Patterns and Trends in Antipsychotic Prescribing for Parkinson Disease Psychosis

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Background: Antipsychotic (AP) use is common in Parkinson disease (PD), but APs can worsen parkinsonism, evidence for efficacy is limited, and use in patients with dementia increases mortality.

Objective: To examine the frequency and characteristics, including changes over time, of AP use in a large cohort of patients with PD.

Design: Using Veterans Affairs data from fiscal year (FY) 2008, rates and predictors of AP prescribing were determined for patients with PD and psychosis stratified by dementia status (N=2597) and a comparison group of patients with dementia and psychosis without PD (N=6907). Fiscal year 2008 and FY2002 data were compared to examine changes in AP prescribing over time.

Setting: Department of Veterans Affairs outpatient facilities.

Participants: Outpatients with PD and psychosis and outpatients without PD with dementia and psychosis, all receiving care at Veterans Affairs facilities in FY2002 and FY2008.

Main Outcome Measure: Antipsychotic prescribing, including overall, class, and specific medications.

Results: In FY2008, 50% of patients with PD having a diagnosis of psychosis were prescribed an AP. Among treated patients, the atypical AP quetiapine was most frequently prescribed (66%), but approximately 30% received high-potency APs. Clozapine was rarely prescribed (<2%). In multivariate models, diagnoses of PD and dementia were associated with AP use. Comparing FY2008 with FY2002, AP use in PD was unchanged, with decreases in risperidone and olanzapine use offset by an increase in quetiapine prescribing and the introduction of aripiprazole.

Conclusions: Half of the patients with PD and psychosis receive APs, not uncommonly high-potency agents associated with worsening parkinsonism, and frequency of use has been unchanged since the “black box” warning for AP use in patients with dementia was issued. Recent trends are a shift to quetiapine use and the common use of aripiprazole. As psychosis and dementia are frequently comorbid in PD, safety risks associated with AP use in this population need to be assessed.
Little is known about the frequency and patterns of AP use in PD in routine clinical care. In one study using administrative data, the cumulative probability of starting AP therapy within 7 years of starting a dopaminergic medication for PD was 35%. Further study of this issue is critical given both the high prevalence of psychosis in this population and that parkinsonian symptoms and frequent comorbid dementia may make this population more likely to experience adverse outcomes, including mortality, with AP treatment.

The objectives of this study were to examine the frequency and characteristics, including changes over time, of AP use in patients with PD. We studied patients with PD and psychosis, stratified by dementia status, and included a comparison group of patients with non-PD dementia and psychosis to study the impact of a diagnosis of PD on AP prescribing.

STUDY POPULATION

Data were derived from national Department of Veterans Affairs (VA) databases for patients seen in fiscal years (FYs) 2002 and 2008. Estimates are that 60,000 patients in the VA system have a diagnosis of PD (information provided by Office of the Director of Neurology, Veterans Health Administration, September 10, 2010). Information regarding data extraction from these databases was described in detail in previous publications that have examined psychotropic use in patients with dementia and patients with PD and psychosis stratified by dementia status. Participants with idiopathic PD were identified using the following code of the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM, WHO 1994): 332.0; patients with a diagnosis of secondary parkinsonism (332.1) and dementia with Lewy bodies (331.82) were excluded. Psychosis diagnoses included ICD-9-CM codes: 293.81, 293.82, 297.0, 297.1, 297.2, 297.3, 297.8, 297.9, 298.0, 298.1, 298.2, 298.3, 298.4, 298.8, 298.9, 368.16, and 780.1; patients with schizophrenia and bipolar diagnoses were excluded. Dementia diagnoses included ICD-9-CM codes: 290.0, 290.1, 290.11, 290.12, 290.13, 290.2, 290.21, 290.3, 290.4, 290.41, 290.42, 290.43, 290.44, 291.2, 294.1, 294.11, 331.0, 331.1, 331.11, 331.19, and 331.2; again, patients with a diagnosis of dementia with Lewy bodies were excluded. Patients with an ICD-9-CM dementia code of 290.12, 290.2, or 290.42 were not required to have a separate psychosis diagnosis, as these diagnostic codes are for dementia with psychotic features.

CLASSIFICATION OF APs

Atypical APs were clozapine, olanzapine, quetiapine, risperidone, ziprasidone, and aripiprazole (aripiprazole was included only in the FY2008 analyses as it was not approved for use in the VA in FY2002). Typical or conventional APs included only in the FY2008 analyses as it was not approved for use in the VA in FY2002). Typical or conventional APs included a subclass for high-potency medications (fluphenazine, haloperidol, perphenazine, trifluoperazine, and thiothixene), as these are the typical APs most associated with causing or worsening parkinsonism. Atypical AP use was recorded for any time point in the year, and in the course of 1 year, some patients were prescribed more than 1 AP, leading to cumulative AP use greater than 100%.

DEMOGRAPHIC VARIABLES

Age, race, and marital status were included to examine their association with AP prescribing. Descriptive statistics were used to examine the frequencies of overall and specific AP use in the patients with PDP with and without dementia and the comparison dementia group. χ² and t tests were used to analyze differences for categorical and continuous variables, respectively.

χ² Tests were used to test for between-group cross-sectional differences and within-group changes over time in AP prescribing. A multiple logistic regression model was used to examine the impact of PD diagnosis, dementia diagnosis, and demographic variables on AP use. When examining changes in AP prescribing over time, patients identified in both cohorts were excluded from the FY2002 and FY2008 cohorts prior to analyses because the goal was to identify overall changes in prescribing patterns, not changes in individual patients.

Point estimates (odd ratios [ORs]) and 95% confidence intervals (95% CIs) are reported. P < .05 was considered statistically significant. All analyses were performed with commercially available statistical software (SAS, version 9.2; SAS Institute, Inc, Cary, North Carolina).

METHODS

RESULTS

CHARACTERISTICS OF PARTICIPANTS

For the main analysis using FY2008 data, a total of 9504 patients were included, 2597 patients with PDP (n = 793; PDP + D) or without (n = 1804; PDP − D) dementia) and 6907 patients without PD with dementia and psychosis (D + P) (Table 1). The study sample was 97.3% male. Patients with PDP + D were older, more likely to be married, and more likely to be white compared with patients with PDP − D and patients with D + P.

AP PRESCRIBING IN PD

Antipsychotics were prescribed in 50.0% of all the patients with PD and comorbid psychosis (Table 2). High-potency APs were prescribed in 3.4% of all the patients or in 6.8% of treated patients. Atypical APs were prescribed in 48.2% of all the patients or 96.3% of treated patients. Among atypical APs, quetiapine was most commonly prescribed (33.0% of all the patients or 65.9% of treated patients), followed by risperidone (8.6% or 17.3%), aripiprazole (6.0% or 12.1%), and olanzapine (5.7% or 11.5%). Clozapine (0.9% or 1.8%) was rarely prescribed.

Within the PD group, both overall AP prescribing (χ² = 21.69, P < .001) and atypical AP use (χ² = 22.00, P < .001) was higher in patients with PDP + D. Regarding specific atypical APs, quetiapine was prescribed more commonly in patients with PDP + D (χ² = 16.36, P < .001).

AP PRESCRIBING IN PATIENTS WITH PDP + D AND D + P

Examining the impact of PD on AP prescribing in patients with any dementia diagnosis, overall AP use was greater in patients with PDP + D than in patients with D + P (χ² = 19.94, P < .001) (Table 2). High-potency typical APs were less commonly used in patients with PDP + D (χ² = 7.89, P = .005), and atypical APs were more com-
associated with AP use in PD (Table 4). Younger age was also associated with AP use in this population (P < .001).

**CHANGES OVER TIME IN AP PRESCRIBING (FY2002 TO FY2008)**

Changes were noted in AP prescribing patterns over a 6-year period in both PD groups and the D + P group (eTable; http://www.archneurol.com). In PD, overall and any atypical AP use was unchanged in patients with PDP + D and those with PDP – D, but the examination of classes and individual medications revealed the following: (1) decreases in risperidone and olanzapine use in both groups, (2) increases in quetiapine and ziprasidone use in both groups, and (3) frequent use of aripiprazole after its introduction. There was a slight increase over time in overall and atypical AP use in the D + P group, with the same class and individual medication patterns noted as for the PD population.

### Table 1. Demographic Characteristics of Patients With Psychosis by Parkinson Disease and Dementia Status (FY2008)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>With Dementia (n=793)</th>
<th>Without Dementia (n=1804)</th>
<th>Non-PD Dementia Group (n=6907)</th>
<th>Test of Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td>77.7 (7.9)</td>
<td>74.7 (9.8)</td>
<td>76.8 (10.2)</td>
<td>F=40.73, df=2, P&lt;.001bc</td>
</tr>
<tr>
<td>Age group, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65</td>
<td>8.1</td>
<td>17.7</td>
<td>15.1</td>
<td>x^2=86.82, P&lt;.001bc</td>
</tr>
<tr>
<td>65-74</td>
<td>29.4</td>
<td>22.8</td>
<td>16.6</td>
<td></td>
</tr>
<tr>
<td>≥75</td>
<td>71.5</td>
<td>59.5</td>
<td>68.3</td>
<td></td>
</tr>
<tr>
<td>Marital status, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>71.5</td>
<td>64.9</td>
<td>57.0</td>
<td></td>
</tr>
<tr>
<td>Ethnic group, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>80.6</td>
<td>78.4</td>
<td>72.4</td>
<td>x^2=44.98, P&lt;.001c</td>
</tr>
</tbody>
</table>

**Abbreviation:** PD, Parkinson disease.

**a** Reference group.

**b** Significant differences between patients with PD with and without dementia.

**c** Significant difference between patients with dementia with and without PD.

### Table 2. Antipsychotic Prescribing in Patients With Psychosis by Parkinson Disease and Dementia Status (FY2008)

<table>
<thead>
<tr>
<th>AP Prescribing</th>
<th>PD Group, No. (%)</th>
<th>Non-PD Dementia Group, No. (%)</th>
<th>Test of Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AP use</td>
<td>451 (56.9)</td>
<td>3350 (48.5)</td>
<td>x^2=23.35, P&lt;.001bc</td>
</tr>
<tr>
<td>Any typical AP</td>
<td>35 (4.4)</td>
<td>500 (7.2)</td>
<td>x^2=33.50, P&lt;.001c</td>
</tr>
<tr>
<td>High-potency AP</td>
<td>32 (4.0)</td>
<td>456 (6.6)</td>
<td>x^2=37.00, P&lt;.001c</td>
</tr>
<tr>
<td>Any atypical AP</td>
<td>437 (55.1)</td>
<td>3110 (45.0)</td>
<td>x^2=29.63, P&lt;.001bc</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>306 (38.6)</td>
<td>1522 (22.0)</td>
<td>x^2=139.36, P&lt;.001bc</td>
</tr>
<tr>
<td>Risperidone</td>
<td>81 (10.2)</td>
<td>1282 (18.6)</td>
<td>x^2=141.98, P&lt;.001c</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>41 (5.2)</td>
<td>273 (4.0)</td>
<td>x^2=21.16, P&lt;.001</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>56 (7.1)</td>
<td>458 (6.6)</td>
<td>x^2=5.87, P=.05</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>18 (2.3)</td>
<td>100 (1.4)</td>
<td>x^2=3.44, P=.18</td>
</tr>
<tr>
<td>Clozapine</td>
<td>5 (0.6)</td>
<td>4 (0.1)</td>
<td>x^2=48.27, P&lt;.001c</td>
</tr>
</tbody>
</table>

**Abbreviations:** AP, antipsychotic; PD, Parkinson disease.

**a** Reference group.

**b** Significant differences between patients with PD with and without dementia.

**c** Significant difference between patients with dementia with and without PD.

Commonly used (χ^2^= 29.09, P < .001). In terms of specific AP use, quetiapine (χ^2^= 107.64, P < .001) and clozapine (χ^2^= 19.98, P < .001) were used more commonly, and risperidone less commonly (χ^2^= 34.02, P < .001), in the PDP + D group.

**PREDICTORS OF AP USE IN PATIENTS WITH PD**

In a multiple logistic regression analysis that included age, race, and marital status as covariates, a diagnosis of comorbid dementia (OR = 1.74; 95% CI, 1.46-2.07; P < .001) was associated with AP use in PD (Table 3). Younger age was also associated with AP use in this population (P < .001).

**PREDICTORS OF AP USE IN PATIENTS WITH DEMENTIA**

In a multiple logistic regression analysis that included age, race, and marital status as covariates, a diagnosis of PD (OR = 1.46; 95% CI, 1.26-1.70; P < .001) was associated with AP use in patients with dementia and psychosis (Table 4). Younger age was also associated with AP use in this population (P < .001).
We found that half of patients with PDP are prescribed an AP in routine clinical care, most commonly an atypical AP. In addition, comorbid dementia in a patient with PD and comorbid PD in a patient with dementia increase the likelihood of AP use. Finally, despite 2005 and 2008 FDA warnings regarding associations between AP use and mortality in patients with dementia, a common comorbid condition in PD, overall AP use in PD was unchanged between FY2002 and FY2008.

The overwhelming majority of AP prescriptions in PD were for atypical agents. Clinical trials and case series suggest that olanzapine and risperidone have limited efficacy in PD and can worsen parkinsonism, so their frequent use would be expected. However, we found that risperidone or olanzapine were prescribed in almost 30% of treated patients with PDP. Also of concern, 7% of treated patients with PD were prescribed atypical APs, especially clozapine, which is generally not recommended for use in patients with PD. Finally, by FY2008, aripiprazole was the third most commonly prescribed AP in patients with PDP, although initial open-label experience suggests poor tolerability of aripiprazole in PD.

Anecdotally, quetiapine has become the most frequently prescribed AP for PD, and our data confirm this impression, with two-thirds of treated patients taking this medication. Clinical experience suggests that quetiapine is well tolerated from a motor standpoint and often effective at commonly used doses, but the findings of all 3 placebo-controlled studies in patients with PDP have been negative, perhaps related in part to methodological issues.

Only clozapine has demonstrated efficacy for the treatment of psychosis in PD and only its use has been recommended by a Quality Standards Subcommittee of the American Academy of Neurology and on the basis of a meta-analysis. However, clozapine accounted for less than 2% of AP prescriptions in our PD sample. The length of the application process to get approval from the National Clozapine Center, concern for the rare but potentially life-threatening adverse effect of agranulocytosis, and requirements for routine blood cell count monitoring are likely deterrents to greater clozapine use.

For all the patients with a diagnosis of dementia, a comorbid PD diagnosis increased the likelihood of AP use. Approximately one-third of our PD sample had comorbid dementia, and many more likely had mild cognitive impairment (MCI). This has significant clinical implications in PD given the increased morbidity and mortality associated with typical and atypical AP use in dementia populations. As the cumulative dementia rate in PD may be as high as 80% to 90%, of concern is the impact of AP use on morbidity and mortality in patients with PD and comorbid dementia. However, it is also possible that the higher rates of AP use in patients with PD compared with patients without PD was an artifact of clinician coding, with a higher severity of psychosis being required in patients with PD for clinicians to code psychosis as a comorbid disorder. The association between younger age and AP prescribing in PD may reflect the fact that clinicians have less concern about AP adverse effects in younger patients with PD, who also have less severe disease on average.

Antipsychotic use in PD was unchanged over a period that encompassed the publication of black box warnings for AP use in patients with dementia. Within PD, over this period there was a significant decrease in high-potency atypical AP (olanzapine and risperidone) use, increases in quetiapine and ziprasidone use, and the introduction and relatively common use of aripiprazole. Thus, there has been a recent shift in AP use in PD to medications that overall may be better tolerated from a motor standpoint but not clearly more efficacious or safer. There is preliminary research reporting that patients with PD treated with atypical APs lose weight, while comparable patients with Alzheimer disease gain weight, so future research needs to determine if the increased mortality and morbidity associated with patients with dementia in general extend to patients with PD.

The fact that almost half of patients who have PDP are not treated with an AP suggests several possibilities. First, the recommended initial management strategy for patients with PDP focuses on the treatment of medical comorbidities and the discontinuation of non-PD medications that might cause or contribute to psychosis, in conjunction with a decrease in the number or dosage of nonessential PD medications. Such a strategy has been shown to decrease the need for acute AP treatment in a substantial percentage of patients with PD. Second, psychotic symptoms in PD may often not be clinically significant enough to warrant treatment. Third, clinicians...
may not perceive a favorable risk-benefit ratio for AP use in many patients with PD, given concerns over possible worsening of parkinsonism and other problematic adverse events.21,40

This study has several limitations. First, the databases we used lacked data about the severity of PD, dementia, and psychosis, including if psychotic symptoms were active. Such factors potentially impact providers’ AP prescribing, both in frequency and type. Second, diagnoses were based on coding entered by health care providers, and these data could not be verified. Third, we only included patients with a comorbid psychosis diagnosis, which may have biased our sample toward those patients with more severe psychosis, as well as have obscured long-term changes in AP prescribing that others have reported for patients with dementia in general.20 Fourth, our results may not be generalizable to prescribing practices for psychosis in patients with PD outside the VA system, due to complex issues such as cost, formulary guidelines, and policies on who can prescribe APs. Fifth, because updated diagnostic criteria for dementia with Lewy bodies were not published until 2005,44 it is impossible to know what percentage of patients with PDP + D actually met clinical criteria for dementia with Lewy bodies.

Given the high frequency of psychosis and common use of APs in PD, as well as frequent comorbidity of dementia, additional research is needed to further understand what factors contribute to both overall and specific AP use in this population, and longitudinal studies should assess the impact of AP treatment on morbidity, mortality, and progression of parkinsonism.

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Author Contributions: Study concept and design: Weintraub, Chen, Ignacio, and Kales. Acquisition of data: Ignacio and Kales. Analysis and interpretation of data: Weintraub, Chen, Ignacio, and Kales. Drafting of the manuscript: Weintraub, Chen, Ignacio, Mamikonyan, and Kales. Critical revision of the manuscript for important intellectual content: Weintraub, Chen, Ignacio, and Kales. Administrative, technical, and material support: Mamikonyan.

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Online-Only Material: The eTable is available at http://www.archneurol.com.

REFERENCES


