Published in final edited form as:

J Geriatr Psychiatry Neurol. 2007 September ; 20(3): 161–165.

Antidepressant Treatment of Veterans With Parkinson's Disease and Depression:

Analysis of a National Sample

Peijun Chen, MD, MPH, PhD, Helen C. Kales, MD, Daniel Weintraub, MD, Frederic C. Blow, PhD, Lan Jiang, MS, and Alan M. Mellow, MD, PhD

Division of Geriatric Psychiatry, Department of Psychiatry, University of Michigan, Ann Arbor, Michigan (Drs Chen, Kales, Mellow); VA National Serious Mental Illness Treatment Research and Evaluation Center, Ann Arbor, Michigan (Drs Kales, Blow, and Ms Jiang); Geriatric Research Education and Clinical Center, VA Ann Arbor Healthcare System, Ann Arbor, Michigan (Dr Kales); University of Pennsylvania, Department of Psychiatry, Philadelphia VA Medical Center, Parkinson's Disease and Mental Illness Research, Education and Clinical Centers, Philadelphia, Pennsylvania (Dr Weintraub); VISN 11 Mental Health Service Line, Department of Veterans Affairs (Dr Mellow); Department of Psychiatry, Case Western Reserve University, Cleveland VA Medical Center, Cleveland, Ohio (Dr Chen).

Abstract

We examined the impact of comorbid Parkinson's disease (PD) on depression treatment. Using national Veterans Affairs (VA) databases, fiscal year 2002 data were examined for 283 273 elderly males seen for depression. We compared 2 matched depression groups, one with (N = 7868) and one without (N = 7868) PD. In the 12-month period following a depression-related clinic visit, PD and non-PD patients were equally likely to fill an antidepressant prescription (77.8% vs. 77.4%), most commonly for a selective serotonin re-uptake inhibitor (SSRI) (62.9% vs 62.6%). Depressed PD patients had slightly higher rates of newer non-SSRI use (20.6% vs 19.2%, $P < .05$) and lower rates of tricyclic antidepressant use (7.4% vs 8.9%, $P < .001$). The presence of a PD diagnosis appears to have little impact on the frequency and type of antidepressant treatment. Efforts to improve the care of depressed PD patients should focus instead on improving recognition, ensuring adequacy of treatment, and evaluating the efficacy of existing antidepressants.

Keywords

Parkinson's disease; depression; antidepressants

In recent years, depression in primary care settings and the elderly has received increasing attention, and intervention strategies to improve the detection and management of depression in these populations have been studied.¹ In the geriatric population, depression commonly co-occurs with other medical conditions, including neurological disorders. Parkinson's disease (PD), the second most common neurodegenerative disorder after Alzheimer's disease, affects approximately one million persons, and up to 40% of PD patients experience comorbid depression.^{2,3} In addition to the emotional distress produced by depression, its occurrence in PD has been associated with more rapid decline in motor symptoms,⁴ cognitive decline and the development of dementia,⁵ reduced quality of life,⁶ and excess disability.⁷

For the aforementioned reasons, diagnosing and treating depression in PD is important. However, possible barriers to the management of depression in PD include the underreporting and underrecognition of symptoms, patient reluctance to take antidepressants, and provider concerns about the propensity of antidepressants to worsen parkinsonism.

There has been limited study on the use of antidepressants in PD. In a survey of antidepressant use conducted by the Parkinson Study Group, 26% of PD patients were currently taking an antidepressant.⁸ The use of antidepressants was reported in 22% of PD patients in a study using French pharmacovigilance data.⁹ In the only study to directly examine the recognition and treatment of depression in PD, it was reported in a sample of 100 patients at a PD center that 65% of patients diagnosed with major or minor depression using a diagnostic interview were not currently receiving antidepressant treatment, and 47% of those on an antidepressant remained depressed.¹⁰ However, the relatively small sample size and the use of a single PD center in this study do not allow the results to be generalized to the recognition and treatment of PD depression in routine clinical care.

Using data from the Department of Veterans Affairs (VA) National Registry for Depression, the goal of this study was to examine the impact of a diagnosis of PD on the frequency and type of pharmacological treatment for depression in the context of routine clinical care. Given potential concerns of both providers (eg, possible worsening of parkinsonism) and patients (eg, reluctance to take another medication) regarding antidepressant use in PD, we hypothesized that the presence of PD would lead to less frequent treatment of depression in this population.

METHODS

Data were derived from VA national databases for patients seen in fiscal year 2002. Pharmacological data were collected from patients who filled at least one antidepressant prescription within 12 months of a clinical visit for depression. Medications considered antidepressants for the purposes of this study were amitriptyline, desipramine, doxepin, imipramine, clomipramine, nortriptyline, phenelzine, tranylcypromine, citalopram, fluoxetine, paroxetine, sertraline, fluvoxamine, bupropion, nefazodone, venlafaxine, and mirtazapine.

Subjects with PD were identified using the following ICD9CM codes: idiopathic PD (332.0), other degenerative diseases of the basal ganglia (333.0), and unspecified extrapyramidal disease (333.90). The latter 2 diagnoses, which accounted for only 3% of our PD sample, were included as part of an inclusive approach to diagnostic criteria, given the diagnostic imprecision commonly seen in primary care settings in VA medical centers. Abnormal involuntary movements (781.0) and secondary parkinsonism due to drugs (332.1) were not included. In the VA database registry, there were a total of 43 383 subjects with a diagnosis of PD as defined above. As our focus of this paper is on older adults, the subjects aged 54 or younger ($n = 1637$) were excluded from our analyses. Of these age 55 and older ($n = 41\,746$), the overwhelming majority ($n = 41\,191$, or 99% of sample) of patients were males, thus we restricted our analyses to this group.

As in other studies examining depression in nonpsychiatric settings,^{11,12} subjects with depression were identified using ICD9CM codes for major depressive disorder (296.2x and 296.3x); dysthymia (300.4); depressive disorder, not otherwise specified (311); mood disorder, not otherwise specified (296.90); and mood disorder resulting from a general medical condition (293.83). In the VA database registry, we searched the registry for male patients aged 55 and older seen at any clinic visit in which depression as defined above was coded as a diagnosis in fiscal year 2002 ($N = 283\,273$). There were 7939 subjects with diagnoses of both PD and depression.

To control for confounders that might affect treatment of depression in older patients, depressed patients without PD (group B) were randomly selected to match (1:1) depressed patients with PD (group A) on age (± 5 years) and major comorbid psychiatric and medical disorders (ie, psychosis, dementia, cerebrovascular accident [CVA], congestive heart failure [CHF], diabetes, and chronic obstructive pulmonary disease [COPD]). Matching on these variables, 7868 out of 7939 (99% of sample of depressed PD patients) Group A patients were matched to 7868 subjects in group B. Subsequent to generating the matched groups, between-group comparisons in the frequency and type of antidepressant prescribed were made using Pearson's chi-square test for categorical data and Student *t* tests for continuous variables.

RESULTS

Characteristics of Depressed Patients by Presence of PD

Table 1 lists the age distribution and the type of depression for PD and non-PD patients. In the unmatched samples, depressed patients with PD were significantly older than their non-PD counterparts (mean $\pm$ SD: 74.4 ± 7.8 vs 67.9 ± 9.4 , $P < .001$). In addition, major depression was significantly less frequent, and minor depression more common, in PD patients than in the non-PD sample.

Impact of Age on Frequency of Comorbid PD in Depression

Figure 1 shows the frequency of PD in older subjects with a diagnosis of depression. It demonstrates that the likelihood of a depressed patient having comorbid PD increased with increasing age ($P < .001$). Although PD was present as a comorbid condition in less than 1% of all older depressed patients, approximately 3% of depressed patients between the ages of 65 and 74 and over 5% of patients over 75 years of age had a concurrent diagnosis of PD.

Frequency of Antidepressant Prescribing by Presence of PD

Depressed patients with and without PD were equally likely to fill an antidepressant prescription at least once in the 12 months following a visit for depression (77.8% vs 77.4%, $P > .1$). Patients with PD filled a slightly higher mean total number of antidepressant prescriptions during this time period (mean $\pm$ SD: 2.50 ± 2.33 vs 2.37 ± 2.22 , $P < .001$).

Patterns of Antidepressant Use by Presence of PD

Of antidepressant prescriptions filled by patients with a diagnosis of depression, almost two thirds were for selective serotonin re-uptake inhibitors (SSRIs) in both the PD and non-PD groups (Table 2). The most commonly prescribed non-SSRI antidepressants were bupropion, venlafaxine, mirtazapine, and tricyclic antidepressants (TCAs). Depressed PD patients were significantly more likely to be treated with venlafaxine and mirtazapine, and less likely to be treated with a TCA, than depressed patients without PD.

DISCUSSION

Contrary to our hypothesis, we found that the frequency and patterns of antidepressant prescribing for depressed patients with and without PD were similar, which is surprising given anecdotal experience that there are ongoing concerns among both clinicians and patients about the use of antidepressants in PD. These findings reflecting current VA clinical practice are supported by recent research suggesting that antidepressant treatment is safe and overall well-tolerated in PD. Specifically, a recent review and meta-analysis of antidepressant studies found that over 85% of PD patients enrolled in treatment studies were able to tolerate antidepressant treatment.¹³ In addition, concerns about the possible occurrence of serotonin syndrome in patients taking anti-Parkinson monoamine oxidase B inhibitor drugs (MAO B, eg, selegiline

or rasagiline), together with an SSRI have been somewhat allayed by a large survey of clinicians, which found very low occurrence rates of both possible (0.24% [11/4568]) and definitive (0.04% [2/4568]) serotonin syndrome with this combination of medications.¹⁴ Nevertheless, caution is advised when combining an MAO B inhibitor and a SSRI or a tricyclic antidepressant.¹⁵

Our findings suggest that once depression is diagnosed in PD, the frequency and type of pharmacological treatment is not different from that received by elderly depressed patients without PD. Thus underrecognition, not patient or clinician concerns about antidepressant treatment, may be the main reason that a significant percentage of depressed PD patients do not receive pharmacological treatment for depression. Therefore, future interventions should strive to improve depression screening and diagnosis.

Regarding specific antidepressant use, in the decade prior to the collection of our data a substantial percentage of depressed PD patients were treated with a TCA.⁸ However, about two-thirds of depressed PD patients in our sample were prescribed an SSRI, suggesting that prescribing trends for PD have mirrored trends for the treatment of depression in general (ie, the shift from the use of non-SSRI antidepressants to the use of predominantly SSRIs).

The only statistically significant differences between the 2 groups in terms of antidepressant treatment were that PD patients were slightly less likely to take a TCA, and slightly more likely to take either venlafaxine or mirtazapine. The use of TCAs in PD is somewhat controversial, as their anticholinergic properties can improve motor symptoms but worsen autonomic symptoms and cognitive impairment, both of which are common in PD. Neither mirtazapine nor venlafaxine has been well studied in PD, but both affect multiple neurotransmitter systems, and there is evidence of both serotonergic and noradrenergic impairment in PD.^{3,16}

It is important to state that although PD patients seen for depression were in general receiving similar treatment to that of depressed elderly patients without PD, this does not mean that the care being provided was optimal. For instance, the efficacy of SSRIs for depression in PD has not been established, and it is possible that they are not as effective in this population as in non-PD patients.¹³ In addition, there is evidence that once treatment for depression is initiated in PD, patients receive only a single antidepressant trial at submaximal dosages, even in the face of persistent depression.¹⁷ Therefore, clinical and research efforts should focus on optimizing treatment strategies for depressed PD patients who do not respond to an initial trial of an SSRI at a low to moderate dose.

Our study also revealed that with advancing age, PD is increasingly likely to be a comorbid condition in patients with depression; in our sample, PD was present in over 5% of depression cases in patients aged 75 years and older. This finding likely reflects the fact that increasing age is the primary risk factor for the development of PD. Regardless, it is important that clinicians are aware of the possibility of a comorbid PD diagnosis when formulating treatment strategies for depression in the elderly.

Our results should be interpreted with caution, given that all patients studied were male veterans. Thus, the findings cannot be generalized to nonveterans or females. Other limitations include the retrospective nature of the study and certain constraints imposed by the registry data that were used. For instance, we were not able to assess the accuracy of diagnoses or the use of antidepressants for purposes other than depression (eg, insomnia and chronic pain). Clearly, PD or non-PD patients with unrecognized depression cannot be identified using registry data, and because of diagnostic overlap, PD patients may be somewhat more likely than non-PD patients to have unrecognized depression. Finally, we were not able to assess antidepressant adherence, only whether a prescription was filled.

Our primary finding that a Parkinson's disease diagnosis had minimal impact on the frequency and type of antidepressant treatment is important. Given that previous research suggests underrecognition and suboptimal treatment of depression in PD, future clinical interventions and research in this population should target depression screening and diagnosis, as well as establish the efficacy of different antidepressants and other depression treatment strategies in this population.

Acknowledgements

This research was supported by the Rachel Upjohn Clinical Scholar Program from the University of Michigan Department of Psychiatry to Dr Chen and by a VA HSRD Career Development Award to Dr Kales. This paper was presented in part at the 18th annual meeting of the American Association for Geriatric Psychiatry, March 2005, San Diego, California.

References

1. Gilbody S, Whitty P, Grimshaw J, Thomas R. Educational and organizational interventions to improve the management of depression in primary care: a systematic review. *JAMA* 2003;289:3145–3151. [PubMed: 12813120]
2. Slaughter JR, Slaughter KA, Nichols D, Holmes SE, Martens MP. Prevalence, Clinical manifestations, etiology, and treatment of depression in Parkinson's Disease. *J Neuropsychiatry Clin Neurosci* 2001;13:187–196. [PubMed: 11449025]
3. Cummings JL. Depression and Parkinson's disease: A review. *Am J Psychiatry* 1992;149:443–454. [PubMed: 1372794]
4. Starkstein SE, Mayberg HS, Leiguarda R, Preziosi TJ, Robinson RG. A prospective longitudinal study of depression, cognitive decline, and physical impairments in patients with Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1992;55:377–382. [PubMed: 1602311]
5. Marder K, Tang M-X, Cote L, et al. The frequency and associated risk factors for dementia in patients with Parkinson's disease. *Arch Neurol* 1995;52:695–701. [PubMed: 7619026]
6. Kuopio AM, Marttila RJ, Helenius H, Toivonen M, Rinne UK. The quality of life in Parkinson's disease. *Mov Disord* 2000;15:216–223. [PubMed: 10752569]
7. Weintraub D, Moberg PJ, Duda JE, et al. Impact of psychiatric and other non-motor symptoms on disability in Parkinson's disease. *J Am Geriatr Soc* 2004;52:784–788. [PubMed: 15086662]
8. Richard IH, Kurlan R. A survey of antidepressant drug use in Parkinson's disease. *Parkinson Study Group. Neurology* 1997;49:1168–1170.
9. Gony M, Lapeyre-Mestre M, Montastruc JL. French Network of Regional Pharmacovigilance Centers. Risk of serious extrapyramidal symptoms in patients with Parkinson's disease receiving antidepressant drugs: a pharmacoepidemiologic study comparing serotonin reuptake inhibitors and other antidepressant drugs. *Clinical Neuropharmacology* 2003;26:142–145. [PubMed: 12782916]
10. Weintraub D, Moberg PJ, Duda JE, Katz IR, Stern MB. Recognition and treatment of depression in Parkinson's disease. *J Geriatr Psychiatry Neurol* 2003;16:178–183. [PubMed: 12967062]
11. Alexopoulos GS, Katz IR, Bruce ML, et al. Remission in depressed geriatric primary care patients: a report from the PROSPECT study. *Am J Psychiatry* 2005;162:718–724. [PubMed: 15800144]
12. Unutzer J, Katon W, Callahan CM, et al. Collaborative care management of late-life depression in the primary care setting: a randomized controlled trial. *JAMA* 2002;288:2836–2845. [PubMed: 12472325]
13. Weintraub D, Morales KH, Moberg PJ, et al. Antidepressant studies in Parkinson's disease: a review and meta-analysis. *Mov Disord* 2005;20:1161–1169. [PubMed: 15954137]
14. Richard IH, Kurlan R, Tanner C, et al. Serotonin syndrome and the combined use of deprenyl and an antidepressant in Parkinson's disease. *Neurology* 1997;48:1070–1077. [PubMed: 9109902]
15. Eldepryl® Data Sheet. Douglas Pharmaceuticals, Ltd Lincoln, Auckland New Zealand Available at: <http://www.medsafe.govt.nz/Profs/Datasheet/e/Eldepryltab.htm> Accessed August 8, 2006
16. Mayeux R, Stern Y, Sano M, et al. The relationship of serotonin to depression in Parkinson's disease. *Mov Disord* 1998;3:237–244. [PubMed: 2461509]

17. Weilburg JB, O'Leary KM, Meigs JB, Hennen J, Stafford RS. Evaluation of the Adequacy of Outpatient Antidepressant Treatment. *Psychiatr Serv* 2003;54:1233–1239. [PubMed: 12954939]

Figure 1.
Frequency of Parkinson's Disease (PD) in subjects with diagnosis of depression.

Table 1
Age Distribution and Type of Depression by Diagnosis of Parkinson's Disease (PD)

	Depression With PD N = 7939		Depression Without PD* N = 275 334	
	n	%	n	%
Age, y				
55-59	521	6.56	78 773	28.61
60-64	490	6.17	38 682	14.05
65-69	897	11.30	37 996	13.80
70-74	1508	18.99	40 213	14.61
75-79	2311	29.11	43 398	15.76
80+	2212	27.86	36 272	13.17
Type of depression				
Major depression	1812	22.8	77 682	28.2
Nonmajor depression	6127	77.2	197 652	71.8

* P values < .001 for between-group comparisons in age and in type of depression.

Table 2

Type of Antidepressant Prescribed by Diagnosis of Parkinson's Disease (PD)*

Antidepressants	Depression With PD N=7868		Depression Without PD N=7868*		χ^2 value	P value
	n	%	n	%		
Amitriptyline	281	3.57	360	4.58	10.15	.001
Desipramine	25	0.32	28	0.36	0.17	.680
Doxepin	77	0.98	130	1.65	13.75	.001
Imipramine	45	0.57	43	0.55	0.05	.831
Clomipramine	10	0.13	13	0.17	0.39	.531
Nortriptyline	159	2.02	151	1.92	0.21	.646
AnyTCA	584	7.42	702	8.92	11.79	.001
Phenelzine	3	0.04	6	0.08	1.00	.317
Tranylcypromine	1	0.01	2	0.03	0.33	.564
Any MAOI	4	0.05	8	0.10	1.33	.248
Citalopram	1555	19.76	1513	19.23	0.71	.398
Fluoxetine	756	9.61	772	9.81	0.19	.667
Paroxetine	995	12.65	997	12.67	0.00	.962
Sertraline	2038	25.90	2009	25.53	0.28	.597
Fluvoxamine	17	0.22	15	0.19	0.13	.723
Any SSRI	4950	62.91	4923	62.57	0.20	.656
Bupropion	535	6.80	580	7.37	1.95	.162
Nefazodone	142	1.80	170	2.16	2.56	.109
Venlafaxine	536	6.81	437	5.55	10.74	.001
Mirtazapine	585	7.44	494	6.28	8.24	.004
Any other antidepressant	1623	20.63	1514	19.24	4.73	.030

Note: TCA, tricyclic antidepressant; MAOI, monoamine oxidase inhibitor; SSRI, selective serotonin re-uptake inhibitor.

* Prescriptions filled over 12 months following a clinical visit for depression in fiscal year 2002. The 2 groups were matched for age and comorbid psychiatric and medical conditions.