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Increased all-cause mortality with psychotropic medication in Parkinson's disease and controls: A national register-based study

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ABSTRACT

Aim: Use of medication and polypharmacy is common as the population ages and its disease burden increases. We evaluated the association of antidepressants, benzodiazepines, antipsychotics and combinations of psychotropic drugs with all-cause mortality in patients with Parkinson's disease (PD) and a matched group without PD.
Method: We identified 5861 PD patients and 31,395 control subjects matched by age, gender and marital status, and obtained register data on medication use and vital status between 1997 and 2007.
Results: All-cause mortality was significantly higher with the use of most groups of psychotropic medication in PD patients and controls. Hazard ratios were as follows for the medication types: selective serotonin reuptake inhibitors or serotonin-noradrenalin reuptake inhibitors, PD HR = 1.19, 95% CI = 1.04–1.36; Control HR = 1.77, 95% CI = 1.64–1.91; benzodiazepines, PD HR = 1.17, 95% CI = 0.99–1.38; Control HR = 1.39, 95% CI = 1.29–1.51; benzodiazepine-like drugs, PD HR = 1.33, 95% CI = 1.11–1.59; Control HR = 1.27, 95% CI = 1.18–1.37; first-generation antipsychotics, PD HR = 1.89, 95% CI = 1.42–2.53; Control HR = 2.12, 95% CI = 1.82–2.47; second-generation antipsychotics, PD HR = 1.46, 95% CI = 1.20–1.76; Control HR = 2.00, 95% CI 1.66–2.43; and combinations of these drugs compared with non-medicated PD patients and controls. Discontinuation of medication was associated with decreased mortality in both groups.
Conclusions: The use of psychotropic medication in the elderly is associated with increased mortality, independent of concurrent neurodegeneration due to PD. Confounding by indication may partly explain the higher hazard ratios in medicated controls compared with medicated PD patients. Our findings indicate that neurodegeneration should not be a separate contraindication per se for the use of psychotropic drug in patients with PD, but its use should be based on careful clinical evaluation and follow-up.

1. Introduction

Antidepressants, hypnotics and antipsychotics are widely used among patients with neurodegenerative disorders because of concurrent depression, anxiety, sleep complaints, confusion/hallucinations and behavioral disturbances. Despite the frequent use of psychotropic drugs, there is only limited evidence of efficacy in patients with Parkinson's disease (PD) [1]. Recent studies have raised concerns about their use since there is evidence of an association with increased mortality [2]. For example, this is the case for benzodiazepines used to treat primary insomnia [3] and for the use of polypharmacy with antipsychotics and benzodiazepines to treat patients with schizophrenia [4,5].

PD causes loss of dopaminergic neurons in the substantia nigra, resulting in bradykinesia, tremor and rigidity [6,7]. However, other regions of the brain are affected that are associated with non-motor symptoms [8], such as mood changes, depression [9], hallucinations, and sleep complaints including a type of increased motor

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activity during dreaming known as rapid eye movement (REM) sleep behavioral disorder (RBD) [10]. Such symptoms may occur years before the onset of motor symptoms or may be considered to be part of the complex of PD symptoms [11,12]. These symptoms make it likely that patients with pre-Parkinsonism and PD are treated with psychotropic drugs. Recognizing the vulnerability of the brain, comorbid conditions, and the higher mortality rates of PD patients, we aimed to determine whether treatment with psychotropic drugs (antidepressants, benzodiazepines, antipsychotics) is associated with higher mortality [13] and, if so, whether such an association is also present in subjects without PD.

2. Method

2.1. Subjects

In Denmark, all subjects with hospital contacts are recorded in the National Patient Registry (NPR) by date of contact. The NPR includes administrative information, ICD-10 (International Classification of Diseases) [14] somatic diagnoses, diagnostic procedures and treatment procedures. A separate database of medications dispensed by Danish pharmacies (the Register of Medicinal Product Statistics) was linked with the NPR. This is possible because individuals' personal social security numbers are used in all national registers.

Using the NPR, we retrospectively identified 10,490 patients aged 20 years and above who were diagnosed with PD (ICD-10 G20.9) between 1997 and 2007. Only patients diagnosed or receiving treatment at a hospital (as an inpatient or outpatient) are registered in the NPR. Milder cases with a diagnosis of PD with contacts solely in the primary sector were therefore not included in this study.

Using data from Denmark's Civil Registration System, we randomly selected citizens of the same age, sex and marital status as the patients but who differed in not having a diagnosis of PD when cross-referenced with the NPR. Parity of socioeconomic status (SES) was ensured by selecting control subjects from the same part of the country (at the sub-county level, based on the Danish postal code system). Four times as many controls (42,505) as PD patients were selected. Patients and controls were matched at the time of the PD patients' diagnosis.

Not all PD patients are diagnosed when their first symptoms appear; for some people the diagnosis may be delayed for years. As the disease progresses, more patients will be diagnosed in relation to a hospital contact. To control for the difference in time of diagnosis and to ensure a more homogenous group of patients, the observation period begins four years after the date of diagnosis for the PD patients and 4 years after the date of match for the controls. After these restrictions, 5861 PD patients and 31,395 controls were included in the study, other exclusion criteria being death (within the four-year pre-observation period) and immigration. The observation period is the period beginning four years after diagnosis. The observation period ends at either death of the subject or December 31, 2007.

2.2. Medications

The following medication classes were included in the study (World Health Organization Anatomical Therapeutic Chemical Classification (ATC) system code numbers in brackets) [15]: selective serotonin re-uptake inhibitors (SSRIs) (ATC-code: N06AB), serotonin-noradrenaline re-uptake inhibitors (SNRIs) (06AX), tricyclic antidepressants (TCAs) (N06AA), benzodiazepines (BZDs) (N05BA, N03AE01, N05CD), benzodiazepine-like drugs (BZD-like) (N05CF), first-generation antipsychotics (FGAs) (N05A, excluding N05AX08-12-13, N05AL05, N05AH02-03-04-05, N05AE03–04, N05AN01) and second-generation antipsychotics (SGAs) (N05AX08-12-13, N05AL05, N05AH02-03-04-05, N05AE03-04).

These drugs were chosen on the basis of the frequency of their use and their effect on the central nervous system. SSRIs, SNRIs and TCAs act on the serotonergic/noradrenergic system, benzodiazepines potentiate the GABAergic system, and antipsychotics block the D2 dopaminergic receptor. The neurodegeneration in PD is known to act primarily on the dopamine system, but the wide range of symptoms indicates that other neurotransmitter systems are also affected.

Patients who did not use any of these medications during the observation period were classified as the no-medication group. Data concerning SSRIs and SNRIs were aggregated because there were so few observations of the latter type. The small number of observations of FGAs meant that further subdivision of this group was not warranted.

Patients were registered as medication users if they had collected at least three prescriptions of a particular drug from the start of the observation period to death or the end of the observation period. Patients who had collected fewer than three prescriptions were assumed not to use the medication regularly and were classified in the no-medication group. In the analysis, use of medication was divided into monotherapy (SSRI/SNRI, TCA, BZD, BZD-like, FGA, SGA) and polytherapy with the following subgroups:

- SSRI_All: comprising SSRIs, SNRIs and TCAs.
- BZD_All: comprising BZDs and BZD-like drugs.
- AntiPsyc_All: comprising FGAs and SGAs.
- The combination of the SSRI_All and BZD_All groups.
- The combination of the SSRI_All and AntiPsyc_All groups.
- The combination of the BZD_All and AntiPsyc_All groups.
- The combination of the SSRI_All, BZD_All and AntiPsyc_All groups.

2.3. Use of medication before the diagnosis of Parkinson's disease

A substantial number of patients used medication before they were diagnosed with PD. We initially used a dummy to control for this in the regression, but having been previously medicated proved to have no significant effect on all-cause mortality, and no influence on the medicine parameters. The variable was therefore not included in the final regression models.

2.4. Discontinuation of medication

Some patients discontinued medication, as indicated by their most recently collected prescription. If three prescriptions were collected, but then no prescriptions were collected for 2 years prior to death, or the end of the observation period, the patient was registered as discontinuation of medication.

2.5. Statistical methods

Statistical analyses were done with SAS 9.1.3 (SAS, Inc., Cary, NC). Survival statistics and hazard ratios were estimated by nonparametric bootstrap methods. The analysis was based on a population conditioned on survival for at least four years after the year of diagnosis. Separate analyses were carried out for PD patients and controls, but their results can be compared since age and gender were controlled for in both groups. In estimating the hazard function we controlled for age, gender and medication discontinuation.

2.6. Study approval

Data were provided in a form that did not reveal the identity of any patients or control subjects, so neither individual nor ethical approval was required.

3. Results

Differences in medication of PD patients and controls are presented in Table 1. The 5861 PD patients had a markedly different pattern of use of most psychotropic medication when compared with the 31,395 controls. SSRI and FGA use was similar in PD patients and controls, use of single medication with BZD or BZD-like drugs was significantly more frequent in controls than in PD patients. Use of SGAs or TCAs as single medications, and all combinations of medication was significantly more frequent in PD patients than in controls. Overall, 74.0% of the PD population used one or more of the types of drug examined, whereas 40.7% of controls used such medication. The greatest difference was in the combination of the three major groups of SSRIs, BZDs and antipsychotics, whereby 12.3% of PD patients received all three drugs compared with 2.8% of controls. Differences in medication of PD patients and controls are shown in Table 1.

Table 2 lists the hazard ratios and confidence intervals for all groups of medication and their combinations. All-cause mortality was significantly higher with the use of most groups of psychotropic medication in PD patients and controls. The highest hazard ratio for PD patients was 1.89 (95% CI = 1.42–2.53) for the use of FGA; in comparison, controls had a hazard ratio of 2.12 (95% CI = 1.82–2.47). The highest hazard ratio for controls was 2.23 (CI = 1.99–2.49), when using a combination of antipsychotics and benzodiazepines, whereas the equivalent group of PD patients had a hazard ratio of 1.32 (CI = 1.13–1.54). For controls, the inclusion of antipsychotic medication either alone or in combination with other medication resulted in increased mortality, with a hazard ratio greater than 2. The hazard ratio for each psychotropic medication group was lower in PD than in controls (except for the benzodiazepine-like drugs).

Discontinuation of psychotropic medication was associated with lower mortality in PD patients and controls compared with the corresponding groups who continued their medication.