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Use of antidepressants and the risk of Parkinson's disease in the Local Health Trust of Bologna: A historical cohort study

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ABSTRACT

Background: Depression is considered one of the prodromal symptoms of Parkinson's disease (PD) along with sleep disorders, hyposmia and constipation. Prodromal symptoms refer to the stage wherein early motor symptoms and signs allowing a diagnosis of PD are not yet present. The objective of this study was to investigate the association between the use of antidepressants, as indirect measure of depression, and subsequent PD onset, clinically diagnosed, in the Local Health Trust of Bologna, Italy.

Methods: Historical cohort study with use of antidepressants as exposure and PD onset as outcome. The cohort considered consisted of inhabitants of Bologna aged ≥35 years in 2005; those who had used antidepressants in the previous 3 years were excluded. Subjects were followed up from 2006 and until PD onset, migration out of Bologna, death or end of the study period (2017), whichever came first. "The ParkLink Bologna" system was used to detect disease onset. "ParkLink Bologna" is a research study including patients with a clinical diagnosis of PD residing in Bologna. Residents that used antidepressants for at least 180 consecutive days within 1 year were considered exposed. Hazard ratios (HR) and 95% confidence interval (CI) were estimated with Cox proportional hazards models, using exposure as time-dependent variable and adjusting for potential confounders: age, gender, use of medical care and comorbidities.

Results: From 2006 to 2017 199,093 person-years were exposed and 4,286,470 not exposed. Fifty-one subjects with PD were identified in the exposed group and 556 subjects in the non-exposed showing an association of adjusted HR = 1.7 (CI 1.3–2.3). The association was stronger for males (HR 2.2, CI 1.5–3.2) compared to females (HR 1.2, CI 0.8–1.9), for subjects ≤65 years of age (HR 2.4, CI 1.6–3.6) vs. > 65 years (HR 1.3, CI 0.8–1.9) and for those with less comorbidities. Age and gender were confounders in the associations between antidepressant use and PD onset.

Conclusions: The use of antidepressants as indirect measure of depression is associated with the subsequent development of PD. Our findings confirm that depression may precede the onset of motor symptoms in PD. The association is stronger for younger subjects, who are males and with fewer comorbidities.

1. Introduction

The relationship between depression and the subsequent risk of Parkinson's Disease (PD) has been largely investigated with two main hypotheses: depression is a premotor symptom of PD (prodromal PD) [1,2] and depression shares some common genetic risks with PD [3–6]. The first hypothesis is supported by the observation that the association between depression and subsequent PD is stronger in the few years preceding the onset of motor symptoms. The second one is based on the observation that depression may precede the diagnosis of PD by many years and that an increased prevalence of mental illness was observed among relatives of PD patients. Recently, in a nationwide nested case-control cohort study, a significant association between depression and diagnosis of PD from 15 to 25 years afterwards has been observed [6]. Only two previous studies have investigated exposure to antidepressant drugs and risk of PD. In the Danish population, an increased risk of

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treatment with antiparkinsonian drugs following exposure to antidepressants and lithium was observed [7]. In another study, performed within the General Practice Research Database in UK, an increased risk of PD was observed after antidepressant exposure [8]. In all the above studies, PD onset was established according to administrative databases: date of first diagnosis of PD or first prescription of antiparkinsonian drugs. However, it is well known that subtle and mild motor symptoms may precede the appearance of clear PD motor phenomena by some years. Since depression may accompany the onset of PD [9], it is important to consider the precise date of onset of motor symptoms to establish the risk of PD after exposure. The main objective of this study was to investigate the association between the use of antidepressants, as a proxy of depression, and risk of subsequent PD within our study "ParkLink Bologna", where neurologists ascertained PD diagnosis and year of onset.

2. Materials and methods

This study has a historical cohort design with use of antidepressants as exposure and PD onset as outcome.

The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines [10] were followed.

The ethics committee of Bologna (Local Health Trust) approved the study protocol (N. 501/CE).

2.1. Study population

All residents in the area of the Local Health Trust (LHT) of Bologna (Emilia-Romagna region, North-East Italy) aged > 35 years as of December 31st, 2005 were eligible for inclusion in the cohort. Those subjects who had used antidepressants (for at least 180 consecutive days during 1 year) in the previous 4 years or those who had PD onset before 2006 were excluded, so as to have only incidence cases. This cohort was therefore followed up from 2006 and until PD onset, migration out of Bologna, death or end of study period (2017), whichever came first.

2.2. Exposure to antidepressants

All antidepressants included in the N06A group of the WHO ATC [11] and reimbursed by the Italian Health Service were considered for the exposure detection: N06AA (Non-selective monoamine reuptake inhibitors), N06AB (Selective serotonin reuptake inhibitors) and N06AX (Other antidepressants: mianserine, trazodone, mirtazapine, venlafaxine, duloxetine, reboxetine).

Subjects that used antidepressants for at least 180 consecutive days during 1 year were considered exposed. The year in which the 6-month threshold was exceeded has been used as the start time of exposure; from that year, a subject was exposed for the entire follow-up period. Data were collected from the healthcare databases of the LHT of Bologna (reliable data available from 2002), which record all reimbursed dispensations of medicines to outpatients (AFT – Assistenza Farmaceutica Territoriale and FED – Farmaci Erogazione Diretta). The number of days of therapy was estimated by using the "Defined Daily Dose" (DDD) as measure unit: for each prescription, the number of DDDs was calculated by dividing the specific DDD of the active substance by the quantity of the substance in the prescription.

2.3. Outcome: PD onset

The PD onset was obtained from the "ParkLink Bologna" project. This project is part of a larger one aiming to link the clinical diagnoses of main neurological diseases to administrative databases available in the LHT of Bologna. Among public facilities, three hospital outpatient services are dedicated to movement disorders and four additional neurologists work in the Community Health Centers of the LHT area. Further, several neurologists practice in private clinics. Since 2016, both public and private practice neurologists working in the LHT area have been invited to participate in the "ParkLink Bologna" study by recruiting all patients with a suspicion of PD or parkinsonism. By June 302,018 24 neurologists were involved. After signing an informed consent, patient data are recorded in an e-CRF and stored in a secure database: unique identification code, name and surname, date of birth, diagnosis, year of onset (as reported by the patient or in medical records), motor symptoms at onset (tremor or akinesia), side of onset (unilateral, asymmetric or bilateral) and Hoehn and Yahr score for each patient. Diagnosis was recorded according to the following criteria: Gelb criteria for PD [12], other specified parkinsonisms [13–15] or "unspecified parkinsonism "in case of patients with a not well characterized parkinsonism (as in recent onset symptoms). Drug-induced parkinsonism was excluded. The above clinical data could be updated at every follow-up visit, performed at least yearly or according to clinical practice. Through the unique identification code, patient data are linked to the following LHT administrative databases: Drugs, Hospital Discharges, Copayment Exemption, Medical home-care and Mortality.

2.4. Confounders and effect modifiers

The potential confounding factors and effect modifiers evaluated in the association between antidepressant use and PD onset were age, gender, district of residence, comorbidities (Chronic Disease Score) [16] and use of medical care [17]. The Chronic Disease Score (CDS) was a measure of comorbidity based on the aggregate number of prescription medications for a patient. The index contains 24 categories and was based on the Anatomical Therapeutic Chemical (ATC) codes of medications used in the treatment of different chronic diseases. The index to use for medical care was total number of visits (inpatient and outpatient) in the 4 years before starting the follow-up (2002–2005).

2.5. Statistical analysis

In the descriptive analysis, the characteristics between subjects exposed and not exposed were presented as mean and standard deviation (SD) for the continuous variables and with absolute and relative frequency for categorical variables. The normality of distribution was evaluated with Shapiro-Wilk test and the variables turning out to be asymmetric were presented in quartiles. Chi-square test was used to evaluate the univariate association between outcome, exposure and other variables.

We used Cox regression analysis to estimate the hazard ratio (HR) and the corresponding 95% confidence interval (95% CI) associating PD onset with antidepressants. The exposure was evaluated as a time-dependent variable.

The *p*-value for interaction was computed from the log-likelihood ratio test comparing models with and without the interaction term. We presented stratified HR (95% CI) for the variables turning out to be effect modifiers (*p*-value for interaction < .05). For the variables divided into quartiles, we merged the stratum with the similar estimate of the association. We compared models with and without confounder variables and we presented crude and adjusted HR (95% CI) for the variables turning out to be confounders [18,19]. The proportional hazards assumption was tested ($p > .05$) using Schoenfeld residuals.

Data linkage and statistical analysis were conducted using Stata SE version 14.2 [20].

3. Results

The final cohort included 424,298 subjects (4,484,498 person-years) residing in the LHT area of Bologna, older than 35 years of age. We excluded 18,830 subjects for use of antidepressants from 2002 to 2005 and 39 subjects for disease onset before 2006 (Fig. 1). From 2006

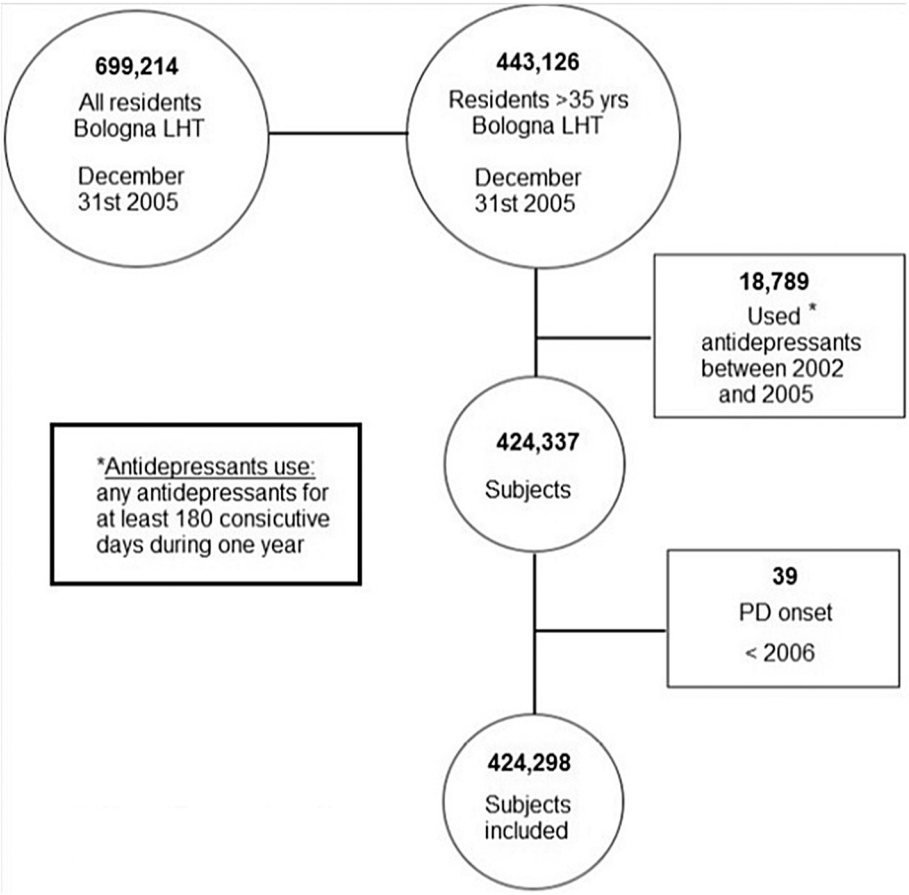

Fig. 1. Flow-chart of the subjects' recruitment.

to 2017, 34,620 subjects (199,093 person-years) were exposed to AD and 389,678 subjects were not exposed (4,286,470 person-years).

We included 607 patients with PD and their demographic and clinical characteristics are summarized in Table 1. The median difference between year of onset and year to first prescription of antiparkinsonian drugs (ATC code: N04) was 1 year (IQR = 0–2). Thirty-one patients (5%) never took antiparkinsonian drugs between 2002 and 2017.

The characteristics in the year 2005 between exposed and unexposed subjects were different ($p < .001$): the exposed group was older (mean age = 58 vs. 54 years), with a greater female frequency (70% vs. 50%), with more comorbidities and more access to use of medical care (Table 2).

From 2006 to 2017 we observed 51 subjects with PD in the exposed and 556 subjects in the non-exposed with crude HR = 1.7 (95% CI = 1.3–2.3). The median time between the beginning of antidepressant exposure and the onset of PD was 3 years (IQR = 2–4) in the exposed, whereas in the non-exposed the median time from the beginning of observation (2006) to PD onset was 7 years (IQR = 4–9).

Age and gender acted as confounders and effect modifiers in the association between antidepressant use and PD onset. Comorbidities and access to the use of medical care were effect modifiers. The association was stronger for men (adj. HR = 2.2, 95% CI = 1.6–3.6) compared to women (adj. HR = 1.2, 95% CI = 0.8–2.0) and for subjects ≤65 years of age (adj. HR = 2.4, 95%CI = 1.6–3.6) vs. > 65 years (HR = 1.3, 95% CI = 0.8–1.9). The association was stronger for subjects with less comorbidities and less access to use of medical care (Table 3).

Table 1
Demographic and clinical characteristics for the 607 ParkLink patients included in the study.

Variables	N (%)
Age at onset, mean (SD)	70.9 (8.8)
Gender	
Male	376 (61.9)
Female	231 (38.1)
District	
Bologna	258 (42.5)
Reno	74 (12.2)
Pianura Ovest	126 (20.8)
Pianura Est	67 (11.0)
Appennino	40 (6.6)
San Lazzaro	42 (6.9)
Year of onset	
2006–2008	63 (10.4)
2008–2010	166 (27.3)
2011–2013	185 (30.5)
2014–2017	193 (31.8)
Gelb's criteria	
Possible	164 (33.7)
Probable	322 (66.3)
Hoehn and Yahr scale	
1	80 (13.2)
1.5	108 (17.8)
2	180 (29.7)
2.5	82 (13.5)
3	81 (13.3)
4	54 (8.9)
5	22 (3.6)
Type of onset	
Unilateral	470 (77.4)
Bilateral	137 (22.6)

Table 2
Characteristics of the subjects by exposure.

Variables	No use of antidepressants	Use of antidepressants
	N (%)	N (%)
Age, mean (SD)	53.7 (12.9)	58.3 (13.6)
Age		
36–43 years (Q1)	110,798 (28.4)	6504 (18.8)
44–53 years (Q2)	95,973 (24.7)	7196 (20.8)
54–65 years (Q3)	91,705 (23.5)	7867 (22.7)
> 65 years	91,202 (23.4)	13,053 (37.7)
Gender		
Male	191,195 (49.1)	10,438 (30.2)
Female	198,483 (50.9)	24,182 (69.8)
District		
Bologna	173,439 (44.5)	15,882 (45.9)
Reno	49,505 (12.7)	4761 (13.7)
Pianura Ovest	69,292 (17.8)	5348 (15.4)
Pianura Est	35,872 (9.2)	3138 (9.1)
Appennino	26,260 (6.7)	2421 (7.0)
San Lazzaro	35,310 (9.1)	3070 (8.9)
CDS: < 1 points (Q1)	139,682 (35.9)	6465 (18.7)
1–2 points (Q2)	85,141 (21.8)	7165 (20.7)
3–4 points (Q3)	79,415 (20.4)	8591 (24.8)
> 4 points	85,440 (21.9)	12,399 (35.8)
Index to use of medical care		
< 5 visits (Q1)	104,137 (26.7)	3977 (11.5)
5–13 visits (Q2)	98,740 (25.4)	6787 (19.6)
13–24 visits (Q3)	95,166 (24.4)	9638 (27.8)
≥24 visits	91,635 (23.5)	14,218 (41.1)
Total	389,678 (91.8)	34,620 (8.2)

Chi-square test: p-value < .001 for all variables.
Q1 = first quartile, Q2 = median, Q3 = third quartile.

Table 3
Associations between antidepressants use and PD onset stratified by age, gender, Chronic Disease Score and access to use of medical care.

Variables	Crude HR (CI 95%)	Adjusted HR[a] (CI 95%)
Age		
≤65 years	2.22 (1.50–3.29)	2.42 (1.63–3.60)
> 65 years	1.05 (0.68–1.61)	1.25 (0.81–1.92)
Gender		
Male	2.60 (1.79–3.81)	2.19[b] (1.50–3.20)
Female	1.44 (0.92–2.27)	1.23[b] (0.78–1.94)
CDS		
0–4 points	2.00 (1.38–2.90)	1.88 (1.29–2.73)
> 4 points	1.19 (0.75–1.90)	1.38 (0.86–2.20)
Index to use of medical care		
< 5 visits	3.06 (1.28–7.34)	2.62 (1.07–6.37)
5–13 visits	2.38 (1.20–4.73)	2.36 (1.19–4.69)
13–24 visits	1.73 (1.03–2.92)	1.76 (1.04–2.97)
≥24 visits	1.13 (0.70–1.82)	1.14 (0.71–1.84)

[a] Adjusted for gender and age in continuous.
[b] Adjusted for age in continuous only.

4. Discussion

In this cohort study of the LHT of Bologna, the use of antidepressants was associated with the subsequent development of PD. Our findings confirm that depression may precede the onset of motor symptoms in PD. The median time of PD onset after exposure was 3 years (IQR = 2–4). The association was stronger for younger patients, who are men, have less comorbidities and less access to use of medical care.

Since the use of antidepressants may be considered a proxy of depression, our study supports the hypothesis that depression could be a non-motor manifestation preceding PD, or a risk factor for the disease even before involvement of dopaminergic nerve cells in the "substantia nigra" [1–8]. Instead, it is unlikely that antidepressants may have a causative role for PD since such an effect was never observed among thousands of patients included in clinical trials of depression treatment.

The main strength of this study is having the diagnosis performed by a neurologist. The year of PD onset was detected by medical records or reported by the patients retrospectively. Most neurologists knew the whole history of the patient and the clinical data could be updated at every follow-up visit, performed usually yearly. Furthermore, in a retrospective study, diagnostic assessment by a qualified neurologist is highly preferable than relying on other methods based on administrative claims data only. This point is supported by the observation that the median time lag between the PD onset and first prescription of antiparkinsonian drug was 1 year. Moreover, the use of a large, population-based dataset provided a good statistical power over 11 years of follow-up.

There are some limitations, as a possible misclassification in both exposure and outcome. Misclassification of the exposure could have occurred because the antidepressant use was based on prescriptions, therefore we could not ascertain whether the patients actually took those drugs or in which dose. However, we considered exposure if there were at least 6 months of prescription before the year of onset and it seems unlikely that patients receiving continuous prescriptions for 6 months did not take the drugs. Furthermore, antidepressants could have been prescribed for other conditions other than depression, although other indications are usually treated with shorter cycles of therapy.

Misclassification of the outcome may have occurred because the "ParkLink Bologna" system is not yet at its full capacity and, having begun the recruitment in January 2015, it has been estimated that about a third of the subjects present in the LHT of Bologna area were recruited until June of 2018. Therefore, we cannot be sure that the rate of exposure to AD is similar both in patients recruited with the "ParkLink Bologna "system and in the others not yet recruited.

However, we hypothesized a non-differential misclassification of the outcome that leads to the estimation of the association towards the no association (null hypothesis). In fact, it was not plausible that non-depressed PD patients have less chances of being seen by neurologist. Moreover, PD diagnosis ("ParkLink Bologna" flow) was independent of the definition of exposure, coming from the drug prescription administrative database.

Another possible misclassification of the outcome derives from the "survival effect": the recruitment of the subjects was from January 2015 to June 2018 and the cohort starts in 2005 because the PD onset was detected retrospectively. Therefore, we could not recruit dead people or people who changed residence (out of Bologna) between 2005 and 2015 and with PD onset between 2005 and 2015. This "survival effect" could be a limitation of the study. However, we suppose that this misclassification, also in this case, was non-differential because it is not plausible that non-depressed PD has a major risk of migration or death compared to depressed PD.

Finally, information regarding other possible confounders was lacking: the family history of PD, lifestyle factors (consumption of coffee and tobacco), environmental factors (exposure to pesticides and herbicides) and education or socio-economic condition.

We observed that the risk of PD following the exposure to PD was higher in young men while it was lower in people with higher comorbidities. This may be explained by the increased risk of depression in the latter conditions, competing with the risk related to the premotor physiopathology of PD. Indeed the fact that the risk of PD is higher among patients without other physical conditions favoring depression confirms the link between depression itself and subsequent PD.

This is the first study where the clinical diagnosis according to international established criteria and the essential clinical inform16421ation were directly recorded by a neurologist and linked to administrative databases. Our results show that such a methodology may be useful to perform epidemiological studies on neurological

diseases.•.

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Statement of ethics

Subjects have given their written informed consent. The ethics committee of the Bologna Local Health Trust approved this study (Reference: N.501/CE).

Disclosure of competing interests

The authors have no conflicts of interest to declare.

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