diseases. While some studies have suggested that the use of antidepressants can reduce the mortality rate,[32,33] others have not found such an effect.[34] This inconsistency in results has also been observed in PD patients, with some studies reporting an increased risk of mortality in antidepressant users versus non-users,[35] and other studies reporting the opposite.[36] Variation in the association between antidepressant use and mortality risk might be due to the level of adherence to the medications,

associated comorbidities and polypharmacy, or the extent of PD progression.[37] To our knowledge, no previous studies have examined such associations in newly diagnosed PD patients using a large-scale data-linkage databank in which the role of disease progression has been minimized and comorbidities and polypharmacy have been controlled for.

Thus, the primary objective of this study was to assess the 1-year risk of IHD among antidepressant users compared with non-users in newly diagnosed PD patients. The risk of all cardiovascular events and all-cause mortality were also assessed as a secondary objective of the study.

Patients and Methods
Design and Data Source
This retrospective cohort study used data from the Welsh Secure Anonymized Information Linkage (SAIL) databank from 2000 to 2016. SAIL is a data-linkage system that covers 80% of Welsh general practice (GP) surgeries and is linked to other Welsh databases that contain additional patient-related data;[32] these include demographic, hospitalization, and mortality data stored in the Welsh Demographic Service database, Patient Episode Database, and Annual District Death Extract (ADDE), respectively.[38] Social deprivation status data were available from SAIL and measured using the Welsh Index of Multiple Deprivation (WIMD) scale.[38] The Patient Episode Database was utilized to determine patients' comorbidities and first cardiovascular hospitalization episode. Cardiovascular and all-cause mortality data were obtained using the ADDE. All data used in this study were anonymized and the protocol was approved by the Information Governance Review Panel (IGRP; reference number 0507).

Study Population and Definitions
The study population included all individuals older than 40 years who had a first definitive PD diagnosis Read code in SAIL and started taking PD medication between 2000 and 2016 (Appendix 1). Patients who were diagnosed with PD within 6 months of the SAIL registration date and/or had been prescribed antipsychotics in the year preceding diagnosis were excluded from the study.[39]

The index date was defined as the day of the first prescription of antidepressant medication in newly diagnosed PD patients. Patients were followed up for 1 year after the index date until the occurrence of an outcome of

interest classified as model 1 (first IHD event), model 2 (first cardiovascular event such as arrhythmia, heart failure, IHD, stroke, or cardiovascular death), or model 3 (all-cause mortality). Survival times were measured in days. For all models, patients were censored if they transferred out from SAIL, if the study period ended without the occurrence of an outcome of interest, if antidepressant users changed or ceased the medications, or if the time between two consecutive prescriptions for the same antidepressant exceeded 30 days. Patients in model 1 were also censored if death or any cardiac hospitalization other than IHD (that is, arrhythmia, stroke, or heart failure) occurred. Patients in model 2 were also censored if non-cardiac death occurred.

The covariates extracted at the time of PD diagnosis from SAIL included age, gender, health-board location, WIMD deprivation status, previous comorbidities, and previous consumption of medications that might cause cardiovascular side effects. Appendix 2 details the covariate definitions.

Statistical Methods
Descriptive statistics (means and percentages) were used to examine demographics and other patient covariates.

Propensity Score Calculation and Matching
All confounding covariates with a p-value ≤0.20 for the Wald test in the bivariate logistic regression were used to calculate the propensity score estimates,[34] which described the probability of receiving antidepressants on the index date. Data from antidepressant users and non-users were then subjected to propensity score-matching analysis using a 1:1 ratio with the nearest neighbor method without replacement. The caliper size was set at 0.2-times the standard deviation (SD) of the logit of the propensity scores.[34]

Time to Event Survival Analysis
Cox proportional hazards regression was used to examine the hazard ratio (HR) of IHD (model 1), cardiac events (model 2), and all-cause mortality (model 3) for propensity score-matching samples. The covariates included in the model were those with a p-value ≤0.20 according to single Cox regression.

To explore as many statistical associations as possible, two Cox regression approaches were utilized in this study. The first was multivariate Cox regression, in which all

candidate covariates were incorporated in the regression model.

The second was propensity score adjusted Cox regression, in which a new propensity score estimate was calculated for every model, which represented the probability of developing the outcome of interest. Consequently, the calculated propensity score was added to the Cox regression model as a covariate, instead of the aforementioned covariates.[40] Additionally, the main explanatory variable, which was the use of antidepressants, was added to all models. To maintain the linearity assumption of the propensity scores, they were divided into five groups as follows: 0–0.2, 0.21–0.4, 0.41–0.6, 0.61–0.8, and 0.81–1. The Schoenfeld test was utilized to verify the assumption of proportional hazards; the results confirmed that this assumption was met in all three models. Kaplan–Meier graphs were used to express the probability of IHD, cardiac events, and all-cause mortality from the index date until the event or exclusion date. All statistical analyses were conducted using SPSS version 25. A p-value <0.05 was considered statistically significant.

Results
Patient Characteristics
Between January 1, 2000 and December 31, 2016 there were 13,293 PD patients in the SAIL databank. After applying the exclusion criteria, 9142 patients remained (Figure 1). Propensity score matching analysis identified 3364 patients, 1682 (50%) of whom were treated with antidepressants and 1682 (50%) of whom were untreated (Figure 1). The main characteristics of the antidepressant user and non-user groups are shown in Table 1. Overall, the mean age of the participants was 75.9 years (SD=7.5), the most common age group was 61–80 years (1845 cases, 54.8%), and there were more males (2034 cases, 60.4%) than females. Most participants were prescribed levodopa as the first-line PD medication (2876 cases, 85.4%) followed by dopamine agonists (306 cases, 9.1%), and then monoamine oxidase-B (MAO-B) inhibitors (182 cases, 5.4%). Among the antidepressant users included in the matched cohort, 57.5% received SSRIs, whereas 26.5% received TCAs, and the remaining 16% received other antidepressants (Table 1). Citalopram (SSRI drug) compromised almost third of all antidepressants prescribed (33.7%), followed by amitriptyline (TCA drug) (14.9%) and fluoxetine (SSRI) (10.6%) (Table 2). In the antidepressant-users group and over one year after the first antidepressants prescription, 31 IHD cases (n=31), 58
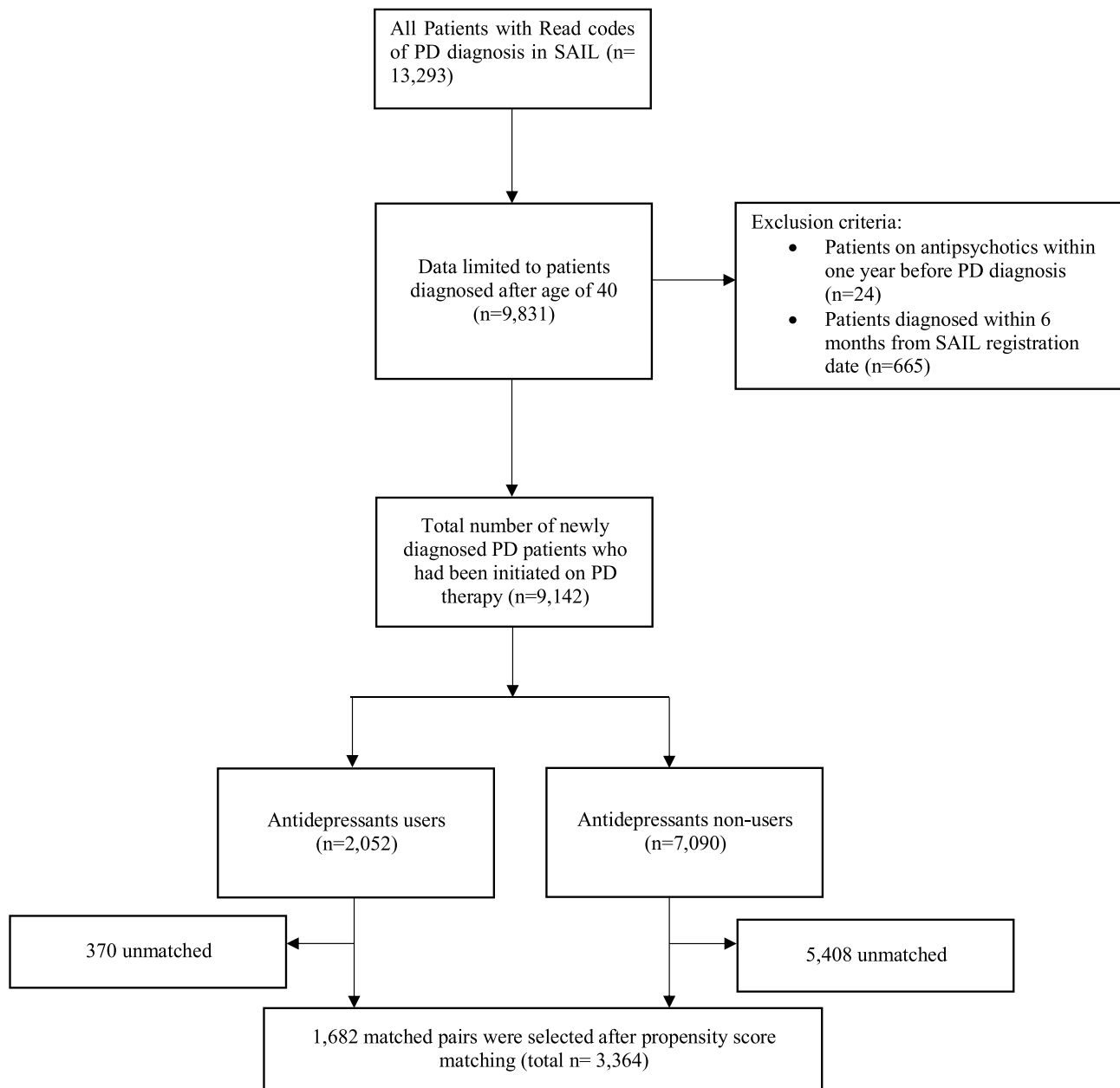
Figure 1 Cases selection and exclusion process.

cardiovascular events (3.4%), and 136 death (8.1%) occurred (Table 1).

Hospitalization Due to IHD

Appendix 3 illustrates the detailed outcomes of univariate and multivariate Cox regression analyses in all three models examined. The propensity score-adjusted model and the relevant HR in antidepressant users are shown in Table 3. Overall, the propensity score-adjusted model showed that taking antidepressants in PD patients had no significant association with the risk of IHD compared to non-users (HR =

1.05, 95% confidence interval [CI] 0.63–1.75). No significant interactions were reported between any of the different antidepressant categories or individual drugs and IHD (Table 3).

Hospitalization Due to All Cardiovascular Events

The propensity score-adjusted model suggested that there was no significant difference between patients who used antidepressants and non-users in terms of developing cardiovascular events, specifically arrhythmia, heart failure, IHD, stroke, or cardiovascular death (HR = 1.01, 95% CI

Table 1 Patients Demographics

Demographic	Mean (SD) or n (%) for the Antidepressants Non-Users N=1682	Mean (SD) or n (%) for the Antidepressants –Users N=1682
Age, years (at PD incidence)	75.7 (7.97)	76.1 (8.21)
Age group		
40–60 years	50 (2.97)	54 (3.21)
61–80 years	940 (55.89)	905 (53.8)
>80 years	692 (41.14)	723 (42.98)
Sex, male	1028 (61.12)	1006 (59.81)
Health board (geographical health board location)		
Abertawe Bro Morgannwg	402 (23.9)	437 (25.98)
Aneurin Bevan	235 (13.97)	195 (11.59)
Betsi Cadwaladr	335 (19.92)	311 (18.49)
Cardiff & Vale	272 (16.17)	289 (17.18)
Cwm Taf	149 (8.86)	124 (7.37)
Hywel Dda	237 (14.09)	227 (13.5)
Powys	52 (3.09)	98 (5.83)
PD medications		
Dopamine agonists	136 (8.09)	170 (10.11)
Levodopa	1460 (86.8)	1416 (84.19)
MAO-B inhibitors	86 (5.11)	96 (5.71)
Antidepressants medications		
Tricyclic antidepressants (TCA)	NA	447 (26.5)
Selective serotonin reuptake inhibitors (SSRI)	NA	968 (57.5)
Other antidepressants	NA	269 (16)
Total number of the outcome of interest		
Ischemic heart disease (IHD)	28 (1.66)	31 (1.84)
All cardiac events including cardiac mortality	72 (4.28)	58 (3.45)
All-cause mortality	208 (12.37)	136 (8.09)
Mean time from the index date until the outcome of interest (days) (only those who developed the outcome)		
Ischemic heart disease (IHD)	164.31	170.7
All cardiac events including cardiac mortality	192.1	184.2
All-cause mortality	156.6	183.1

0.71–1.45) (Table 3). Non-significant associations with all cardiovascular events were also reported among different antidepressant categories and individual drugs (Table 3).

All-Cause Mortality

The propensity score-adjusted model showed that the use of any antidepressant, regardless of its category, had no statistically significant association with all-cause mortality (HR = 0.81; 95% CI 0.65–1.02) (Table 3 and Figure 2). This association reached statistical significance in the multivariate adjusted model (HR = 0.67, 95% CI 0.54–0.84). Multivariate analysis of the TCA- and SSRI-user groups showed reduced mortality in the latter (HR = 0.7, 95% CI 0.54–0.91), and to a lesser extent in the former (HR= 0.84; 95% CI 0.48–0.98) (Table 3). Both TCAs and SSRIs showed no significant associations in the propensity score-adjusted model (Table 3 and Figure 3). Among the individual antidepressants, mirtazapine had the lowest HR (0.43, 95% CI 0.21–0.87) in the all-cause mortality multivariate adjusted model, followed by citalopram (HR=0.65, 95% CI 0.47–0.91) (Table 3). The propensity score model, however, revealed no significant association between any of the individual antidepressants and all-cause mortality (Table 3 and Figure 4).

Table 2 Number of Antidepressants in Antidepressant Users Cohort

Antidepressants	N (% Out of All Antidepressants, n=1682)
Citalopram (SSRI)	567 (33.71)
Amitriptyline (TCA)	251 (14.92)
Fluoxetine (SSRI)	179 (10.64)
Mirtazapine (Other)	171 (10.17)
Sertraline (SSRI)	129 (7.67)
Paroxetine (SSRI)	92 (5.47)
Venlafaxine (Other)	89 (5.29)
Dosulepin (TCA)	69 (4.1)
Lofepramine (TCA)	46 (2.73)
Trazadone (Other)	40 (2.38)
Nortriptyline (TCA)	16 (0.95)
Clomipramine (TCA)	15 (0.89)
Trimipramine (TCA)	Less than 5
Imipramine (TCA)	Less than 5
Doxepin (TCA)	Less than 5
Isocarboxazid (Other)	Less than 5
Moclobemide (Other)	Less than 5
Fluphenazine (Other)	Less than 5
Fluvoxamine (SSRI)	Less than 5
Maprotiline (Other)	Less than 5
Mianserine (Other)	Less than 5
Reboxetine (Other)	Less than 5

Discussion

There is growing evidence that individuals with PD are more likely to develop cardiovascular diseases, particularly IHD.[25] Several factors increase the risk of developing IHD in PD patients, including hereditary inclination, heavy smoking, and diabetes mellitus.[25] Furthermore, because PD is more common among the elderly, patients are likely to have higher cardiovascular morbidity profiles and an increased prevalence of polypharmacy.[41] On average, a PD patient will be prescribed five different drugs, and this number rises with increasing age and as motor and non-motor symptoms worsen.[42] Certain medications that are commonly used in PD patients, such as non-steroidal anti-inflammatory drugs (NSAIDs)[43] and antipsychotics,[44] are associated with an increased risk of cardiovascular events. Other medications, such as antidepressants, may also increase the risk of cardiovascular events, particularly IHD,[45] although they have yet to be evaluated in PD patients.

This study analyzed data collected from almost 80% of the Welsh population over a period of 17 years. Among antidepressant users, citalopram (SSRI) constituted almost a third of prescribed antidepressants, which is in line with guidelines that recommend use of an SSRI as a first-line therapy to treat depression in PD patients.[3] While there is evidence of its efficacy to treat depression,[3] which could explain why it was the second most common antidepressant prescribed in this cohort (14.9%), amitriptyline (TCA) is not highly recommended in PD patients due its anticholinergic side effects.[3] Although the current study only included antidepressants prescribed to PD patients after a diagnosis of depression, it is still possible that the relatively high prescribing rate of amitriptyline in this study might be explained by the fact that amitriptyline can be used to treat conditions other than depression, such as migraine and tension headaches.[24]

No significant association was found between antidepressant use and IHD and other cardiovascular event risks during the first year after PD diagnosis in patients taking these medications compared with non-users. Similar findings were observed for the associations of each antidepressant category and individual antidepressants with IHD and other cardiovascular event risks. Previous studies have reported inconsistent findings in this regard. Some have suggested that SSRIs may increase the risk of IHD while TCAs and other types of antidepressant do not carry such a risk.[46,47] In contrast, others have found that TCAs are associated with cardiovascular risk (including IHD), while SSRIs appear to be safer in this regard.[6,48] Moreover, a meta-analysis of 16 observational studies found that neither SSRIs nor TCAs increased the risk of IHD and other cardiac events.[49] These inconsistent results might be due to differences in the inclusion and exclusion criteria have been applied in each study. The current study did not find any such association in PD patients during a short follow-up period of 1 year. The current study examined the immediate cardiovascular risk of antidepressants in patients who were diagnosed with depression after their PD diagnosis compared to those who were free from depression. This might have introduced an indication bias, since depression itself is a risk factor that could contribute to IHD; however, this possibility was minimized by restricting the follow-up period to 1 year, minimizing the effect of depression on IHD and other cardiovascular risks.[50] In diseases like PD, in which the cardiovascular risks are high[51] and the progressive and complex nature of the disorders exacerbate them over time,[52] it is difficult for long-term follow-up studies to attribute IHD risks to either depression or antidepressant use, even when applying sophisticated statistical analysis that are intended to control for all possible confounders.[53]

Table 3 Results of Multivariate and Propensity Scores Adjusted Cox Regression Models That Examining the Relationship Between Antidepressants and the Study Outcomes

Variable	Ischemic Heart Disease Model		Cardiovascular Events Model		All-Cause Mortality Model	
	Multivariate Adjusted Model (HR (95% CI)) (p value)	Propensity Score Adjusted Model (HR (95% CI)), (p value)	Multivariate Adjusted Model (HR (95% CI)), (p value)	Propensity Score Adjusted Model (HR (95% CI)), (p value)	Multivariate Adjusted Model (HR (95% CI)), (p value)	Propensity Score Adjusted Model (HR (95% CI)), (p value)
Use of Antidepressants	0.91 (0.55–1.52) (0.714)	1.05 (0.63–1.75) (0.862)	1.16 (0.82–1.64) (0.410)	1.01 (0.71–1.45) (0.939)	**0.67 (0.54–0.84) (0.001)**	0.81 (0.65–1.02) (0.07)
Type of antipsychotics (Ref= no use of antidepressants)						
Tricyclic antidepressants	1.28 (0.6–2.72) (0.522)	1.22 (0.58–2.59) (0.601)	0.9 (0.52–1.55) (0.708)	1.03 (0.59–1.78) (0.921)	**0.84 (0.48–0.98) (0.039)**	0.92 (0.59–1.19) (0.324)
Selective serotonin reuptake inhibitors	1.16 (0.65–2.08) (0.621)	1.09 (0.6–1.96) (0.785)	0.94 (0.63–1.4) (0.729)	1.07 (0.72–1.61) (0.728)	**0.7 (0.54–0.91) (0.007)**	0.85 (0.65–1.1) (0.209)
Others	0.62 (0.19–2.06) (0.437)	0.63 (0.19–2.07) (0.447)	0.49 (0.2–1.22) (0.125)	0.56 (0.22–1.39) (0.208)	**0.55 (0.33–0.9) (0.018)**	0.66 (0.4–1.08) (0.096)
Antidepressants medication (Ref= non users of the drug)						
Citalopram (SSRI)	1.49 (0.78–2.84) (0.222)	1.46 (0.77–2.77) (0.25)	1.2 (0.77–1.87) (0.424)	1.36 (0.87–2.14) (0.178)	**0.65 (0.47–0.91) (0.009)**	0.79 (0.57–1.09) (0.156)
Amitriptyline (TCA)	1.26 (0.49–3.27) (0.634)	1.22 (0.47–3.17) (0.678)	0.99 (0.51–1.92) (0.971)	1.12 (0.58–2.18) (0.739)	0.68 (0.43–1.08) (0.103)	0.83 (0.53–1.3) (0.409)
Fluoxetine (SSRI)	0.56 (0.13–2.37) (0.428)	0.38 (0.08–1.9) (0.241)	0.66 (0.27–1.64) (0.369)	0.76 (0.31–1.88) (0.552)	0.58 (0.33–1.02) (0.06)	0.7 (0.4–1.22) (0.209)
Mirtazapine (Other)	1.01 (0.31–3.35) (0.981)	1.01 (0.31–3.32) (0.987)	0.3 (0.07–1.24) (0.096)	0.35 (0.08–1.42) (0.14)	**0.43 (0.21–0.87) (0.019)**	0.5 (0.25–1.02) (0.058)
Sertraline (SSRI)	0.51 (0.07–3.78) (0.513)	0.48 (0.07–3.52) (0.47)	0.61 (0.19–1.92) (0.394)	0.68 (0.21–2.17) (0.516)	1.05 (0.62–1.79) (0.844)	1.23 (0.72–2.09) (0.444)
Paroxetine (SSRI)	1.34 (0.32–5.62) (0.694)	1.31 (0.31–5.5) (0.712)	0.48 (0.12–1.97) (0.311)	0.56 (0.14–2.3) (0.423)	0.83 (0.43–1.62) (0.588)	1.01 (0.52–1.98) (0.972)
Venlafaxine (Other)	0 (0–4.09) (0.962)	0 (0–2.21) (0.959)	0.93 (0.29–2.96) (0.897)	1.03 (0.32–3.29) (0.96)	0.71 (0.35–1.46) (0.354)	0.87 (0.43–1.76) (0.698)

Note: Bold values indicated significant numbers.
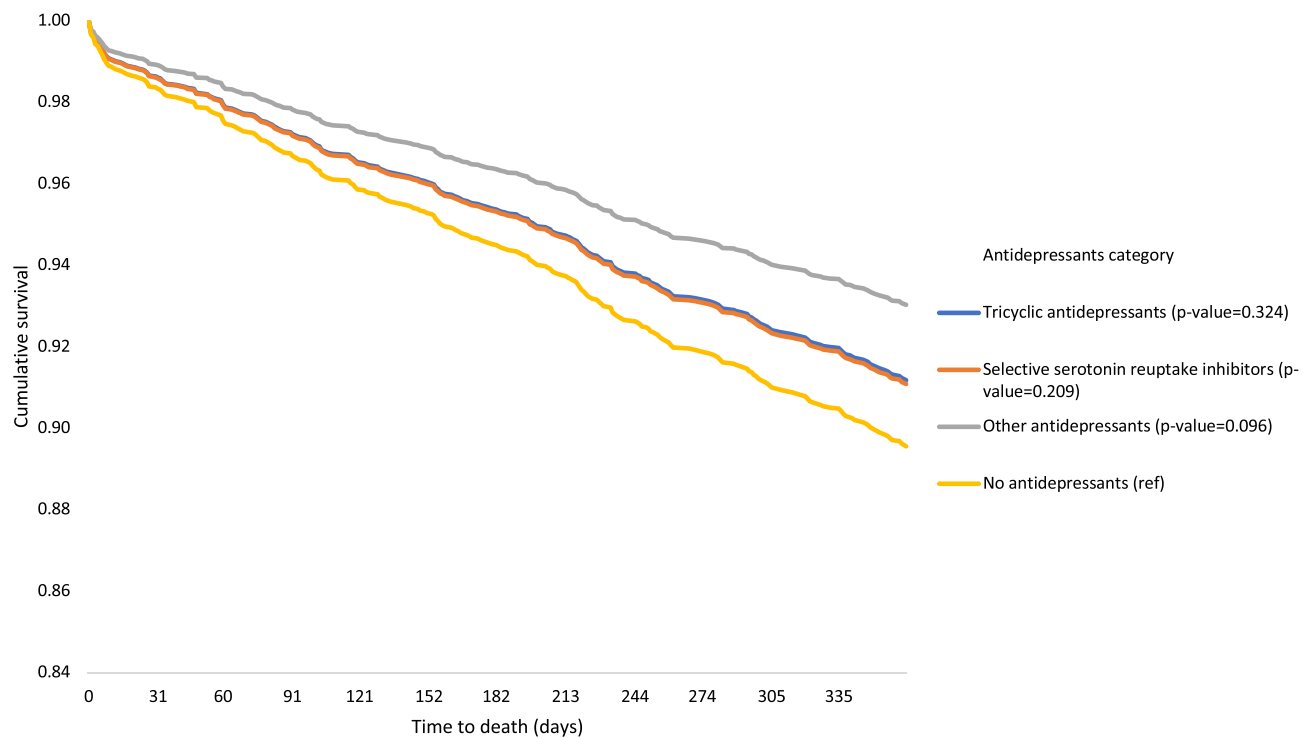
Figure 2 Kaplan–Meier estimates of all-cause mortality according to the status of antidepressant use in PD patients. *p*-values indicate the differences in survival compared to the reference group in the Cox regression equation.
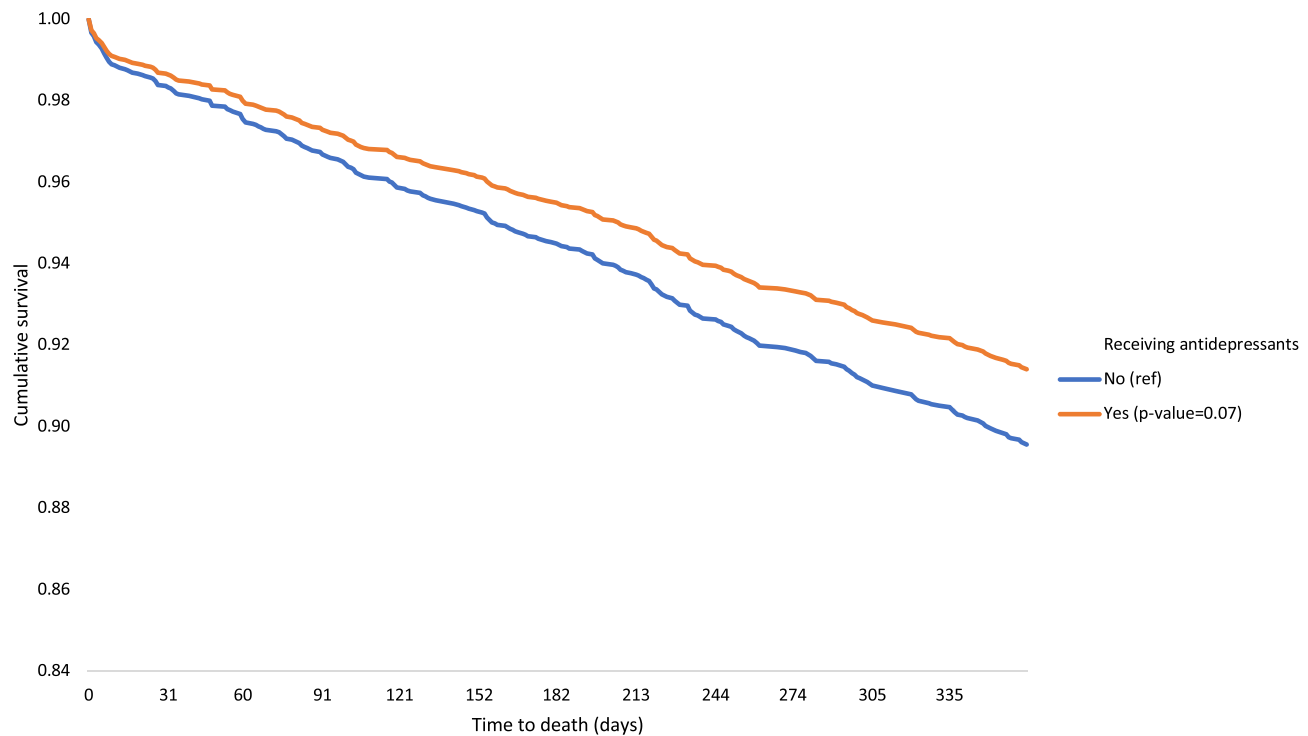
Figure 3 Kaplan–Meier estimates of all-cause mortality according to the category of antidepressant in PD patients. *p*-values indicate the differences in survival compared to the reference group in the Cox regression equation.
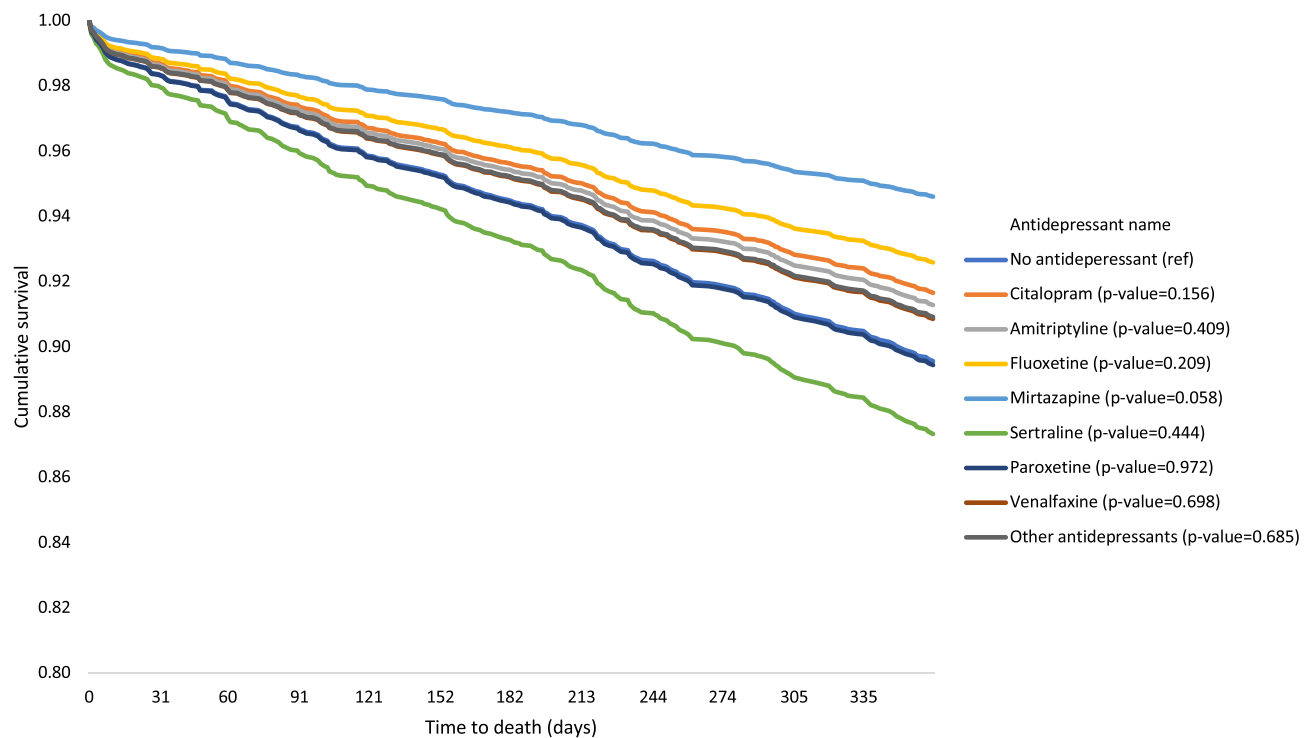
Figure 4 Kaplan–Meier estimates of all-cause mortality according to antidepressant in PD patients. *p*-values indicate the differences in survival compared to the reference group in the Cox regression equation.

Mitigating the effect of PD progression by shortening the follow-up period may therefore be the most appropriate approach to test the direct effect of antidepressants on IHD risk, although this approach has its drawbacks as it cannot test the risk in the long term.

Previous reports suggested that TCAs can cause weight gain[54] and exacerbate cardiotoxic effects, such as postural hypotension and QT interval prolongation,[55,56] by blocking the norepinephrine and serotonin reuptake at nerve terminals and blocking sodium channels.[57] By contrast, SSRIs were reported to have both cardioprotective and cardiotoxic properties. SSRIs inhibit serotonin reuptake in presynaptic terminals, which could lead to increased heart rate and constriction of the coronary arteries;[58] however, they can also have cardioprotective properties by inhibiting platelet aggregation, reducing inflammation, and improving endothelial function.[8] These pharmacological effects of both TCAs and SSRIs did not appear to have a direct clinical impact on newly diagnosed PD patients who used antidepressants in the short term, according to the current study. However, this did not preclude cardiac risk in the long term.

The multivariate adjusted model in this study suggested that the general use of antidepressants significantly decreased all-cause mortality risk in PD patients. This reduction in mortality risk was observed across different antidepressant categories (that is, TCAs, SSRIs, and other antidepressants), as well as in two individual antidepressants (that is, citalopram and mirtazapine) in the multivariate adjusted model. Although the propensity score-adjusted model did not reach statistical significance; the results of the multivariate model highlight the possible role of antidepressants in reducing the mortality rate in PD patients. Previous studies have reported a reduction in mortality rate among antidepressant users compared to non-users in patients with dementia,[33] cardiovascular disease,[59] and some other disorders.[60,61] In PD patients, only two previous studies examined the association between antidepressants and mortality rate, and they reported contradictory results: Frandsen et al found that the general use of antidepressants was associated with an increased mortality rate,[35] whereas Shoval et al found the opposite.[36] This divergence could be attributed to the confounding factors that affected both studies. For example, Frandsen et al did not account for any comorbidities that the PD patients may have suffered from, which could have resulted in inaccurate estimates.[35] The results of the current study were similar to those of Shoval et al.[36] An

additional finding of the current work was that among the individual antidepressants, only citalopram and mirtazapine were associated with a significant reduction in the multivariate adjusted model. It is unlikely that mirtazapine has pharmacological proprieties that lead to a reduction in mortality rate; in fact, previous studies reported that it could increase the mortality rate due its association with cardiovascular mortality and weight gain in the general population.[62,63] However, no studies so far have examined the association of mirtazapine with mortality rate in PD patients, and this requires further investigation.

There are several possible interpretations of the reduction in mortality rate associated with antidepressant use in newly diagnosed PD patients in this study. For instance, PD patients who use antidepressants might have regular contact with movement disorder specialists or PD nurses, resulting in better outcomes for depression and other comorbidities.[64] Moreover, the control group in the current study included PD patients who might have been suffering from undiagnosed depression without treatment, which in itself is a cause of mortality.[65] Indeed, underrecognized depression in newly diagnosed PD patients has been reported as a critical problem in the literature.[66] Caution should therefore be taken when attributing the reduction in mortality rate observed in the current study only to the use of antidepressants.

This was the first study to explore the relationship between antidepressant use and cardiovascular events, particularly IHD, in newly diagnosed PD patients. It benefitted from having a large sample size and utilizing a comprehensive population database. Furthermore, the propensity score-matching model used in the analysis boosted the statistical significance of the study findings.[67]

The current study had some limitations. Medical record codes were utilized to identify patients with PD and other diagnoses, without validation from neurologists or movement-disorder specialists. Also, the results might have been skewed by indication bias. For example, the patients who used antidepressants may have had more severe PD, resulting in a greater mortality rate. Therefore, causality could not be concluded. However, action was taken to minimize this bias by restricting the analysis to newly diagnosed PD patients. The short follow-up period could be a limitation; however, it could also be seen as a necessity when pursuing the goal of analyzing the immediate risks of antidepressants. Further research to assess the long-term effects of antidepressants while controlling for the confounding effects of PD neurodegenerative progression is needed.

Conclusions

Although antidepressants play an important role in treating patients with PD, their use has been associated with certain risks in the general population.[10,68] This study revealed no association between antidepressant use and either IHD or all cardiovascular events in newly diagnosed PD patients. Additionally, the multivariate model suggested that the use of antidepressants reduced the mortality rate at 1 year of follow up. These findings highlighted that TCAs, SSRIs, and other antidepressants might be safe for use in the treatment of depression in patients with PD. There is a need for further research with larger sample sizes and longer follow-up periods. In the meantime, the advantages of antidepressants for treating patients with PD must continue to be balanced against the safety concerns.

Abbreviations

CI, confidence interval; GP, general practice; HR, hazard ratio; IGRP, Information Governance Review Panel; IHD, ischemic heart disease; MAO-B, monoamine oxidase-B; NSAID, non-steroidal anti-inflammatory drug; PD, Parkinson's disease; SAIL, Secure Anonymized Information Linkage; SD, standard deviation; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; WHO, World Health Organization; WIMD, Welsh Index of Multiple Deprivation.

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