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RESEARCH ARTICLE

Psychotropic medication use and Parkinson's disease risk amongst older women

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Abstract

Objective: To examine associations of antidepressant, anxiolytic and hypnotic use amongst older women (≥65 years) with incident Parkinson's Disease (PD), using data from Women's Health Initiative linked to Medicare claims. **Methods**: PD was defined using self-report, first diagnosis, medications and/or death certificates and psychotropic medications were ascertained at baseline and 3-year follow-up. Cox regression models were constructed to calculate adjusted hazard ratios (aHR) with 95% confidence intervals (CI), controlling for socio-demographic, lifestyle and health characteristics, overall and amongst women diagnosed with depression, anxiety and/or sleep disorders (DASD). **Results**: A total of 53,996 WHI participants (1,756 PD cases)—including 27,631 women diagnosed with DASD (1,137 PD cases)—were followed up for ~14 years. Use of hypnotics was not significantly associated with PD risk (aHR = 0.98, 95% CI: 0.82, 1.16), whereas PD risk was increased amongst users of antidepressants (aHR = 1.75, 95% CI: 1.56, 1.96) and anxiolytics (aHR = 1.48, 95% CI: 1.25, 1.73). Compared to non-users of psychotropic medications, those who used 1 type had ~50% higher PD risk, whereas those who used ≥2 types had ~150% higher PD risk. Women who experienced transitions in psychotropic medication use ('use to non-use' or 'non-use to use') between baseline and 3-year follow-up had higher PD risk than those who did not. We obtained similar results with propensity scoring and amongst DASD-diagnosed women. **Interpretation**: The use of antidepressants, anxiolytics or multiple psychotropic medication types and transitions in psychotropic medication use was associated with increased PD risk, whereas the use of hypnotics was not associated with PD risk amongst older women.

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disorder and the most frequently diagnosed movement disorder affecting nearly 1 million individuals in the United States.[1–3] PD is the outcome of progressive degeneration of dopaminergic neurons in the nigrostriatal pathway, which leads to dopamine deficiency in the substantia nigra pars compacta located in the midbrain.[2,4,5] PD dementia is likely related to Lewy bodies

which are cytoplasmic aggregates of insoluble α-synuclein.[2,4,5] Whereas 30% of PD is heritable, the majority of PD cases are sporadic in nature or have been attributed to environmental influences.[5–7] According to the biopsychosocial model, stressful life events and chronic stress can lead to a maladaptive state that can adversely impact an individual's physical and mental health through neuroendocrine, immune and behavioural mechanisms and potentially lead to neurodegeneration.[8–10] Depression, anxiety and sleep disorders are frequently co-morbid non-motor symptoms (NMS) of PD, which may precede or co-occur with PD motor symptoms, are highly prevalent but often unrecognized or under-treated and may be detrimental to a PD patient's quality of life.[2,3,11] There is growing evidence from case–control and retrospective cohort studies that widely used psychotropic medications—including antidepressants, anxiolytics and hypnotics for the treatment of depression, anxiety and sleep disorders—can impact PD risk, progression and outcomes with implications for public health and preventive medicine.[4,12–15] Previous studies have also suggested that psychiatric disorders, such as depression and anxiety, as well as psychotropic medications used to treat these disorders, may be prodromal to the onset of PD motor symptoms.[3,13,16] Despite the fact that sleep disorders may be linked to neurodegeneration,[3] few studies have evaluated the role of hypnotics in PD.[17,18] In a case–control study of 959 prevalent cases of parkinsonism (767 with PD) and 1989 controls, Dick and colleagues[4] found that antidepressant (OR = 1.92, 95% CI: 1.49, 2.49), anxiolytic (OR = 1.95, 95% CI: 1.54, 2.47) and hypnotic (OR = 1.33, 95% CI: 1.07, 1.65) medication use for >1 year were independent predictors of PD/parkinsonism.[4] Available studies have separately examined distinct types of psychotropic medications but have not examined concurrent use or trajectories in the use of distinct psychotropic medication types in relation to PD risk.[13,19] More importantly, the extant literature often failed to establish a temporal relationship between psychotropic medication use and PD risk by the use of longitudinal study designs or the exclusion of PD cases that occur within a few years of follow-up. In addition, the extant literature often failed to deal with issues of confounding by indication through propensity score analysis or by restricting their samples to individuals affected by depression, anxiety and/or sleep disorders.

Women are considered a high-risk group for depression, anxiety and/or sleep disorders as well as psychotropic medication use for the treatment of these conditions particularly after menopause.[20,21] To date, no studies have adequately targeted older women ≥65 years of age who account for a large proportion of late-onset PD cases having characteristically more severe motor symptoms, more frequent NMS, a faster course and shorter survival than early-onset PD.[22,23] We performed a secondary analysis of longitudinal data from the Women's Health Initiative (WHI) study to evaluate whether antidepressant, anxiolytic and hypnotic medication use was associated with incident PD in women ≥65 years of age, overall, and amongst those diagnosed with depression, anxiety and/or sleep disorders, by applying risk adjustment and propensity score analysis. We hypothesized that psychotropic medication use, at baseline and over time, is causally or non-causally related to PD, by being a modifiable risk factor for PD, a marker of disease severity or a prodromal feature of PD and can, therefore, identify high-risk groups for future PD diagnosis amongst women ≥65 years of age, which may benefit from monitoring for the development of PD motor and non-motor symptoms within healthcare settings.

Methods

Women's Health Initiative

WHI collected longitudinal data on a multiethnic sample of postmenopausal women who were recruited and enrolled between 1993 and 1998 at 40 geographically diverse clinical centres (24 states and the District of Columbia) in the United States. The WHI study received institutional review board approval with informed consent from all participating clinical centres. The WHI study design, eligibility criteria, recruitment methods and measurement protocols are described elsewhere.[24,25] Briefly, the WHI clinical trials (WHI-CTs) (n = 68,132) and the WHI observational study (WHI-OS) (n = 93,676) are two components of the WHI (n = 161,808). Within the clinical trial component, four overlapping WHI-CTs evaluated outcomes of menopausal hormone therapy (hormone therapy [HT] trials), calcium and vitamin D supplementation ([CaD] Trial) and a low-fat eating pattern (Dietary Modification Trial). The WHI-OS evaluated causes of morbidity and mortality outcomes. The main WHI studies ended in 2005 and of 150,076 participants who were actively followed up at the end of these studies, 76.9% participated in Extension Study 1 (2005–2010) and 86.9% of those eligible participated in Extension Study 2 (2010–2020).[26,27] At baseline, WHI participants, 50–79 years of age, completed the same self-administered questionnaire covering demographics, general health, clinical and anthropometric characteristics, medical history, personal habits as well as medication use and several of these characteristics were assessed at later follow-up times. In this study, we followed WHI participants using linked WHI-Medicare data. The research was conducted in accordance with the Helsinki Declaration as revised in 1989. This

study received an exempt determination from the institutional review board at Walter Reed National Military Medical Center.

Design and participants

In this retrospective cohort study, WHI-CT and WHI-OS participants, ≥65 years of age at baseline, were included in the study if they had available WHI-Medicare (Part A and/or Part B) linked data. Furthermore, we excluded women with self-reported PD or International Classification of Diseases (9th Revision, Clinical Modification) [ICD-9-CM] primary or secondary codes from Medicare data that reflect a PD diagnosis at WHI baseline. We also excluded WHI participants with ICD-9-CM Clinical Classification Software (CCS) codes indicating other mental health problems besides depression and/or anxiety disorders, with the exception of those having ICD-9-CM codes for sleep disorders. We further excluded WHI participants who reported using medications at baseline or during the follow-up visits with Assigned Therapeutic Classes of 'Antipsychotic/Antimanic', 'Attention deficit hyperactivity disorder (ADHD)/Anti-narcoplepsy/Anti-obesity/Anorexiants' and 'psychotherapeutic and neurological agents (miscellaneous)' as well as those with a comorbidity of delirium, dementia and amnestic and other cognitive disorders based on Medicare data. These subjects were excluded because healthcare-seeking behaviours linked to these medications and diagnoses can result in differential misclassification of a PD diagnosis. Finally, we excluded women who had <12 months of WHI-Medicare linked data after the baseline visit and those with missing data on key variables. A sub-analysis was performed which excluded women without a history of depression, anxiety and/or sleep disorders at baseline (Tables S1-S2).

Linkage of Women's Health Initiative to medicare data

The U.S. Centers for Medicare & Medicaid Services (CMS) Medicare is the federal health insurance program for individuals ≥65 years and those <65 years who have disabilities or end-stage renal disease. The WHI and CMS Medicare data were linked together amongst consenting participants using their social security number, date of birth and, if needed, date of death and residential zip code. Nearly 97% of Medicare-eligible participants were successfully linked. Data linkage was made for participation in traditional fee-for-service (80%) but not Medicare Health Maintenance Organization programs (20%). The linkage between WHI and Medicare data was approved by the Institutional Review Board of the Fred Hutchinson Cancer Research Center. Details regarding Medicare files can be obtained from the Research Data Assistance Center (http://www.resdac.org/cms-data).[28–33] Study analyses were restricted to WHI participants who were ≥65 years and enrolled in fee-for-service Medicare Parts A and B at baseline.

Study variables

Depression, anxiety and/or sleep disorders

Diagnoses of mental health problems were based on twelve ICD-9-CM CCS codes.[34] We used available Medicare (Medicare Provider Analysis and Review [MEDPAR], outpatient and carrier) data to define depression (CCS codes for 'mood disorders') and anxiety (CCS codes for 'anxiety disorders') disorders at baseline as dichotomous ('yes' or 'no') variables. Additionally, ICD-9-CM primary and secondary diagnostic codes classified sleep disorders as insomnia, sleep-related breathing disorders, hypersomnia, circadian rhythm sleep disorder, parasomnia, sleep-related movement disorder and other sleep disorders.[35] We used available Medicare (MEDPAR, outpatient and carrier) data to define sleep disorders at baseline as a dichotomous ('yes' or 'no') variable. Depression, anxiety and sleep disorders at baseline were examined in relation to psychotropic medication use in bivariate and propensity score analyses. Furthermore, a sub-sample of study-eligible WHI participants was defined using ICD-9-CM/CCS codes to include those diagnosed with depression, anxiety and/or sleep disorders at baseline (Table S1).

Psychotropic medication use

Antidepressant, anxiolytic and hypnotic use

WHI participants were instructed to bring prescription and non-prescription medication containers to the baseline and follow-up visits. For medications used for >2 weeks, drug names and doses were entered into a medications database and assigned therapeutic class codes using the Master Drug Data Base (MDDB: Medi-Span, Indianapolis, IN; Medi-Span software: First DataBank, Inc., San Bruno, CA) (Table S2). Dichotomous ('yes' or 'no') antidepressant, anxiolytic and hypnotic use were ascertained at baseline (form 44) and 3 years of follow-up (form 153). Amongst study-eligible participants who completed both visits, slight agreement existed between baseline and 3-year follow-up visits on psychotropic medication use in the overall sample (antidepressant (κ = 0.36, 95% CI: 0.34, 0.37), anxiolytic (κ = 0.26, 95% CI: 0.24, 0.28), hypnotic (κ = 0.19, 95% CI: 0.17, 0.21)) and a sub-sample of women diagnosed with depression, anxiety and/or sleep disorders (antidepressant (κ = 0.33,

95% CI: 0.31, 0.35), anxiolytic (κ = 0.27, 95% CI: 0.25, 0.30) and hypnotic (κ = 0.19, 95% CI: 0.17, 0.22)). As such, psychotropic medication use was carried forward for women with no follow-up data, and a sensitivity analysis that relied on baseline data alone was performed.

Patterns of psychotropic medication use

Antidepressants, anxiolytics and hypnotics were considered three distinct psychotropic medication types. Amongst subjects having medication use data at baseline and 3 years of follow-up, patterns of psychotropic medication use were defined as a categorical variable ('no psychotropic medication [baseline and follow-up]'; '1 type of psychotropic medication [baseline and/or follow-up]'; '≥2 types of psychotropic medications [baseline and/or follow-up]').

Transitions in psychotropic medication use

Amongst subjects having medication use data at baseline and on 3 years of follow-up, transitions in any type of psychotropic medication (antidepressant, anxiolytic and/or hypnotic) between baseline and 3-year follow-up were evaluated as follows: *Increase* ('non-use to use') for at least one type of psychotropic medication; *Decrease* ('use to non-use') for at least one type of psychotropic medication without an increase in other types; *No change* in use of psychotropic medication types. A more detailed definition that relies on patterns of psychotropic medication use was evaluated in relation to PD risk for exploratory purposes.

Parkinson's disease

Incident PD was defined at each available year of follow-up, including self-reported PD from the WHI medical update form, Medicare (MEDPAR, outpatient and carrier) codes that reflect the first occurrence of PD primary or secondary diagnosis using ICD-9-CM and International Classification of Diseases (10th Revision [ICD-10]) diagnostic codes (as appropriate), use of medications consistent with PD diagnosis (forms 44 and 153) and/or deaths attributed to PD (Tables S1-S2).[36] The level of agreement between PD definitions with and without ICD-9-CM/ICD-10 diagnostic codes was estimated amongst eligible subjects (κ = 0.44, 95% CI: 0.42, 0.47). Time-to-event, whether PD onset, loss to follow-up or death, were calculated from the baseline questionnaire until December 31, 2018, whichever came first, whilst ensuring the exclusion of PD cases and follow-up time between baseline and 3 years of follow-up to account for immortal time bias.

Socio-demographic, lifestyle and health characteristics

Besides WHI component, socio-demographic (age, race/ethnicity, marital status, education, household income, lifestyle (smoking status, alcohol use, physical activity) and health (body mass index (BMI), history of cardiovascular disease, history of hypertension, history of diabetes, history of hyperlipidemia, self-rated health) characteristics were collected at baseline. Frequency and duration of walking, mild, moderate and strenuous physical activities over the past week were assessed and total weekly kilocalories of energy expenditure were calculated in metabolic equivalents. History of cardiovascular disease was defined in terms of previous coronary heart disease, angina, aortic aneurysm, carotid endarterectomy or angioplasty, atrial fibrillation, congestive heart failure, cardiac arrest, stroke or transient ischemic attack. History of diabetes was defined as physician-diagnosed diabetes or use of diabetes medications. History of hyperlipidemia was defined as using lipid-lowering medications or having been told of high cholesterol by a physician. Self-rated health was assessed using one item: 'In general would you say your health is excellent, very good, good, fair or poor?[26,37]

Statistical analysis

All statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC). Summary statistics included means (±standard deviations) for continuous variables and frequencies with percentages for categorical variables. Bivariate associations were examined using Chi-square, independent samples t-tests or one-way analysis of variance, as appropriate. We also fit Cox proportional hazards models to examine associations of psychotropic medication use with incident PD, after controlling for socio-demographic, lifestyle and health characteristics through risk adjustment and propensity scoring. These two methods were applied in order to examine hypothesized associations, before and after taking into account confounding by indication. The proportional hazards assumptions were assessed using Schoenfeld residuals. Hypothesized relationships were examined in the overall sample and amongst a sub-sample of women diagnosed with depression, anxiety and/or sleep disorders at baseline. Propensity score analysis is an alternative method to multivariable regression that ensures treatment groups have equal distribution on characteristics affecting outcome and that differences in outcomes between various treatments can be attributed to treatment.[38,39] We calculated propensity scores or predicted probabilities of antidepressant, anxiolytic and hypnotic use for each

subject based on a set of relevant characteristics using a two-step procedure: (1) Use of antidepressants, anxiolytics and hypnotics were modelled as outcome variables in *a priori* stepwise logistic regression models whereby the disorder of concern along with a subset of WHI component, socio-demographic, lifestyle and health characteristics were selected as predictors; (2) predicted probabilities of antidepressant, anxiolytic or hypnotic use ('propensity scores') were calculated and used as weights within Cox regression models that examined these exposures as predictors of PD risk. We further applied the CAUSALTRT procedure with the inverse probability of treatment weighting (IPTW) option to graphically examine and verify the balance in propensity scores as well as socio-demographic, lifestyle and health characteristics according to treatment selection. Furthermore, we stratified risk-adjusted models by (1) time-to-event (<5 years vs. ≥5 years), (2) age at baseline (<70 vs. ≥ 70) and (3) WHI component (CT vs. OS) to account for the potential violation of the proportional hazards assumption as well as temporality and design differences between WHI components. Finally, we performed sensitivity analyses in fully risk-adjusted models, to assess: (1) validity of PD definition by repeating key analyses without ICD-9-CM/ICD-10 codes; (2) validity of antidepressant, anxiolytic and hypnotic use definitions by repeating key analyses with only baseline exposure data; (3) association of antidepressant and anxiolytic medication use with PD amongst individuals with sleep disorders only; (4) interaction effects of psychotropic medication and self-rated health in relation to PD. Since <5% of potentially eligible subjects had missing data on covariates, complete subject analyses were performed. Two-tailed statistical tests were assessed at $\alpha = 0.05$.

Results

As shown in Figure 1, 71,010 of 161,808 WHI participants reported age ≥ 65 years at baseline and of those 53,996 remained after applying all eligibility criteria; these women were followed for an average of 14.39 (±6.18) years, yielding 1,756 (3.25%) PD cases. Of those, 17,266 subjects had psychotropic medication data available at baseline and follow-up visits. A sub-sample of 27,631 subjects was diagnosed with depression, anxiety and/or sleep disorders at baseline and followed for an average of 14.29 (±5.93) years, yielding 1,137 (4.11%) PD cases. Of those, 14,803 subjects had psychotropic medication data available at baseline and follow-up visits.

Psychotropic medication use by socio-demographic, lifestyle and health characteristics of the overall analytic sample are displayed in Tables 1-4. The estimated prevalence rates of antidepressant, anxiolytic and hypnotic medication use were ~15%, ~7% and ~8%, respectively. Whereas ~23% used one type of psychotropic medication, 5% used two or three types of psychotropic medications simultaneously. Between baseline and follow-up visits, approximately 23% experienced a change in psychotropic medication use including ~13% who switched from non-use to use of any medication type [Increase] and 10% who switched from use to non-use of any medication type without an increase in other types [Decrease]. Psychotropic medication use generally varied significantly according to baseline characteristics. White, Asian, younger and obese women (with a history of cardiometabolic risk factors) and those with worse self-rated health were more likely to use anti-depressants, anxiolytics and/or hypnotics. Furthermore, psychotropic medication use differed significantly amongst those with and without a diagnosis of depression, anxiety and/or sleep disorders.

Psychotropic medication use as risk or protective factors for PD is presented in the overall analytic sample (Table 5) and amongst a sub-sample of WHI participants diagnosed with depression, anxiety and/or sleep disorders (Table 6). In fully adjusted Cox regression models, the use of hypnotics was not significantly associated with PD risk in the overall sample (HR = 0.98, 95% CI: 0.82, 1.16, $p = 0.80$) or the sub-sample (HR = 0.93, 95% CI: 0.77, 1.13, $p = 0.47$). By contrast, PD risk was increased amongst users of antidepressants in the overall sample (HR = 1.75, 95% CI: 1.56, 1.96, $p < 0.0001$) and the sub-sample (HR = 1.62, 95% CI: 1.43, 1.84, $p < 0.0001$). Similarly, PD risk was increased amongst users of anxiolytics in the overall sample (HR = 1.48, 95% CI: 1.25, 1.73, $p < 0.0001$) and the sub-sample (HR = 1.36, 95% CI: 1.14, 1.62, $p < 0.0001$). Compared to non-users of psychotropic medications, those who used one type of psychotropic medications had ~50% increased risk of PD in the overall sample (HR = 1.49, 95% CI: 1.29, 1.72, $p < 0.0001$) and the sub-sample (HR = 1.58, 95% CI: 1.32, 1.88, $p < 0.0001$) and those who used ≥2 types of psychotropic medications had ~150% increased PD risk in the overall sample (HR = 2.43, 95% CI: 1.92, 3.06, $p < 0.0001$) and the sub-sample (HR = 2.25, 95% CI: 1.74, 2.93, $p < 0.0001$). In the overall sample, women who experienced an increase (HR = 1.62, 95% CI: 1.37, 1.92, $p < 0.0001$) or a decrease (HR = 1.30, 95% CI: 1.05, 1.61, $p = 0.0145$) in psychotropic medication use between baseline and follow-up were at elevated risk for PD compared to those without medication change. Similar results were obtained amongst sub-sample women with an increase (HR = 1.57, 95% CI: 1.29, 1.89, $p < 0.0001$) or a decrease (HR = 1.28, 95% CI: 1.00, 1.64, $p = 0.0491$) in psychotropic medication use. Besides WHI participants censored within 5 years from baseline,

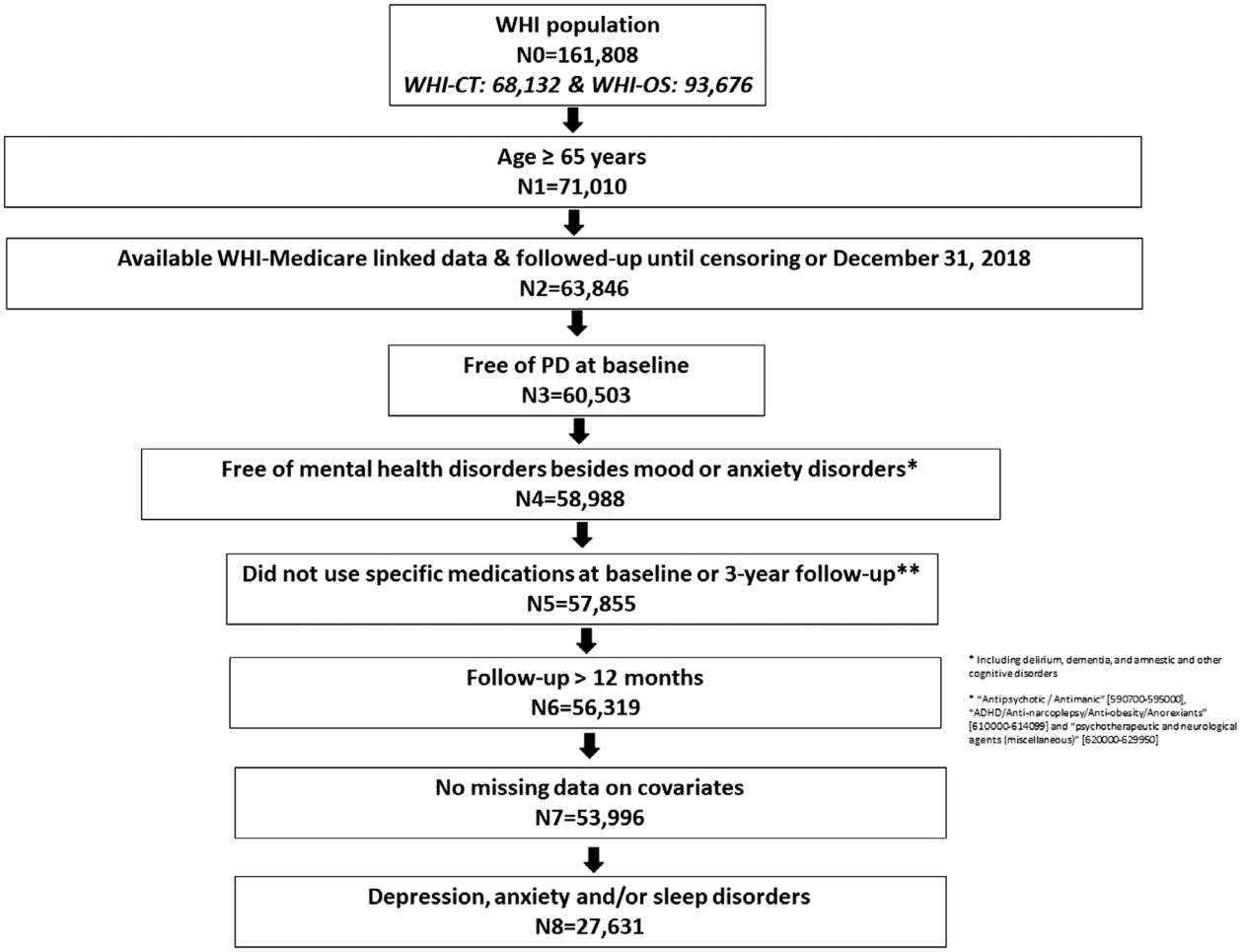

Figure 1. Study Flowchart.

sub-group analyses based on time-to-event, age and WHI component revealed similar results to the main analyses with respect to the relationship between psychotropic medication use and PD risk (Tables S3-S4). We observed similar results after using a PD definition that did not cover ICD-9-CM/ICD-10 codes or, defining antidepressant, anxiolytic and hypnotic medication use according to baseline data alone (Tables S5-S6). A detailed definition for transitions suggested distinct levels of PD risk according to baseline and 3-year follow-up psychotropic medication use, with the highest risk amongst those having ≥2 psychotropic medication types at baseline and 1 psychotropic medication type at 3-year follow-up visit (Table S7). Moreover, individuals with sleep disorders only who used antidepressants or anxiolytics were not at significantly higher risk of PD than non-users (Table S8) and the relationship between psychotropic medication use and PD risk did not vary according to self-rated health (Table S9).

Propensity score analyses indicated that the use of antidepressants (HR = 1.34, 95% CI: 1.23, 1.46, $p < 0.0001$) and anxiolytics (HR = 1.29, 95% CI: 1.18, 1.40, $p < 0.0001$) but not hypnotics (HR = 0.97, 95% CI: 0.89, 1.07, $p = 0.56$) were positively associated with PD risk in the overall sample. Similar results were obtained for antidepressants (HR = 1.39, 95% CI: 1.25, 1.55, $p < 0.0001$), anxiolytics (HR = 1.26, 95% CI: 1.13, 1.41, $p < 0.0001$) and hypnotics (HR = 0.98, 95% CI: 0.87, 1.19 = 0, $p = 0.73$) in the sub-sample of women diagnosed with depression, anxiety and/or sleep disorders (Table 7).

Discussion

Longitudinal studies of psychotropic medications, including those used to treat depression [antidepressants], anxiety [anxiolytics] and sleep disorders [hypnotics], remain scarce in the context of PD.[40–42] Several studies have

Table 1. Antidepressant, anxiolytic, hypnotic and patterns of psychotropic medication use by socio-demographic characteristics of study sample—Women's Health Initiative (n = 53,996)[a].

	Overall	N = 53,996			Patterns of psychotropic medication use (N = 29,537)		
	N (%)	Antidepressant %	Anxiolytic %	Hypnotic %	0 %	1 %	≥2 %
Overall	53,996 (100)	14.97	6.77	7.86	72.55	22.96	4.50
WHI component		$p < 0.0001$	$p = 0.22$	$p < 0.0001$	$p < 0.0001$		
CT	20,576 (38.11)	17.34	6.94	9.14	71.13	23.77	5.10
OS	33,420 (61.89)	13.52	6.67	7.07	73.56	22.37	4.07
Age (years)		$p < 0.0001$	$p = 0.09$	$p = 0.03$	$p = 0.24$		
65–69	27,021 (50.04)	15.97	6.81	7.90	72.31	23.12	4.57
70–74	18,950 (35.10)	14.67	6.94	8.09	72.53	22.89	4.58
>74	8,025 (14.86)	12.31	6.23	7.17	74.01	22.20	3.80
Race/Ethnicity		$p < 0.0001$	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$		
White	41,558 (76.96)	16.02	6.98	8.65	71.97	23.35	4.68
Black	2,431 (4.50)	10.16	5.92	4.81	79.16	18.11	2.73
Asian	8,707 (16.13)	12.60	6.56	5.72	70.84	25.31	3.85
Other	1,300 (2.41)	6.31	3.00	2.62	87.83	11.02	1.15
Marital status		$p < 0.0001$	$p = 0.002$	$p < 0.0001$	$p < 0.0001$		
Married/Partnered	30,330 (56.17)	15.68	7.08	8.30	71.76	23.50	4.74
Single	2,122 (3.93)	11.69	5.37	5.89	77.55	19.12	3.33
Divorced	6,526 (12.09)	15.89	6.67	7.26	71.40	23.87	4.73
Widowed	15,018 (27.81)	13.60	6.39	7.51	74.31	21.73	3.95
Education		$p = 0.0005$	$p < 0.0001$	$p = 0.16$	$p < 0.0001$		
Less than high school	3,172 (5.87)	14.50	9.17	6.90	71.17	23.66	5.17
High school graduate	10,395 (19.25)	15.97	7.46	8.08	70.82	24.06	5.12
Some college	20,794 (38.51)	15.23	6.97	7.95	71.54	23.84	4.62
College graduate	19,635 (36.36)	14.24	5.80	7.79	74.38	21.57	4.04
Household income		$p = 0.046$	$p < 0.0001$	$p = 0.0003$	$p = 0.07$		
< $20,000	10,978 (20.33)	15.07	7.68	7.45	71.63	23.65	4.72
$20,000–$49,999	25,784 (47.75)	15.33	6.77	8.04	71.95	23.45	4.60
$50,000–$99,999	10,861 (20.11)	14.64	6.16	8.33	73.32	22.29	4.39
≥$100,000	2,685 (4.97)	14.38	5.66	8.16	74.79	21.22	3.99
Unknown	3,688 (6.83)	13.61	6.64	6.21	74.51	21.49	4.00

Abbreviations: CT, clinical trial; OS, observational study; WHI, Women's Health Initiative.

[a]p values were the outcome of Pearson's Chi-square tests, independent samples t-tests or one-way analysis of variance tests, as appropriate.

implicated dysfunctional immunity, psychological stress, anxiety, depression and sleep disorders in PD onset, progression and altered outcomes,[8,43–46] highlighting the importance of investigating psychotropic medications often used to treat these disorders in relation to PD risk.

In this longitudinal study, we performed secondary analyses of existing data from the WHI-CTs and WHI-OS to evaluate antidepressant, anxiolytic and hypnotic use and their associations with PD risk, overall and amongst women with depression, anxiety and/or sleep disorders. In contrast with a previously published cohort study evaluating a specific hypnotic medication [zolpidem],[18] we found that the use of hypnotics was not significantly related to incident PD after controlling for confounders. In the National Health Insurance System of Taiwan cohort, first-time users of zolpidem for >3 months (1998–2000) had greater PD incidence (HR = 1.88, 95% CI: 1.45, 2.45) as compared to a randomly selected frequency-matched (age, sex and index date) sample of individuals without a history of zolpidem use.[18] However, after 5 years of follow-up there was no difference in PD incidence, and zolpidem use with concurrent depression (HR = 4.79) increased the risk of PD compared to zolpidem use without concurrent depression.[18]

This study found that the use of antidepressants and/or anxiolytics may be prodromal to future PD onset, after controlling for socio-demographic, lifestyle and health characteristics using risk adjustment or propensity score analysis. The use of antidepressants or anxiolytics may be

Table 2. Antidepressant, anxiolytic, hypnotic and patterns of psychotropic medication use by lifestyle and health characteristics of study sample—Women's Health Initiative (n = 53,996).[a]

	Overall	N = 53,996			Patterns of psychotropic medication use (N = 29,537)		
	N (%)	Antidepressant %	Anxiolytic %	Hypnotic %	0 %	1 %	≥2 %
Overall	53,996 (100)	14.97	6.77	7.86	72.55	22.96	4.50
Smoking status		$p < 0.0001$	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$		
Never	28,686 (53.13)	13.92	6.22	7.07	74.68	21.28	4.04
Past	22,622 (41.90)	16.11	7.27	8.75	70.32	24.71	4.97
Current	2,688 (4.98)	16.56	8.44	8.74	65.81	28.21	5.98
Alcohol use		$p < 0.0001$	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$		
Non-drinker	6,671 (12.35)	13.22	6.24	5.80	75.66	21.06	3.27
Former drinker	10,299 (19.07)	18.03	8.00	7.24	68.62	26.01	5.37
<1 drink / week	16,995 (31.47)	14.77	6.40	7.43	73.46	22.25	4.30
≥1 drink / week	20,031 (37.10)	14.18	6.63	9.23	72.54	22.82	4.63
Physical activity (Met-hours/week)		$p < 0.0001$	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$		
Mean (SD)	12.62 (13.39)	11.47 (12.91) 12.83 (13.47)	11.36 (13.11) 12.72 (13.40)	11.74 (12.74) 12.70 (13.44)	13.87 (13.79)	12.57 (12.86)	11.25 (13.37)
Body Mass Index (kg/m^2)		$p < 0.0001$	$p = 0.05$	$p = 0.18$	$p < 0.0001$		
<25	19,607 (36.31)	13.12	6.95	7.58	74.30	21.44	4.27
25–29.9	19,692 (36.47)	15.31	6.91	7.98	72.24	23.13	4.62
≥30	14,697 (27.22)	16.99	6.33	8.07	70.40	24.95	4.65
Medical history							
Cardiovascular disease		$p < 0.0001$	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$		
Yes	14,267 (26.42)	18.01	8.66	8.73	66.74	27.43	5.83
No	39,729 (73.58)	13.88	6.09	7.54	74.23	21.66	4.11
Hypertension		$p < 0.0001$	$p < 0.0001$	$p = 0.007$	$p < 0.0001$		
Yes	27,774 (51.44)	19.74	7.47	8.16	70.14	24.94	4.92
No	26,222 (28.56)	14.32	6.03	7.54	74.70	21.18	4.12
Diabetes		$p < 0.0001$	$p < 0.0001$	$p = 0.76$	$p < 0.0001$		
Yes	6,515 (12.07)	16.42	7.98	7.95	68.01	26.87	5.12
No	47,481 (87.93)	13.44	6.60	7.85	73.18	22.41	4.41
Hyperlipidemia		$p < 0.0001$	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$		
Yes	9,672 (17.91)	17.38	8.09	8.89	68.81	25.43	5.76
No	44,324 (82.09)	14.45	6.48	7.63	73.30	22.46	4.24
Self-rated health		$p < 0.0001$	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$		
Excellent	7,778 (14.40)	10.23	4.37	6.83	79.60	17.79	2.61
Very good	22,249 (41.20)	12.98	5.47	7.52	74.98	21.30	3.72
Good	19,073 (35.32)	17.10	7.86	8.23	67.78	26.46	5.76
Fair	4,580 (8.48)	22.79	12.05	9.69	56.70	33.03	10.11
Poor	316 (0.59)	29.75	15.19	7.91	52.70	41.89	4.51
Depression, Anxiety and/or sleep disorders		$p < 0.0001$	$p < 0.0001$	$p < 0.0001$	$p < 0.0001$		
Yes	27,631 (51.17)	6.23	9.75	10.55	59.27	33.11	7.62
No	26,365 (48.32)	23.31	3.64	5.04	85.90	12.75	1.36

Abbreviations: CT, clinical trial; OS, observational study; WHI, Women's Health Initiative.

[a]p values were the outcome of Pearson's Chi-square tests, independent samples t-tests or one-way analysis of variance tests, as appropriate.

interpreted as an indication of depression/anxiety severity; as such, disentangling diagnosis and treatment are critical. In this study, we found a persistently strong and positive association between antidepressant/anxiolytic use and PD risk even after restricting the study sample to older women with a baseline diagnosis of depression, anxiety and/or sleep disorders as well as propensity score analysis. This suggests that these psychotropic medications may be associated with PD risk, independent of the presence or absence of these psychiatric disorders. An alternative explanation is that the use of psychotropic medications is a maker of disease severity and that the underlying

Table 3. Transitions in psychotropic medication use by sociodemographic characteristics of study sample—Women's Health Initiative (n = 29,537).[a]

	Overall *N* (%)	Transitions in psychotropic medication use (N = 29,537)		
		Decrease %	Same %	Increase %
Overall	29,537 (100)	9.48	77.25	13.26
WHI component		$p < 0.0001$		
CT	12,271 (41.54)	11.72	76.27	12.01
OS	17,266 (58.46)	7.89	77.95	14.15
Age (years)		$p = 0.012$		
65–69	16,948 (57.38)	9.82	8.77	9.88
70–74	9,665 (32.72)	77.07	77.39	77.87
>74	2,924 (9.90)	13.12	13.83	12.24
Race/Ethnicity		$p < 0.0001$		
White	26,578 (89.98)	9.67	76.75	13.59
Black	1,209 (4.09)	8.11	82.55	9.35
Asian	1,142 (3.87)	9.46	76.53	14.01
Other	608 (2.06)	4.28	90.13	5.59
Marital status		$p < 0.0001$		
Married/Partnered	17,977 (60.86)	9.21	76.81	13.98
Single	1,051 (3.56)	8.75	81.16	10.09
Divorced	3,276 (11.09)	10.01	76.13	13.86
Widowed	7,233 (24.49)	10.02	78.29	11.68
Education		$p < 0.0001$		
Less than high school	1,103 (3.73)	10.43	77.15	12.42
High school graduate	5,316 (18.00)	11.14	75.34	13.53
Some college	11,150 (37.75)	10.01	76.54	13.45
College graduate	11,968 (40.52)	8.17	78.78	13.05
Household income		$p < 0.0001$		
<$20,000	4,618 (15.63)	11.00	76.68	12.32
$20,000–$49,999	14,419 (48.82)	9.86	76.38	13.77
$50,000–$99,999	6,946 (23.52)	8.45	78.55	13.00
≥$100,000	1,781 (6.03)	7.58	79.23	13.19
Unknown	1,773 (6.00)	8.46	78.79	12.75

Abbreviations: CT, clinical trial; OS, observational study; WHI, Women's Health Initiative.

[a]p values were the outcome of Pearson's Chi-square tests or one-way analysis of variance tests, as appropriate.

psychiatric disorders, namely depression/anxiety, are the actual predisposing factors for PD.

The study also found positive associations of PD risk with concurrent use of psychotropic medications as well as change in the use of psychotropic medications over time. Patients treated for PD motor symptoms are prone to polypharmacy if they also use medication to treat NMS, including antidepressants, anxiolytics and hypnotics.[47,48] In addition, psychotropic medication use may add to the risk of other PD-related effects such as higher all-cause mortality, cognitive deficits and falls.[14,49] The finding that change (increase and decrease) in psychotropic medications over time also hastens PD onset is likely due to the fact that PD degeneration is ongoing and that depression/anxiety are part of a changing, progressing disease, with changing manifestations that can result in changing treatments. Possibly PD-related morbidities resulted in a change in the prescription of psychotropic medications, a hypothesis that may be explored with a more granular examination of the time-course of PD-related issues such as physical function, affect and cognition. Alternatively, PD and mental health problems may be progressing over time and early medications are likely no longer useful, whilst others are being trialled. In addition, PD is a cause of progressive dementia, which complicates the clinical picture over time if it supervenes.

This study has several strengths. First, the WHI population is large with excellent retention during a lengthy follow-up period. Second, the variable set is comprehensive and was rigorously collected allowing evaluation of many hypotheses whilst adjusting for confounders. Third, the longitudinal design enabled the establishment of a temporal relationship between exposure and outcome measurements. However, there are important limitations to this study. First, selection bias may be a concern given that only fee-for-service (not Health Maintenance Organization) Medicare claims diagnoses can be linked to study data as well as censoring of WHI participants over time which may or may not be informative in nature. Second, several study variables relied on self-report, ICD-9-CM/ICD-10 codes or assigned therapeutic classes potentially causing information bias. Moreover, PD was not amongst the physician-adjudicated health outcomes in WHI, although it was a physician-diagnosed condition available to us through Medicare claims. Sensitivity analyses whereby all data sources except for ICD-9-CM/ICD-10 codes were used to define PD yielded similar results with respect to hypothesized relationships, with the exception of hypnotics which became associated with a 30% increased PD risk. Third, residual confounding due to unmeasured or inadequately measured confounders and confounding by indication in the context of propensity score analysis remain a concern given the observational nature of this study and the inability to control for access to care, patterns of care providers, severity of depression, anxiety and sleep-related symptoms and treatment-resistant psychiatric conditions. Fourth, temporality may still be an issue given the long latency period between the use of psychotropic medications and PD onset. Finally, given that the WHI focuses on postmenopausal women and that this study further restricted eligibility to Medicare-eligible women 65 years and older, findings cannot be generalized to men or women who were less than 65 years of age at baseline.

In conclusion, the use of antidepressants and/or anxiolytics as well as the use of multiple psychotropic

Table 4. Transitions in psychotropic medication use by lifestyle and health characteristics of study sample—Women's Health Initiative (n = 29,537).[a]

	Overall *N* (%)	Transitions in psychotropic medication use (N = 29,537)		
		Decrease %	Same %	Increase %
Overall	29,537 (100)	9.48	77.25	13.26
Smoking status		$p < 0.0001$		
Never	16,196 (54.83)	8.83	78.87	12.30
Past	12,288 (41.60)	10.15	75.59	14.26
Current	1,053 (3.57)	11.78	71.70	16.52
Alcohol use		$p < 0.0001$		
Non-drinker	3,176 (10.75)	8.53	80.67	10.80
Former drinker	4,694 (15.89)	11.48	74.58	13.93
<1 drink / week	9,520 (32.23)	9.47	77.93	12.59
≥1 drink / week	12,147 (41.12)	8.97	76.86	14.18
Physical activity (Met-hours/week)		$p < 0.0001$		
Mean (SD)	13.47 (13.56)	11.33 (12.07)	13.78 (13.74)	13.19 (13.34)
Body Mass Index (kg/m^2)		$p < 0.0001$		
<25	11,061 (37.45)	8.44	78.45	13.12
25–29.9	11,053 (37.42)	9.70	76.99	13.31
≥30	7,423 (25.13)	10.72	75.86	13.42
Medical history				
Cardiovascular disease		$p < 0.0001$		
Yes	6,635 (22.46)	12.01	73.22	14.77
No	22,902 (77.54)	8.75	78.42	12.83
Hypertension		$p < 0.0001$		
Yes	13,923 (47.14)	10.23	75.52	14.26
No	15,614 (52.86)	8.82	78.80	12.38
Diabetes		$p < 0.0001$		
Yes	3,610 (12.22)	11.75	74.54	13.71
No	25,927 (87.78)	9.17	77.63	13.20
Hyperlipidemia		$p < 0.0001$		
Yes	4,951 (16.76)	10.81	74.77	14.42
No	24,586 (83.24)	9.22	77.75	13.03
Self-rated health		$p < 0.0001$		
Excellent	5,255 (17.79)	6.72	82.06	11.23
Very good	13,389 (45.33)	8.35	79.02	12.63
Good	9,305 (31.50)	11.40	73.99	14.61
Fair	1,514 (5.13)	16.91	65.59	17.50
Poor	74 (0.25)	17.57	64.86	17.57
Depression, Anxiety and/or sleep disorders		$p < 0.0001$		
Yes	14,803 (50.12)	13.09	66.93	19.99
No	14,734 (49.88)	5.86	87.63	6.51

Abbreviations: CT, clinical trial; OS, observational study; WHI, Women's Health Initiative.

[a]p values were the outcome of Pearson's Chi-square tests or one-way analysis of variance tests, as appropriate.

medications and change in use of psychotropic medications over time were associated with risk of PD, whereas the use of hypnotics was not clearly associated with PD risk amongst older women. Future PD studies should further explore the issue of confounding by indication by controlling for disease severity in an attempt to disentangle the respective roles of antidepressants and/or anxiolytics from those of underlying psychiatric conditions. In-depth analyses are also needed to understand the role of polypharmacy, transitions in psychotropic medication use and symptomatology over time. Finally, future studies are needed that can examine hypothesized relationships in the context of a broader population of older adults using national and international databases such as the National Health and Nutrition Examination Surveys linked to Medicare data and the UK Biobank. Nevertheless, study findings provide sufficient evidence in favour of monitoring psychotropic medication users, especially those using

Table 5. Psychotropic medication use as a risk factor for Parkinson's disease—Women's Health Initiative (n = 52,700).

	Unadjusted HR (95% CI)	Model I[a]	Model II[b]	Model III[c]
Antidepressants	*n = 52,700*			
Yes	1.81 (1.62, 2.03)	1.85 (1.66, 2.07)	1.86 (1.63, 2.05)	1.75 (1.56, 1.96)
No	Ref.	Ref.	Ref.	Ref.
Anxiolytic	*n = 52,700*			
Yes	1.56 (1.33, 1.83)	1.56 (1.33, 1.83)	1.51 (1.32, 1.82)	1.48 (1.25, 1.73)
No	Ref.	Ref.	Ref.	Ref.
Hypnotic	*n = 52,700*			
Yes	0.98 (0.82, 1.16)	0.99 (0.84, 1.18)	1.00 (0.84, 1.19)	0.98 (0.82, 1.16)
No	Ref.	Ref.	Ref.	Ref.
Patterns	*n = 29,500*			
0	Ref.	Ref.	Ref.	Ref.
1	1.53 (1.32, 1.77)	1.53 (1.33, 1.77)	1.53 (1.32, 1.77)	1.49 (1.29, 1.72)
≥2	2.51 (1.99, 3.16)	2.53 (2.00, 3.19)	2.51 (1.99, 3.16)	2.43 (1.92, 3.06)
Transitions	*n = 29,500*			
Decrease	1.33 (1.08, 1.64)	1.46 (1.09, 1.67)	1.34 (1.08, 1.66)	1.30 (1.05, 1.61)
No change	Ref.	Ref.	Ref.	Ref.
Increase	1.67 (1.42, 1.97)	1.66 (1.41, 1.96)	1.66 (1.40, 1.96)	1.62 (1.37, 1.92)

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a]Model I controls for WHI component and socio-demographic (age, race/ethnicity, marital status, education, household income) factors only.

[b]Model II controls the Model I list of covariates + lifestyle (smoking status, alcohol use, physical activity) factors.

[c]Model III controls for Model II covariates + other clinical characteristics (body mass index, history of cardiovascular disease, history of hypertension, history of diabetes, history of hyperlipidemia, self-rated health).

Table 6. Psychotropic medication use as a risk factor for Parkinson's disease amongst individuals with depression, anxiety and/or sleep disorder diagnoses at baseline—Women's Health Initiative (n = 27,162).

	Unadjusted HR (95% CI)	Model I[a]	Model II[b]	Model III[c]
Antidepressants		*n = 27,162*		
Yes	1.63 (1.44, 1.85)	1.67 (1.47, 1.89)	1.66 (1.46, 1.88)	1.62 (1.43, 1.84)
No	Ref.	Ref.	Ref.	Ref.
Anxiolytic	*n = 27,162*			
Yes	1.42 (1.19, 1.68)	1.41 (1.18, 1.68)	1.42 (1.19, 1.68)	1.36 (1.14, 1.62)
No	Ref.	Ref.	Ref.	Ref.
Hypnotic	*n = 27,162*			
Yes	0.91 (0.75, 1.09)	0.93 (0.77, 1.12)	0.94 (0.78, 1.13)	0.93 (0.77, 1.13)
No	Ref.	Ref.	Ref.	Ref.
Patterns	*n = 14,803*			
0	Ref.	Ref.	Ref.	Ref.
1	1.61 (1.35, 1.92)	1.60 (1.34, 1.92)	1.61 (1.35, 1.92)	1.58 (1.32, 1.88)
≥2	2.32 (1.79, 3.00)	2.32 (1.78, 3.00)	2.32 (1.79, 3.01)	2.25 (1.74, 2.93)
Transitions	*n = 14,803*			
Decrease	1.30 (1.02, 1.66)	1.30 (1.02, 1.67)	1.31 (1.02, 1.67)	1.28 (1.00, 1.64)
No change	Ref.	Ref.	Ref.	Ref.
Increase	1.59 (1.32, 1.93)	1.58 (1.30, 1.91)	1.58 (1.31, 1.92)	1.57 (1.29, 1.89)

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a]Model I controls for WHI component and socio-demographic (age, race/ethnicity, marital status, education, household income) factors only.

[b]Model II controls the Model I list of covariates + lifestyle (smoking status, alcohol use, physical activity) factors.

[c]Model III controls for Model II covariates + other clinical characteristics (body mass index, history of cardiovascular disease, history of hypertension, history of diabetes, history of hyperlipidemia, self-rated health).

Table 7. Propensity score weighting analyses for use of antidepressants, anxiolytics and hypnotics as risk factors for Parkinson's disease overall and amongst individuals with depression, anxiety and/or sleep disorder diagnoses at baseline—Women's Health Initiative.

	Overall (N = 57,200) HR (95% CI)	Depression, anxiety and/or sleep disorders (N = 27,162)
Antidepressant		
Yes	1.34 (1.23, 1.46)[a]	1.39 (1.25, 1.55)[d]
No	Ref.	Ref.
Anxiolytic		
Yes	1.29 (1.18, 1.40)[b]	1.26 (1.13, 1.41)[e]
No	Ref.	Ref.
Hypnotic		
Yes	0.97 (0.89, 1.07)[c]	0.98 (0.87, 1.10)[f]
No	Ref.	Ref.

Abbreviations: CI, confidence interval; HR, hazard ratio.

[a]Propensity score weights generated using stepwise logistic regression (SLENTRY = 0.5 and SLSTAY = 0.5) for predictors of antidepressant use which includes depression disorders, WHI component, age group, race/ethnicity, marital status, education, smoking status, alcohol use, cardiovascular disease, hypertension, diabetes, hyperlipidemia and self-rated health.

[b]Propensity score weights generated using stepwise logistic regression (SLENTRY = 0.5 and SLSTAY = 0.5) for predictors of anxiolytic use which include anxiety disorders, WHI component, age group, race/ethnicity, marital status, education, smoking status, physical activity, body mass index, cardiovascular disease, hypertension, hyperlipidemia and self-rated health.

[c]Propensity score weights generated using stepwise logistic regression (SLENTRY = 0.5 and SLSTAY = 0.5) for predictors of hypnotic use which includes sleep disorder, age group, race/ethnicity, marital status, education, household income, smoking status, alcohol use, physical activity, body mass index, cardiovascular disease, hypertension, diabetes, hyperlipidemia and self-rated health.

[d]Propensity score weights generated using stepwise logistic regression (SLENTRY = 0.5 and SLSTAY = 0.5) for predictors of antidepressant use which includes depression disorders, WHI component, age group, race/ethnicity, marital status, education, smoking status, alcohol use, physical activity, cardiovascular disease, hypertension, diabetes, hyperlipidemia and self-rated health.

[e]Propensity score weights generated using stepwise logistic regression (SLENTRY = 0.5 and SLSTAY = 0.5) for predictors of anxiolytic use which include anxiety disorders, WHI component, age group, race/ethnicity, marital status, education, household income, smoking status, body mass index, cardiovascular disease, hypertension and self-rated health.

[f]Propensity score weights generated using stepwise logistic regression (SLENTRY = 0.5 and SLSTAY = 0.5) for predictors of hypnotic use which include sleep disorder, WHI component, race/ethnicity, household income, smoking status, alcohol use, physical activity, hyperlipidemia and self-rated health.

antidepressants and anxiolytics, amongst women 65 years and older, for PD motor and non-motor symptoms within healthcare settings.

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Author Contributions

Conception and design of the study: HAB, MJN, MAB, RLB, ABZ. Acquisition and analysis of data: HAB, NS, RW, JJC, AHS, RLB. Drafting a significant portion of the manuscript or figures: HA, NS, RW, JJC, MC, MJN, MAB, AHS, ABZ, RLB.

Conflicts of Interest

Nothing to report.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 International Classification of Diseases Codes.
Table S2. Assigned Therapeutic Classes.
Table S3. Psychotropic medication use as a risk factor for Parkinson's disease according to time-to-event, age and Women's Health Initiative components—Women's Health Initiative.
Table S4. Psychotropic medication use as a risk factor for Parkinson's disease amongst individuals with depression, anxiety and/or sleep disorder diagnoses at baseline according to time-to-event, age and Women's Health Initiative components—Women's Health Initiative.
Table S5. Psychotropic medication use as a risk factor for Parkinson's disease (PD) using PD definition that does not cover ICD-9-CM/ICD-10 diagnostic codes—Women's Health Initiative.
Table S6. Antidepressant, anxiolytic and hypnotic medication use as a risk factor for Parkinson's disease (PD) using baseline medications data only—Women's Health Initiative.
Table S7. Detailed definition of transitions in psychotropic medication use as risk factors for Parkinson's disease – Women's Health Initiative.
Table S8. Antidepressant and anxiolytic use as a risk factor for Parkinson's disease (PD) amongst individuals with sleep disorders only—Women's Health Initiative.
Table S9. Psychotropic medication use, self-rated health and their interactions in relation to Parkinson's disease (PD) in the overall sample—Women's Health Initiative.

