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Prevalence of and indications for antipsychotic use in Parkinson disease

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Abstract

Background—The prevalence of patients with Parkinson disease taking anti-psychotics is unknown.

Objective—To measure the prevalence of patients with Parkinson disease taking anti-psychotics.

Methods—We used the medical records-linkage system of the Rochester Epidemiology Project to study the use of antipsychotic medication in all persons with Parkinson disease in Olmsted County, Minnesota on January 1, 2006.

Results—There were 296 patients with PD in Olmsted County on January 1, 2006. The overall prevalence of antipsychotic use was 9.8% (29/296); 95.5% (28/29) of the patients had dementia when initiating antipsychotics. The most frequent indication (71.4%; 20/28) was psychosis or behavior threatening to the patient or others.

Conclusions—The prevalence of antipsychotic use in patients with Parkinson disease is lower than expected from previously reported cumulative incidences. Dementia is highly prevalent in those starting antipsychotics. Most of the patients on antipsychotics had a reasonable risk-benefit ratio for taking them.

Keywords

Parkinson disease; prevalence; antipsychotics; dementia

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AUTHOR ROLES

Dr. Bower was involved in the conception, organization and execution of the project, the design and execution of the statistical analysis, and the drafting and review of the manuscript.

Mr. Grossardt was involved in the execution of the project, the design and execution of the statistical analysis, and the review and critique of the manuscript.

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Dr. Savica was involved in the conception, organization and execution of the project, and the review and critique of the manuscript.

INTRODUCTION

The use of atypical antipsychotics (AP) is associated with increased mortality in those with dementia and parkinsonism. [1–3] The prevalence of psychosis in those with Parkinson disease (PD) has been reported to be as high as 60%. [4, 5] Therefore, clinicians face a quandary of whether to address the psychosis with a medication that may lead to premature death.

Prior studies have reported a high incidence of the use of APs in those with parkinsonism, but the prevalence has never been reported. [6–9] Prevalence data are important for population-based health care planning.

In this study, we determined the point prevalence for the use of APs among all persons with Parkinson disease in Olmsted County, Minnesota. In addition, we investigated the total duration of AP use, and the disease duration, indication, prevalence of dementia, and residence at initiation of AP therapy.

METHODS

Study Population and Case ascertainment

Extensive details about our population and case ascertainment have been reported elsewhere. [Savica et al. Unpublished Observations] [10–15] In brief, we studied the prevalent cases of Parkinson disease in the geographically-defined population of Olmsted County, Minnesota on the prevalence day of January 1, 2006.

Diagnostic Criteria

Criteria for parkinsonism have been described elsewhere. (10–15) Among the patients who fulfilled the criteria for parkinsonism, we applied the diagnostic criteria in Table 1. In this study, we measured the prevalence of AP use in patients with Parkinson disease both with and without dementia. Therefore, we considered those with Parkinson disease without dementia (PD), Dementia with Lewy Bodies (DLB), Parkinson disease with Dementia (PDD), and Parkinson disease/Other dementia (PD/OD). Determining AP use in other types of parkinsonism (e.g., multiple system atrophy or progressive supranuclear palsy) was beyond the scope of this study.

Data Collection

To identify patients taking APs on the prevalence day, we used two sources. First, the Rochester Epidemiology Project collects information on all medications prescribed electronically (county-wide practice since 2003). Second, we had access to the full clinical notes and medication reconciliation history of patients via the medical record.

Although many patients had multiple indications for AP use, we categorized indications into a hierarchical ranking:

1. Other psychiatric indication

2. Psychosis or behavior threatening to self or others
3. Non-threatening psychosis or behavior, but AP used to avoid nursing home placement
4. Psychosis or bothersome behavior but non-threatening to self or others

Statistical Analysis

We report prevalence for each specific Parkinson disease category and for all categories combined. For all durations, we report medians and interquartile ranges (IQR; 25th and 75th percentile values). We used Wilcoxon rank-sum tests to analyze continuous variables and Fisher's exact test to analyze categorical data. Mortality was compared between non-AP users and AP users using Cox proportional hazards regression with age as the time scale. All statistical testing was performed at the conventional two-tailed α level of 0.05 using SAS version 9.4 (SAS Institute, Inc).

Ethical Considerations

This study was approved by the Institutional Review Boards of Mayo Clinic and Olmsted Medical Center, Rochester, MN.

RESULTS

There were 296 patients with Parkinson disease in Olmsted County on the prevalence day: 187 (63.2%) men and 109 (36.8%) women. The prevalence of AP use is shown in Table 2. The overall prevalence of AP use was 9.8% (29/296). The prevalence in men was 9.1% (17/187), and in women was 11.0% (12/109; p for difference = 0.69). The median age on prevalence day for those taking APs was 80.4 years overall (IQR 75.8– 83.6), and was similar in men (80.4; IQR 75.8– 83.6) and women (80.0; IQR 75.8– 83.6; p for difference = 0.91).

The most common AP used was quetiapine ($n=24$) with a median daily dose of 62.5 mg (IQR 25 mg– 125 mg). Three subjects used olanzapine (total daily doses of 2.5 mg, 5.9 mg, and 7.5 mg), and two subjects used risperidone (total daily doses of 0.5 mg, 5 mg).

The pairwise differences in AP use between PD and other subtypes with dementia were all statistically significant (PDD vs. PD, $p<0.0001$; DLB vs. PD, $p<0.0001$; PD/OD vs. PD, $p=0.01$). By contrast, the pairwise differences in AP use between the categories with dementia were not statistically significant (PDD vs. DLB, $p=0.17$; PDD vs. PD/OD, $p=0.99$; DLB vs. PD/OD, $p=0.30$).

Of note, 96.5% (28/29) of those on APs suffered from dementia. The one patient without dementia had an intellectual disability and bipolar disorder.

The median time of AP initiation was 4.87 years (IQR 2.63– 8.38) after motor parkinsonism in 89.7% (26/29) of cases. In three patients, the AP was initiated before motor parkinsonism for psychiatric indications.

The median duration of AP use was 3.74 years (IQR 2.55 – 5.56 years) in 23/29 cases (six were unknown); however, seven of the 23 cases (30.4%) used APs only intermittently through that timeframe. The median time between initiation of the AP and death was 3.74 years (IQR 2.83 – 6.30 years). Persons taking APs on the prevalence day were twice as likely to die by December 31, 2016 as those who were not taking APs on the prevalence day (Hazard ratio (HR) = 2.02; 95% CI = 1.35– 3.01; p = 0.001).

The most frequent indication for AP use was psychosis or behavior that was threatening to the subject or others (71.4%; 20/28 cases). In 14.3% (4/28) of patients there was another psychiatric indication. In one patient with psychosis, the AP was used to avoid nursing home placement. There were only 3 patients (10.7%; 3/28) with psychosis or bothersome behavior without documentation of a clear threat to self or others. One patient had an unknown indication.

Most patients (15/27; 55.6%) resided in a skilled nursing facility at the time of AP initiation; however, twelve patients (12/27; 44.4%) resided in a private home. Of these twelve, three remained at home for the remainder of their life, eight eventually moved to a skilled nursing facility, and the current residential status of one was unknown. The median time to placement in a nursing facility after initiation of AP use was 0.57 years (IQR 0.46 –1.74).

DISCUSSION

We found that 9.8% of persons with Parkinson disease were taking APs in our population on the prevalence day. To our knowledge, this is the first report of prevalence of AP use in those with Parkinson disease. Three other studies reported a cumulative probability of taking APs of 25% by 5 years, [7] 35% by 7 years, [6] and 51% by 6 years. [8] Our rate of AP use is surprisingly low compared to these reports. Our use of prevalence, instead of cumulative probability, could explain this lower rate. This would be true if there is a high mortality rate soon after starting APs, or if persons use the APs only briefly. However, our data does not support that. We are currently studying the cumulative probability of AP use in our population to clarify this discrepancy.

Quetiapine was the most common AP used on our prevalence day of January 1, 2006. We have no reason to suspect that this pattern has substantially changed since then. No typical APs were used. A recent report has shown a higher risk of death in persons using typical vs. atypical APs, and that quetiapine has the lowest risk among the atypical class. [3]

We found that 96.5% of those with Parkinson disease taking APs also had dementia. This is not surprising, but is considerably different from the findings in two prior reports. One study reported that <10% of those with Parkinson disease who initiated AP therapy were diagnosed with dementia.[3] Another study reported that 47% of Parkinson disease patients prescribed APs did not have dementia.[9] This discrepancy needs further study.

There is an increased risk of death in those with Parkinson disease taking APs. [2, 3] Although pimavanserin was approved for Parkinson disease psychosis in 2016, it also carries the black box warning of increased death for those with dementia-related psychosis. In our study, we found that 89.3% (25/28) of cases on APs had an indication with a reasonable

risk-benefit ratio. Specifically, the patients had a co-morbid psychiatric disease, a threatening psychosis or behavior, or the AP was prescribed to avoid nursing home placement. In summary, the use of APs in patients with Parkinson disease should be judicious, and reserved for those in which the family and physician feel the risk-benefit balance is justified. Prescribing an acetylcholinesterase inhibitor first could reduce the hallucinations and prevent the need for an AP.

In spite of their disability with Parkinson disease, dementia, and psychosis, 44.4% of those starting APs resided at home. Unfortunately, 72.7% (8/11) of those eventually moved to a skilled nursing facility within a median time of only 0.57 years after starting the AP. This undoubtedly reflects the difficult burden of these severely affected individuals on the caregiver.

Our study has several strengths. Because we were able to study the entire population of Olmsted County, referral bias was not a concern. Also, we were able to use two complementary sources for medication information. More importantly, we were able to study the medical records of all the patients to get important details on their use of APs.

Our study also had limitations. Because of its population-based design, the power is limited by smaller numbers of cases than studies using large databases. Prescribing practices in Olmsted County may differ from other areas, may have changed since January 1, 2006, or may have been influenced by the 2005 FDA black box warning on the use of APs in dementia. In addition, cases of dementia may have been missed if the clinicians did not document the diagnosis or clinical symptoms.

Lastly, three of our cases started APs before the onset of their motor parkinsonism, possibly suggesting that they could have suffered from drug-induced parkinsonism. One patient had Alzheimer dementia with psychosis and eventually discontinued the AP but continued with parkinsonism for many years. The other two patients were on APs for bipolar disorder but eventually developed clinical symptoms consistent with PD and DLB. Although the APs were never discontinued, their disease progressed in a typical way, so we elected to include them in this study. If we had excluded these three patients, the prevalence rate for AP use in those with Parkinson disease would have been lower.

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Table 1**Diagnostic criteria for Dementia and Types of Parkinson Disease**

Dementia	
1	A physician diagnosis of dementia before prevalence day
2	Documentation in the medical record of loss of independence in everyday activities related to cognitive difficulties (not motor), and not in the context of a delirium or other mental disorder, occurring before and after prevalence day
Parkinson Disease without dementia (PD): All 5 of:	
1	Parkinsonism
2	No other cause <ul style="list-style-type: none"> a. Repeated stroke with step wise progression b. Repeated head injury c. History of encephalitis d. Neuroleptic treatment within 6 months of symptom onset with a static course of parkinsonism e. Hydrocephalus f. Tumor
3	No Levodopa-dopa unresponsiveness (≥ 1 gm /day) was recorded, if applicable
4	No prominent or early (< 1 year) signs of more extensive nervous system involvement not otherwise explained (e.g. dysautonomia)
5	No dementia on prevalence day
Parkinson Disease with Dementia (PDD): Both of:	
1	Fulfilled criteria for PD as above, except had dementia on prevalence day
2	Dementia onset was >1 year after onset of motor symptoms of PD
Dementia with Lewy Bodies (DLB): Both of:	
1	Dementia before or within the first year of motor parkinsonism
2	At least one of 1) visual hallucinations, or 2) cognitive fluctuations
Parkinson Disease/Other Dementia (PD/OD): Both of:	
1	Dementia before or within the first year of motor parkinsonism
2	Neither visual hallucinations nor cognitive fluctuations

Table 2

A comparison of age and duration of disease by anti-psychotic (AP) use separately in men and women and across sub-types of Parkinson disease.

Type of parkinsonism	Non-AP users			AP users		
	All cases N	N (%)	Age on prev day, yrs *	Duration of disease, yrs *	N (%)	Age on prev day, yrs *
PD	186	185 (99.5)	74.5 (68.1–82.2)	5.3 (2.6–9.5)	1 (0.5)	61.7 (61.7–61.7)
Men	116	116 (100.0)	73.7 (68.2–82.1)	5.1 (2.2–9.6)	0 (-)	---
Women	70	69 (98.6)	77.3 (67.1–82.8)	5.6 (3.0–9.5)	1 (1.4)	61.7 (61.7–61.7)
PDD	54	43 (79.6)	83.5 (75.4–88.1)	8.0 (4.9–12.0)	11 (20.4)	78.1 (74.6–83.0)
Men	34	24 (70.6)	79.7 (74.5–84.1)	10.4 (5.7–12.2)	10 (29.4)	78.0 (74.6–83.0)
Women	20	19 (95.0)	85.8 (80.9–89.7)	6.7 (3.6–9.8)	1 (5.0)	80.4 (80.4–80.4)
DLB	43	28 (65.1)	78.1 (73.6–84.5)	3.3 (2.2–6.2)	15 (34.9)	83.1 (77.6–84.7)
Men	29	23 (79.3)	77.7 (74.6–84.4)	3.5 (2.3–6.8)	6 (20.7)	83.1 (78.5–84.7)
Women	14	5 (35.7)	79.2 (71.3–85.9)	2.7 (0.7–3.3)	9 (64.3)	83.2 (77.6–84.0)
PD/OD	13	11 (84.6)	86.0 (82.2–92.6)	2.9 (1.9–8.0)	2 (15.4)	84.1 (75.7–92.5)
Men	8	7 (87.5)	86.0 (79.2–92.6)	2.2 (1.3–4.0)	1 (12.5)	92.5 (92.5–92.5)
Women	5	4 (80.0)	85.8 (82.4–92.2)	6.1 (2.7–10.0)	1 (20.0)	75.7 (75.7–75.7)
All types	296	267 (90.2)	77.6 (69.9–84.4)	5.4 (2.7–9.6)	29 (9.8)	80.4 (75.8–83.6)
Men	187	170 (90.9)	76.8 (69.8–84.0)	5.2 (2.3–9.9)	17 (9.1)	80.4 (75.8–83.6)
Women	109	97 (89.0)	79.7 (70.3–85.8)	5.6 (2.9–9.5)	12 (11.0)	80.0 (75.8–83.6)

AP = anti-psychotic; PD=Parkinson disease without dementia; PDD=Parkinson disease with dementia; DLB=Dementia with Lewy bodies; PD/OD=Parkinson disease/other dementia

* Values reported as median (25th percentile, 75th percentile). None of the comparisons between non-AP users and AP-users overall or separately within a sex were statistically significant for either age on prevalence day or duration of disease (all p-values for Wilcoxon rank-sum tests > 0.05).