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Annual Prevalence of Use of Potentially Inappropriate Medications for Treatment of Affective Disorders in Parkinson's Disease

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Abstract

Objective: To examine the national prevalence of pharmacological treatment of affective disorders in older adults with Parkinson's disease (PD), and determine the prevalence and risk

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AUTHOR CONTRIBUTIONS

DSA: Design of the study, analysis of the data, interpretation of the data, drafting of the manuscript, revising the manuscript for intellectual content, and final approval of the version to be published.

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factors for receipt of an American Geriatrics Society Beers Criteria defined Potentially Inappropriate Medication (PIM) for affective disorder treatment.

Design: Cross-sectional analysis of 2014 Medicare data.

Setting: Research Identifiable File data from the Centers for Medicare and Medicaid Services.

Participants: Individuals ≥65 years of age with PD whose inpatient, outpatient, and prescription care is administered through the U.S. Medicare Program.

Measurements: The 2014 prevalence of affective (i.e., depressive and anxiety) disorders was calculated. We assessed prescription fills for affective disorder treatment and classified prescriptions according to PIM status. Patient and clinician factors associated with PIM prescriptions were determined.

Results: Of 84,323 beneficiaries with PD, 15.1% had prevalent depression only, 7.5% had anxiety only, and 8.5% had comorbid depression and anxiety. Among those with depression only, 80.7% were treated in 2014 (12.8% of treated received at least one PIM). The annual treatment prevalence was 62.9% (75.9% PIM) and 93.1% (63.9% PIM) in the anxiety only and comorbid group, respectively. In most groups, PIM use was less likely among men and those with dementia; geriatricians were less likely to prescribe PIMs.

Conclusions: Treatment of affective disorders in persons diagnosed with PD is high. PIM use is also common, particularly in persons with anxiety. Future research will quantify the potential effects of these PIMs on clinical and patient outcomes.

Keywords

Parkinson’s disease; Potentially Inappropriate Medication List; Depression; Anxiety

OBJECTIVE

Affective disorders, in particular depression and anxiety, are common non-motor disorders in Parkinson’s disease (PD). The burden of depression and anxiety has been studied in several clinical and research setting studies, and the reported prevalence ranges from 3% to 89% for depression[1] and 7% to 55% for anxiety.[2] Additionally, patients commonly present with both disorders.[3] These disorders have negative impacts on disease outcomes; for example, depression in PD is associated with worse disability and health-related quality of life.[4–6]

Persons with PD are typically above age 60,[7] at risk for cognitive impairment,[8,9] and have dysfunctional dopaminergic[10,11] and cholinergic systems,[11–13] which makes treatment selection among those with an affective disorder challenging. Several U.S. Food & Drug Administration (FDA) medications indicated for depression and anxiety have anticholinergic properties, dopamine receptor-blocking properties, or gamma-aminobutyric acid (GABA) effects and are discouraged from use in older adults, individuals with cognitive impairment, or individuals with PD due to adverse event concerns.[14,15] The American Geriatrics Society Beers Criteria identifies these discouraged drugs as potentially inappropriate medications (PIMs).[14] Clinicians, researchers, and regulators can use the Beers Criteria to identify gaps

in care quality and quantify PIM-associated negative health events.[14] Furthermore, based on evidence-based medicine reviews by the Movement Disorders Society and American Academy of Neurology, few of these medications have demonstrated efficacy and safety specifically in persons with PD.[16–19]

Prior studies have quantified the frequency and type of affective disorder treatments PD patients receive.[20–30] Many have been conducted in smaller samples,[20,22–24,29,30] with the largest study sample derived from a specialty center-based PD cohort.[26] However, many persons diagnosed with PD in the United States do not receive care from a neurologist or movement disorders specialist.[31] Prior studies have used self-report[21,24,29] or clinician documentation[30] to collect information about medication use across all health care settings. No prior study has used national data to determine the frequency and type of treatment persons with PD receive for affective disorders in the United States, nor used standardized criteria to evaluate the safety of medications used for affective disorders in older adults with PD. To address these gaps in knowledge, and provide a foundation for interventions with the potential to improve the clinical management of PD, the aims of this study were to 1) examine the proportion of older adults with PD treated for affective disorders, 2) determine the proportion treated receiving a PIM for an affective disorder, and 3) determine whether patient or clinician characteristics were associated with receipt of a PIM for an affective disorder.

METHODS

A waiver of consent was obtained for this study by the University of Pennsylvania Human Research Protections Office and Centers for Medicare and Medicaid Services (CMS).

Data Source

This cross-sectional analysis was conducted with CMS Research Identifiable Files (RIFs). Specifically, Master Beneficiary Summary Files (MBSF) were used to obtain beneficiary enrollment, demographics, and common comorbid condition information. The Carrier file was used to identify PD, other diagnoses, and procedures. Prescription information, including prescriber, was obtained from the Part D Drug Event File.

Study Sample

Analysis was restricted to beneficiaries ≥65 years of age (by January 1,2014) with active part A (inpatient), part B (outpatient), and part D (prescription drug) coverage for all of 2014. We excluded individuals whose benefits were partially administered through health maintenance organizations, state Medicaid programs, or employee or union retiree benefit prescription programs. These beneficiary subgroups may have incomplete data reporting to CMS, atypical health profiles, or atypical healthcare system interactions. Beneficiaries must have also had at least one 2014 prescription fill for any medication. Because chronic conditions are coded in the MBSF based on one- to two-year look-back periods, we required beneficiaries to meet coverage eligibility criteria in 2012 and 2013.

PD patients were identified from eligible beneficiaries as those with two claims for PD (ICD-9 CM code 332.0).[32] We employed several exclusion criteria to remove beneficiaries

whose PD diagnosis may be uncertain or whose clinical and treatment characteristics may be atypical. Specifically, we required that potential PD patients have no claims for other neurodegenerative disorders including atypical parkinsonism (ICD-9 CM 333.0), amyotrophic lateral sclerosis (ICD-9 CM 335.20), dementia with Lewy bodies (331.82), or Alzheimer's disease (AD) (per the MBSF Chronic Conditions segment[33]). The MBSF Chronic Conditions segment was also used to identify and exclude individuals with schizophrenia or bipolar disorder. Lastly, we excluded individuals with evidence of nursing home residence (CPT-4 codes 993.01-993.13)[34,35] or hospice care (at least one hospice stay noted in the MBSF Cost and Utilization segment file).

Variables

Affective Disorders—The MBSF Chronic Conditions segment as well as the MBSF Other Chronic or Potentially Disabling Conditions segment were used to assess prevalent affective disorders.[33] Depression diagnoses were determined from the former and anxiety disorders from the latter segment, based on whether individuals met criteria for the respective affective disorder by the end of 2014.

Treatment

Drug choice identification.: IBM® Micromedex® was used to create a list of all FDA on-label medications indicated for the treatment of anxiety disorders (i.e., generalized anxiety disorder, panic disorder, obsessive-compulsive disorder, post-traumatic stress disorder, and social anxiety disorder) and depression (i.e., depression and major depressive disorder).[36] Although some on-label medications for affective disorders are antipsychotics, these medications were not considered affective disorder treatments for the analysis for several reasons. Antipsychotics are the preferred treatment for psychosis in PD[16,17], and when used for affective disorders, they are used as adjunct therapy. Selegiline, although FDA indicated for mood disorders, was also not considered an affective disorder treatment as it is used primarily to treat the motor symptoms of PD. Drugs used for affective disorders were subsequently classified as PIMs if they were included in the 2019 Beers Criteria list as potentially inappropriate for most older adults (see Table, Supplemental Digital Content 1, which details prescription classifications).[14]

PD cohort drug classification.: The 2014 Part D Drug Event file was searched to determine if each beneficiary received any on-label medication for depression or anxiety, as detailed above. Each individual prescription was classified according to PIM status, irrespective of dosage. To eliminate short-term or trial medication prescriptions, only fills for 30 days or more were considered as qualifying prescriptions.

Covariates—Beneficiary sociodemographic characteristics assessed included sex, age on January 1, 2014 and on date of prescription (65-74, 75-84, ≥85 years of age), race (white, black, other), and geographical residence based on USDA Rural-Urban Continuum Codes Classification (urban, suburban, rural).[37] Beneficiaries with unknown race (n=268) were categorized as "other". We were unable to categorize residence for 100 beneficiaries. These individuals were assigned the most common category, urban residence.

Clinical characteristics included comorbidity burden, psychosis, and non-AD dementia. Comorbidity burden was the sum of the number of conditions indicated at the end of 2014 in the Chronic Conditions segment, excluding dementia and depression.[33,38] Psychosis was captured with ICD-9 CM codes for delusions or hallucinations (ICD-9 CM codes 293.81 or 293.82). Co-occurrence of cognitive deficits and affective disorders is common in PD.[39] Non-AD type dementia was used to assess clinically apparent cognitive impairment. Non-AD dementia was determined by the Chronic Conditions segment indicator for dementia, excluding individuals who also met the segment criteria for AD.

In the Part D Drug Event file, each prescription includes the prescriber's National Provider Identifier (NPI). The prescriber's specialty (neurologist, psychiatrist, geriatrician, or other) was determined by merging in the National Plan and Provider Enumeration System Downloadable file,[40] which includes provider taxonomy codes (indicating specialty) for each NPI. Taxonomy codes were cross-walked to CMS provider specialty codes.[41]

Statistical Analysis

Analysis was performed in SAS v9.4 (Cary, NC). To characterize the final sample, descriptive analysis was conducted on beneficiary-level data. Sociodemographic features, clinical characteristics, and annual prevalence of affective disorder treatment was compared between those with and without affective disorders in 2014. For those with depression only, bivariate analysis was used to examine differences between those who received on-label prescription treatment versus those who did not. Among those who received on-label depression treatment, we compared those who received at least one high PIM medication versus those who did not with Chi-squared, Fisher's exact, and t-tests. Due to large sample sizes, we also used standardized differences, with a threshold of 0.1, as an additional means to assess group differences.[42] The same analysis was repeated for those with anxiety only and comorbid depression and anxiety. For the latter group, we considered individuals to have received on-label treatment if they received an on-label prescription for depression or anxiety.

To determine common treatments and explore the impact of prescribers on PIMs, we examined prescription-level data. The proportion of affective disorder prescriptions stemming from each medication was calculated. Generalized estimating equation (GEE) logistic regression was performed to determine whether beneficiary characteristics or prescriber specialty were associated with receipt of PIMs for affective disorders. Models were fully adjusted, used a compound symmetry correlation structure, and accounted for repeated observations by beneficiary. Because psychosis was rare, it was not included in the adjusted models.

In identifying PIM prescribing for PD, we considered that a single prescription may indicate a medication trial or error, whereas multiple fills reflect a consistent treatment regimen. Therefore, we conducted a sensitivity analysis restricting to 30-day or greater prescriptions with a minimum of two fills over the year. Descriptive analysis and GEE models were replicated.

RESULTS

There were 56,867,603 Medicare beneficiaries in 2014. Of those, 10,364,579 met coverage criteria and were alive at the end of 2014. Restricting to those with PD, a minimum of one prescription fill, and no nursing home/hospice care, resulted in a sample of 104,264 beneficiaries. The exclusion of persons with other neurodegenerative diseases and mental health conditions resulted in a final analytic sample of 84,323 beneficiaries.

By the end of 2014, 23.6% (n=19,866) and 16.0% (n=13,485) of beneficiaries with PD had a new or prevalent diagnosis of depression or anxiety. Examining mutually exclusive groups, 15.1% (n=12,703) had a diagnosis of depression only, 7.5% (6,322) had a diagnosis of anxiety only, and 8.5% (n=7,163) had comorbid depression and anxiety. Significant ($p<0.05$) and meaningful (standardized difference ≥0.1) differences were noted for several characteristics (Table 1). Beneficiaries with an affective disorder diagnosis were more likely to be female, diagnosed with a greater number of chronic conditions, diagnosed with non-AD dementia, and prescribed affective disorder treatment (Table 1). Of note, 20.8% (n=12,090) and 21.1% (n=12,268) of individuals without a formal affective disorder diagnosis received a medication indicated for the treatment of depression or anxiety, respectively.

Of those with depression only, 80.7% (n=10,253) of beneficiaries filled a prescription indicated for the treatment of depression. The five most common prescriptions to treat those with depression only were sertraline (16.0% of all prescriptions), citalopram (15.4%), escitalopram oxalate (12.8%), duloxetine (9.1%), and mirtazapine (8.2%). On-label anxiety treatment was prescribed to 62.9% (n=6,322) of beneficiaries with anxiety only. Alprazolam (18.8% of all prescriptions), clonazepam (17.1%), lorazepam (14.0%), sertraline (12.0%), and escitalopram oxalate (9.6%) were the most common prescriptions for individuals diagnosed with anxiety only. In total, 93.1% (n=6,670) of beneficiaries with comorbid depression and anxiety received at least one affective disorder prescription. Beneficiaries with comorbid depression and anxiety most commonly received prescriptions for clonazepam (10.5% of all prescriptions), sertraline (9.6%), alprazolam (9.6%), escitalopram oxalate (8.4%), and citalopram hydrobromide (8.3%).

Table 2 displays characteristics associated with treatment for each affective disorder group. Treatment prevalence differed by sex; those with depression only undergoing treatment were younger, and those with comorbid depression and anxiety undergoing treatment were more likely to be white (χ^2 test p-values <0.05 and standardized differences ≥0.1).

Among those treated, there were no characteristics that substantially differed between those treated with a PIM versus not treated with a PIM in any of the affective disorder groupings, except that those treated for comorbid depression and anxiety were younger ($X^2_{(df=2)}=19.78$, $p<0.0001$, standardized difference=0.1095) and more likely to be female ($X^2_{(df=1)}=27.06$, $p<0.0001$, standardized difference=−0.132) (Table 3). PIM receipt was least common among persons with depression only (12.8%); on-label PIM use was much higher for persons with anxiety only (75.9%) and with comorbid depression and anxiety (63.8%). Pooling all

groups, clonazepam accounted for 24.2% of all PIM prescriptions, followed by alprazolam (23.8%), lorazepam (18.4%), paroxetine (17.6%), and amitriptyline hydrochloride (4.2%).

In the fully adjusted models of prescription-level data, female sex was significantly associated with PIM prescriptions among those with depression only (aOR=1.18, 95% CI: 1.04, 1.34; $X^2_{(df=1)}$=6.87, p=0.0088) and with both depression and anxiety (aOR=1.15, 95% CI: 1.07, 1.24; $X^2_{(df=1)}$=13.15, p=0.0003) (Table 4). Beneficiaries ≥85 years of age with comorbid depression and anxiety had a lower odds of PIM than those 65-74 (aOR=0.85, 95% CI: 0.76, 0.94; $X^2_{(df=1)}$=9.33, p=0.0023). Among those with anxiety only, each additional comorbidity was associated with an increased odds of PIM receipt (aOR=1.03, 95% CI: 1.00, 1.05; $X^2_{(df=1)}$=4.07, p=0.0436). Dementia was associated with lower odds of receiving PIMs in both the anxiety only group (aOR=0.78, 95% CI: 0.68, 0.90; $X^2_{(df=1)}$=11.39, p=0.0007) and the comorbid group (aOR=0.89, 95% CI: 0.83, 0.97; $X^2_{(df=1)}$=7.78, p=0.0053). In general, psychiatrists and geriatricians were less likely to prescribe PIMs than other clinicians, particularly for anxiety (aOR=0.42, 95% CI: 0.22, 0.78; $X^2_{(df=1)}$=7.51, p=0.0061). Neurologists were more likely to prescribe PIMs for PD patients with comorbid disorders (aOR=1.21, 95% CI: 1.07, 1.38; $X^2_{(df=1)}$=8.67, p=0.0032).

In the sensitivity analysis, the number of treated individuals dropped in all affective disorder groups (74.1% [n=9,410] for depression alone, 55.8% [n=3,525] for anxiety only, and 88.9% [n=6,368] for comorbid depression and anxiety). The proportion treated with PIMs also slightly declined (11.9% [n=1,121] for depression only, 73.2% [n=2,581] for anxiety only, and 58.5% [n=3,725] in the comorbid group). The GEE sensitivity analysis (see Table, Supplemental Digital Content 2, which details the model results) found the same factors significantly associated with PIMs; however, there were two additional significant findings: age (for anxiety alone) and residence (for comorbid depression and anxiety).

CONCLUSIONS

We studied the patterns of diagnosis and treatment of affective disorders among older adults with PD in the United States. Affective disorders are frequently diagnosed in this sample; annual treatment prevalence was high for persons diagnosed with depression with or without comorbid anxiety, but modest for anxiety alone. Prescription management of affective disorders with PIMs was somewhat common, and varied by diagnosis, patient demographic characteristics, comorbid disease, and prescribing physician specialty.

In this nationally representative sample of older adults, 23.6% and 16.0% of individuals diagnosed with PD met criteria for a depressive disorder and an anxiety disorder. The depression estimates we found in this study are consistent with estimates from two meta-analyses conducted in PD, which found prevalence estimates of 17%[1] and 22.9%[43] for major depression and 22%[1] and 31,3%[43] for minor depression. The prevalence of anxiety disorders in our study (16.0%) was lower than that found in a prior meta-analysis (31%).[2] However, that meta-analysis defined anxiety disorders using specialty diagnostic criteria used primarily by psychiatrists (i.e., the Diagnostic and Statistical Manual) and often included studies based in specialty care settings.[2] We found treatment with prescription medication to be particularly high for depression, with 80.7% of those with depression only

receiving prescription treatment, and 93.1% of those with depression and comorbid anxiety receiving treatment. The majority of individuals with anxiety only were also treated (62.9%), but this proportion was lower than that for depression. These treatment rates are higher than previously reported.[20–30] Our claims-based method of identifying affective disorders diagnoses and treatment may have resulted in restricting our sample to individuals with clinically definite or more severe disease, which would represent groups more likely to be treated. Additionally, most prior studies did not examine the use of all FDA on-label treatments.

The presence of an anxiety diagnosis substantially increased the likelihood of PIM receipt, with 75.9% of treated individuals with anxiety alone receiving a PIM and 63.8% of treated individuals with comorbid depression and anxiety receiving a PIM. This PIM use compares to only 12.8% in those with depression alone. This higher prevalence among those with anxiety was driven by benzodiazepine use. Clinical practice guidelines uniformly recommend against using benzodiazepines as first-line treatment for anxiety disorders in older adults [44]; however, benzodiazepines were by far the commonly prescribed PIM (66.4%) in our PD sample. The risks of benzodiazepine use in older adults are well documented and include reduced mobility, decreased ability to drive, cognitive impairment, and increased risk of falls.[45–47] These risks and the associated negative health outcomes may be even greater in persons with underlying PD. Several factors may explain why PD patients are still prescribed benzodiazepines. PD patients may have persistent or resistant anxiety disorders. Competing demands for physician attention and limited time or access to alternative treatments for anxiety, such as cognitive-behavioral therapy, may also result in higher benzodiazepine prescribing. Persons with PD often see multiple clinicians for their PD and non-PD related symptoms/conditions. They may receive benzodiazepines from clinicians without knowledge, experience, or resources to monitor for the harms of or taper these medications. Finally, benzodiazepines are viewed as more useful than alternatives for the treatment of PD-related dystonia and sleep disorders, particularly REM behavior disorder. Our sensitivity analysis suggested that while some benzodiazepine use was short-term, committed PIM use still occurred in at least 50% of individuals with anxiety or anxiety and depression. Future studies should examine longitudinal trends in affective disorder treatment in PD, including the impact of prescription drug monitoring programs on benzodiazepine prescriptions.

Paroxetine, a selective serotonin reuptake inhibitor with high anticholinergic properties, was the most frequently prescribed non-benzodiazepine PIM. Although drugs with high anticholinergic properties are discouraged from use in older adults,[14] the negative impacts of these medications specifically in individuals with PD, who have cholinergic dysfunction at baseline, are just beginning to be studied.[48–50] There are multiple possible explanations for the observed level of paroxetine use. A multi-center randomized controlled trial found paroxetine to be more effective than placebo, and similarly effective to venlafaxine, for depression treatment in PD,[51] although anticholinergic adverse effects were preferentially reported in the paroxetine-treated group. Anxiety is a common non-motor fluctuation symptom, and a manifestation of early cognitive impairment in PD; paroxetine has a clinical indication for mixed anxiety/depression. In spite of these potential benefits, the consistent designation of paroxetine as a Beers Criteria PIM for all older adults, combined with the

possibility that high anticholinergic medications may interfere with acetylcholinesterase inhibitors for the treatment of cognitive impairment highlights the need for additional drug-disease interaction and comparative safety/effectiveness research in PD.

Affective disorders were more common in those diagnosed with dementia. There may be a bidirectional relationship between cognitive impairment and depression in PD.[15] We did also find, in adjusted models, that those with dementia had lower odds of PIM prescriptions in both the anxiety only and comorbid group. The general, decreased likelihood of PIM prescriptions among those with dementia may reflect good adherence to the recommendation against the use of anticholinergics among those with cognitive impairment.[14]

In our study, females were more likely to be diagnosed with an affective disorder. Consistent with our findings, females with PD are known to be more likely to have an affective disorder.[52] Despite a prior study suggesting that males with PD have more negative views about treatment for affective disorders,[21] we found, per standardized differences, inconsistent differences in prescription treatment by sex. Females with depression only, as well as with comorbid depression and anxiety, after adjustment, were slightly more likely to receive PIM prescriptions.

At least one other study has found that females with PD are at greater risk for receiving inappropriate prescriptions.[53] Given the multitude of treatment options, further research is needed to understand why females are not being prescribed more benign treatment options.

A prior study found that geriatricians are less likely to prescribe PIMs.[54] Consequently, our finding that geriatricians less frequently prescribe PIMs for the treatment of depression only and anxiety only is not surprising. Psychiatrists were significantly less likely to prescribe PIMs for those with comorbid affective disorders. No benefit of neurologist prescribing was found; in fact, neurologists were more likely to prescribe PIMs (primarily benzodiazepines) among the anxiety alone group. Again, further study is needed to disentangle benzodiazepine use for anxiety alone (which is potentially inappropriate) versus benzodiazepine use in a patient with multiple motor and non-motor indications (i.e., dystonia, sleep disorders). Studies that quantify the potential harms from short- and long-term benzodiazepine use in persons with PD are needed to support shifts in prescribing practices and modification of PD clinical treatment guidelines.

This study had several strengths, including a large sample that allowed us to produce population-representative estimates of PD care, which does not center around tertiary care centers. However, we were limited in our ability to assess non-medication treatment modalities, such as cognitive-behavioral therapy, in our study. Many of the medications we studied have other off-label and on-label indications, although we attempted to account for this as in the case of antipsychotics and selegiline. PD medications, including dopamine agonists and rasagiline, may have symptomatic benefit for affective disorders in PD.[17] Consequently, we could be over- or under-estimating the treatment prevalence in our study. We also did not examine prescribing patterns among individuals who had depressive or anxiety symptoms or received affective disorder medications, but did not meet study ICD-9

CM diagnostic criteria. Thus, we may have underestimated the total burden of affective disorders in our sample. We also were unable to examine clinical factors that may influence prescribing patterns, such as affective symptoms or severity, motor and cognitive function, previous history of medication response, and patient preference. Although we found several factors to be significantly associated with PIM prescriptions, most associations were reasonably modest; thus the clinical and population-level significance of these initial data remains to be determined. Associations were strongest for prescriber specialty, and future studies will determine whether these associations can be detected in a clinical setting.

Despite these limitations, we present national estimates of affective disorder treatment in PD along with the prevalence and risk factors for PIM receipt. These data add to the growing evidence basis for future updates of clinical guidelines that will approach treatment of PD patients from a drug-disease safety perspective.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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HIGHLIGHTS

Question:

How often are Parkinson's disease (PD) patients with affective disorders treated with guideline-designated potentially inappropriate medications (PIMs), and what factors are related to receipt of PIMs?

Findings:

In this cross-sectional study of Medicare beneficiaries with PD, among those treated for an affective disorder, between 12.8-75.9%, depending on affective disorder diagnosis, received a PIM. Males and those with non-Alzheimer's disease dementia were less likely to receive PIMs; geriatricians were less likely to prescribe PIMs across affective disorder diagnoses.

Meaning:

PIMs are commonly used in the treatment of affective disorders in PD; further research is needed to understand the impact of PIMs, particularly high-potency anticholinergics, on patient outcomes.

Table 1.

Baseline characteristics of 2014 Medicare beneficiaries with Parkinson's disease overall and by affective disorder

	Overall (n=84,323)	Affective Disorder (n=26,188)	No Affective Disorder (58,135)				
Characteristic	**n (%)**	**n (row %)**	**n (row %)**	**Standardized Difference**	**Test Statistic**	**df**	**p-value**
Sex				**−0.309**	**1,709.80**[c]	**1**	**<0.0001**
Male	48,531 (57.6)	12,326 (25.4)	36,205 (74.6)				
Female	35,792 (42.5)	13,862 (38.7)	21,930 (61.3)				
Age Category, in years				0.062	**83.81**[c]	**2**	**<0.0001**
65-74	32,965 (39.1)	10,805 (32.8)	22,160 (67.2)				
75-84	38.872 (46.1)	11,778 (30.3)	27,094 (69.7)				
≥85	12,486 (14.8)	3,605 (28.9)	8,881 (71.1)				
Race				0.064	**119.78**[c]	**2**	**<0.0001**
White	79,543 (94.3)	25,008 (31.4)	54,535 (68.6)				
Black	2,145 (2.5)	452 (21.1)	1,693 (78.9)				
Other	2,635 (3.1)	728 (27.6)	1,907 (72.4)				
Residence				0.029	0.52[c]	2	0.7705
Urban	67,944 (80.6)	21,130 (31.1)	46,814 (68.9)				
Suburban	11,460 (13.6)	3,526 (30.8)	7,934 (69.2)				
Rural	4,919 (5.8)	1,532 (31.1)	3,387 (68.9)				
# of Chronic Conditions[a]**, mean (SD)**	4.1 (2.37)	4.5 (2.47)	3.9 (2.30)	**0.252**	**33.39**[d]	**47,282**	**<0.0001**
Non-AD Dementia				**0.283**	**1,531.45**[c]	**1**	**<0.0001**
Yes	17,173 (20.4)	7,451 (43.4)	9,722 (56.6)				
No	67,150 (79.6)	18,737 (27.9)	48,413 (72.1)				
Psychosis				0.022	**9.60**[c]	**1**	**0.0020**
Yes	99 (0.1)	45 (45.5)	54 (54.6)				
No	84,224 (99.9)	26,143 (31.0)	58,081 (69.0)				
Depression Prescription[b]				**1.304**	**22,880.98**[c]	**1**	**<0.0001**
Yes	31,827 (37.7)	19,737 (62.0)	12,090 (38.0)				
No	52,496 (62.3)	6,451 (12.3)	46,045 (87.7)				
Anxiety Prescription[b]				**1.098**	**17,983.29**[c]	**1**	**<0.0001**
Yes	30,338 (36.0)	18,070 (59.6)	12,268 (40.4)				
No	53,985 (64.0)	8,118 (15.0)	45,867 (85.0)				

[a]Acquired hypothyroidism, acute myocardial infarction, anemia, asthma, atrial fibrillation, benign prostatic hyperplasia, colorectal cancer, endometrial cancer, breast cancer, lung cancer, prostate cancer, cataract, chronic kidney disease, chronic obstructive pulmonary disease, diabetes, glaucoma, heart failure, hip/pelvic fracture, hyperlipidemia, hypertension, ischemic heart disease, osteoporosis, rheumatoid arthritis/osteoarthritis, stroke/transient ischemic attack

[b]At least one prescription, pooled across all affective disorder

[c]Chi-Squared test

[d]Satterthwaite t-test

Table 2.

Characteristics by medication treatment (any treatment versus no treatment), stratified by affective disorder classification

	Depression Only (n=12,703)						Anxiety Only (n=6,322)						Comorbid Depress		
	Depression Treatment						Anxiety Treatment						Affective Disorder[b] Treatment		
	Yes (n=10,253)	No (n=2,450)					Yes (n=3,978)	No (n=2,344)					Yes (n=6,670)	No (n=4 93)	
Characteristic	**n (Row %)**	**n (Row %)**	**Std Diff**	**Test statistic**	**df**	**p-value**	**n (Row %)**	**n (Row %)**	**Std Diff**	**Test statistic**	**df**	**p-value**	**n (Row %)**	**n (Row %)**	**Std Diff**
Sex			−0.121	**28.77**	**1**	**<0.0001**[c]			−0.111	**18.12**[c]	**1**	**<0.0 001**			−0.169
Male	5,258 (78.9)	1,404 (21.1)					1,675 (60.0)	1,116 (40.0)					2,637 (91.8)	236 (8.2)	
Female	4,995 (82.7)	1,046 (17.3)					2,303 (57.9)	1,228 (52.4)					4,033 (94.0)	257 (6.0)	
Age Categor y, in years			**0.140**	**30.63**	**2**	**<0.0001**[c]			0.081	**11.80**[c]	**2**	**0.0027**			0.044
65-74	4,112 (82.2)	889 (17.8)					1,723 (65.3)	916 (34.7)					2,959 (93.5)	206 (6.5)	
75–84	4,669 (80.8)	1,114 (19.2)					1,761 (61.6)	1,096 (38.4)					2,892 (93.1)	216 (7.0)	
≥85	1,442 (76.3)	447 (23.7)					494 (59.8)	332 (40.2)					819 (92.0)	71 (8.0)	
Race			0.085	**20.08**	**2**	**<0.0001**[c]			0.054	**9.17**[c]	**2**	**0.0102**			**0.105**
White	9,800 (81.0)	2,293 (19.0)					3,811 (63.3)	2,206 (36.7)					6,433 (93.3)	465 (6.7)	
Black	173 (70.9)	71 (29.1)					66 (54.6)	55 (45.5)					75 (86.2)	12 (13.8)	
Other	280 (76.5)	86 (23.5)					101 (54.9)	83 (45.1)					162 (91.0)	16 (9.0)	
Residence			0.044	4.27	2	0.1182[c]			0.058	3.69[c]	2	0.1579			0.044
Urban	8,239 (80.5)	1,995 (19.5)					3,130 (62.4)	1,887 (37.6)					5,468 (93.0)	411 (7.0)	
Suburban	1,392 (80.7)	333 (19.3)					600 (65.7)	313 (34.3)					829 (93.4)	59 (6.6)	
Rural	622 (83.6)	122 (16.4)					248 (63.3)	144 (36.7)					373 (94.2)	23 (5.8)	
# of Chronic Conditions[a], mean (SD)	4.4 (2.42)	4.5 (2.46)	−0.026	1.14	3,665.5	0.2557[d]	4.2 (2.41)	4.4 (2.45)	−0.070	**2.67**[a]	**4,860.6**	**0.0076**			−0.008
Non-AD Dementia			0.040	3.13	1	0.0766[c]			−0.070	**7.32**[c]	**1**	**0.0068**			0.008
Yes	2,993 (81.7)	671 (18.3)					852 (59.9)	571 (40.1)					2,203 (93.2)	161 (6.8)	
No	7,260 (80.3)	1,779 (19.7)					3,126 (63.8)	1,773 (36.2)					4,467 (93.1)	332 (6.9)	

	Depression Only (n=12,703)						Anxiety Only (n=6,322)						Comorbid Depress		
	Depression Treatment						Anxiety Treatment						Affective Disorder[b] Treatment		
	Yes (n=10,253)	No (n=2,450)					Yes (n=3,978)	No (n=2,344)					Yes (n=6,670)	No (n=493)	
Characteristic	n (Row %)	n (Row %)	Std Diff	Test statistic	df	p-value	n (Row %)	n (Row %)	Std Diff	Test statistic	df	p-value	n (Row %)	n (Row %)	Std Diff
Psychosis			−0.004	0.2157	1	0.7743[e]			−0.031	0.1025[e]	1	0.2531			0.063
Yes	**	**					**	**					**	**	
No	**	**					**	**					**	**	

Abbreviations: Std Diff, Standardized Difference

[a]Acquired hypothyroidism, acute myocardial infarction, anemia, asthma, atrial fibrillation, benign prostatic hyperplasia, colorectal cancer, endometrial cancer, breast cancer, lung cancer, prostate cancer, cataract, chronic kidney disease, chronic obstructive pulmonary disease, diabetes, glaucoma, heart f ailure, hip/pelvic fracture, hyperlipidemia, hypertension, ischemic heart disease, osteoporosis, rheumatoid arthritis/osteoarthritis, stroke/transient ischemic attack

[b]Treatment with on-label medication for depression OR anxiety

[c]Chi-Squared test

[d]Satterthwaite t-tes

[e]Fisher's exact test

[**]Not displayed due to CMS cell suppression policy

Table 3.

Beneficiary-level characteristics of those treated for an affective disorder, stratified by affective disorder classification and PIM receipt.

	Depression Only (n=10,253)						Anxiety Only (n=3,978)						Comorbid Depressi		
	≥1 PIM (n= 1,314)	No PIM (n=8 , 939)					≥1 PIM (n=3, 020)	No PIM (n=958)					≥1 PIM (n=4, 254)	No PIM (n=2, 416)	
Characteristic	**n (row %)**	**n (row %)**	**Std Diff**	**Test statistic**	**df**	**p-value**	**n (row %)**	**n (row %)**	**Std Diff**	**Test statistic**	**df**	**p-value**	**n (row %)**	**n (row %)**	**Std Diff**
Sex			−0.078	**7.03**[b]	**1**	**0.0080**			−0.032	0.76[b]	1	0.3829			−0.132
Male	629 (12.0)	4,629 (88.0)					1,260 (75.2)	415 (24.8)					1,582 (60.0)	1,055 (40.0)	
Female	685 (13.7)	4,310 (86.3)					1,760 (76.4)	543 (23.6)					2,672 (66.3)	1,361 (33.8)	
Age Category, in years			0.031	3.34[b]	2	0.1879			0.032	0.87[b]	2	0.6462			**0.105**
65-74	544 (13.2)	3,568 (86.8)					1,309 (76.0)	414 (24.0)					1,970 (66.6)	989 (33.4)	
75-84	606 (12.9)	4,093 (87.1)					1,344 (76.3)	417 (23.7)					1,796 (62.1)	1,096 (37.9)	
≥85	164 (11.4)	1,278 (88.6)					367 (74.3)	127 (25.7)					488 (59.6)	331 (40.4)	
Race			0.000	0.53[b]	2	0.7679			0.064	0.22[b]	2	0.8961			0.064
White	1,255 (12.8)	8,545 (87.2)					2,894 (75.9)	917 (24.1)					4,118 (64.0)	2,315 (36.0)	
Black	25 (14.5)	148 (85.6)					51 (77.3)	15 (22.7)					41 (54.7)	34 (45.3)	
Other	34 (12.1)	246 (87.9)					75 (74.3)	26 (25.7)					95 (58.6)	67 (41.4)	
Residenee			0.074	3.70[b]	2	0.1576			0.047	1.38[b]	2	0.5008			0.030
Urban	1,031 (12.5)	7,208 (87.5)					2,375 (75.9)	755 (24.1)					3,473 (63.5)	1,995 (36.5)	
Suburban	192 (13.8)	1,200 (86.2)					463 (77.2)	137 (22.8)					542 (65.4)	287 (34.6)	
Rura1	91 (14.6)	531 (85.4)					182 (73.4)	66 (26.6)					239 (64.1)	134 (35.9)	
# of Chronic Conditions[a], mean (SD)	4.5 (2.44)	4.4 (2.42)	0.059	**1.98**[c]	**1,714.7**	**0.0474**	4.3 (2.43)	4.1 (2.37)	0.076	**2.07**[c]	**1642.4**	**0.0383**	4.8 (2.53)	4.8 (2.58)	−0.014
Non-AD Dementia			−0.015	0.24[b]	1	0.6225			−0.056	2.31[b]	1	0.1285			−0.089
Yes	376 (12.6)	2,617 (87.4)					630 (73.9)	222 (26.1)					1,340 (60.8)	863 (39.2)	
No	938 (12.9)	6,322 (87.1)					2,390 (76.5)	736 (23.5)					2,914 (65.2)	1,553 (34.8)	
Psychosis			−0.024	0.28[d]	1	0.7098			0.017	0.36[d]	1	1.0000			0.011

	Depression Only (n=10,253)						Anxiety Only (n=3,978)						Comorbid Depressi		
	≥1 PIM (n= 1,314)	No PIM (n=8 , 939)					≥1 PIM (n=3, 020)	No PIM (n=958)					≥1 PIM (n=4, 254)	No PIM (n=2, 416)	
Characteristic	n (row %)	n (row %)	Std Diff	Test statistic	df	p-value	n (row %)	n (row %)	Std Diff	Test statistic	df	p-value	n (row %)	n (row %)	Std Diff
Yes	**	**					**	**					**	**	
No	**	**					**	**					**	**	

Abbreviations: Std Diff, Standardized Difference

[a] Acquired hypothyroidism, acute myocardial infarction, anemia, asthma, atrial fibrillation, benign prostatic hyperplasia, colorectal cancer, endometrial cancer, breast cancer, lung cancer, prostate cancer, cataract, chronic kidney disease, chronic obstructive pulmonary disease, diabetes, glaucoma, heart failure, hip/pelvic fracture, hyperlipidemia, hypertension, ischemic heart disease, osteoporosis, rheumatoid arthritis/osteoarthritis, stroke/transient ischemic attack

[b] Chi-Squared test

[c] Satterthwaite t-test

[d] Fisher's Exact t-test

** Not displayed due to CMS cell suppression policy

Table 4.

Generalized estimating equation analysis of factors associated receipt of Potentially Inappropriate Medication (PIM) prescriptions among those treated for an affective disorder, stratified by affective disorder classification

	Depression Only (n=73,880 prescriptions, 9.7% PIMs)		Test statistic[c]	df	p-value	Anxiety Only (n=28,714 prescriptions, 62.6% PIMs)		Test statistic[c]	df	p-value	Comorbid Depression & Anxiety (n=78,873 prescriptions, 37.2% PIMs)		Test statistic[c]	df	p-value
Characteristic	**aOR[a]**	**95% CI**				**aOR[a]**	**95% CI**				**aOR[a]**	**95% CI**			
Sex															
Male	1.00	REF				1.00	REF				1.00	REF			
Female	**1.18**	**(1.04, 1.34)**	**6.87**	**1**	**0.0088**	0.96	(0.85, 1.08)	0.48	1	0.4872	**1.15**	**(1.07, 1.24)**	**13.15**	**1**	**0.0003**
Age Category, in years															
65-74	1.00	REF				1.00	REF				1.00	REF			
75-84	1.00	(0.91, 1.09)	0.00	1	0.9533	1.00	(0.90, 1.10)	0.01	1	0.9318	0.94	(0.88, 1.00)	3.48	1	0.0623
≥85	0.87	(0.73, 1.04)	2.27	1	0.1319	1.12	(0.95, 1.32)	1.74	1	0.1873	**0.85**	**(0.76, 0.94)**	**9.33**	**1**	**0.0023**
Race															
White	1.00	REF				1.00	REF				1.00	REF			
Black	1.12	(0.72, 1.74)	0.24	1	0.6240	1.53	(0.90, 2.60)	2.42	1	0.1199	0.76	(0.52, 1.10)	2.13	1	0.1448
Other	0.99	(0.67, 1.45)	0.01	1	0.9410	0.84	(0.59, 1.19)	0.97	1	0.3241	0.93	(0.72, 1.19)	0.36	1	0.5487
Residence															
Urban	0.87	(0.68, 1.12)	1.17	1	0.2800	1.08	(0.85, 1.38)	0.41	1	0.5222	1.10	(0.95, 1.29)	1.56	1	0.2120
Suburban	1.01	(0.75, 1.34)	0.00	1	0.9720	1.19	(0.90, 1.57)	1.46	1	0.2275	1.19	(0.97, 1.43)	3.71	1	0.0541
Rural	1.00	REF				1.00	REF				1.00	REF			
# of Chronic Conditions[b]	1.01	(0.99, 1.04)	1.20	1	0.2729	**1.03**	**(1.00, 1.05)**	**4.07**	**1**	**0.0436**	1.00	(0.99, 1.02)	0.01	1	0.9120
Non-AD Dementia	0.96	(0.84, 1.11)	0.27	1	0.6044	**0.78**	**(0.68, 0.90)**	**11.39**	**1**	**0.0007**	**0.89**	**(0.83, 0.97)**	**7.78**	**1**	**0.0053**
Prescriber															
Neurologist															
Yes	0.96	(0.75, 1.23)	0.10	1	0.7473	1.08	(0.87, 1.34)	0.44	1	0.5049	**1.21**	**(1.07, 1.38)**	**8.67[c]**	**1**	**0.0032**
No	1.00	REF				1.00	REF				1.00	REF			
Psychiatrist															
Yes	0.79	(0.58, 1.07)	2.35	1	0.1254	0.70	(0.46, 1.05)	2.99	1	0.0836	**0.67**	**(0.60, 0.76)**	**41.06**	**1**	**<0.0001**
No	1.00	REF				1.00	REF				1.00	REF			

	Depression Only (n=73,880 prescriptions, 9.7% PIMs)		Test statistic[c]	df	p-value	Anxiety Only (n=28,714 prescriptions, 62.6% PIMs)		Test statistic[c]	df	p-value	Comorbid Depression & Anxiety (n=78,873 prescriptions, 37.2% PIMs)		Test statistic[c]	df	p-value
Characteristic	**aOR[a]**	**95% CI**				**aOR[a]**	**95% CI**				**aOR[a]**	**95% CI**			
Geriatrician															
Yes	**0.74**	**(0.57, 0.96)**	**5.14**	**1**	**0.0234**	**0.42**	**(0.22, 0.78)**	**7.51**	**1**	**0.0061**	0.75	(0.55, 1.00)	3.76	1	0.0525
No	1.00	REF				1.00	REF				1.00	REF			

[a]Adjusted for sex, time-varying age category, race, residence, # of chronic conditions, non-AD dementia, neurologist prescriber, psychiatrist prescriber, geriatrician prescriber

[b]Acquired hypothyroidism, acute myocardial infarction, anemia, asthma, atrial fibrillation, benign prostatic hyperplasia, colorectal cancer, endometrial cancer, breast cancer, lung cancer, prostate cancer, cataract, chronic kidney disease, chronic obstructive pulmonary disease, diabetes, glaucoma, heart failure, hip/pelvic fracture, hyperlipidemia, hypertension, ischemic heart disease, osteoporosis, rheumatoid arthritis/osteoarthritis, stroke/transient ischemic attack

[c]Chi-squared test