Depression is common in Parkinson’s disease (PD), and a recent analysis of existing research estimated the prevalence of major depression to be 25% and that of all depression types combined to be 42%.1

Although reported to be common, recent research suggests that depressive symptoms in PD are underrecognized in clinical practice,2 perhaps partly due to the many questions that remain concerning the diagnosis of depression in PD. For example, the validity of standard diagnostic criteria in this population is uncertain, as symptom overlap exists between core PD and depression symptoms (eg, psychomotor retardation, fatigue, and insomnia).3-5 In addition, depression is commonly comorbid with other nonmotor symptoms, including anxiety, apathy, and executive dysfunction, any of which may either be a component of or a confounder of depression.6-8 Finally, more recent research has suggested that minor forms of depression are more common than major depression in this population.9

Given the high frequency of depression reported in PD, the lack of controlled antidepressant studies in this population is striking. The most recent analysis of antidepressant studies in PD found only 12 controlled studies of treatment efficacy, and all were thought to have significant methodological flaws.10 Almost all of these studies tested the effects of selegiline, tricyclic antidepressants (TCAs), or bupropion on depressive symptoms, although they were designed primarily to measure changes in motor symptoms instead of depression severity. One placebo-controlled antidepressant study did find that nortriptyline was superior to placebo.11

Selective serotonin reuptake inhibitors (SSRIs) and other newer antidepressants have become first-line antidepressants in general practice, yet there has only been...
1 placebo-controlled study testing their efficacy in PD.12 This small study found no difference between citalopram and placebo for major depression, and only 31% of completers in the citalopram group were considered treatment responders. Although there have been numerous case series reporting that newer antidepressant agents improve depression and are well tolerated in this population, mean decreases in depression rating scales have been between 27% and 50%, lower than that usually reported in open-label studies.13-18 In addition, concerns still exist that newer antidepressants can exacerbate parkinsonism.19

In addition to the absence of controlled antidepressant studies in PD, little is known about the characteristics of antidepressant use in clinical practice. A previous survey of 49 (response rate = 70%) Parkinson Study Group investigators, conducted more than 5 years ago, found that 26% of PD patients were currently being treated with an antidepressant. Of those, 51% were on an SSRI, 41% were taking a TCA, and 8% were taking other (unspecified) agents. Although the most common reasons given for selecting an SSRI were their superior side-effect profile and perceived greater efficacy, 43% of investigators were concerned that SSRIs might worsen motor function. The most commonly prescribed SSRIs (in order of decreasing frequency) were sertraline, paroxetine, fluoxetine, and fluvoxamine, and the majority of patients received antidepressant trials ≥ 6 months in duration.20

A MEDLINE search at the time of this article submission did not produce any more recent articles documenting the recognition and treatment of depression in PD. Herein, we report on the frequency of depression and the characteristics of depression treatment in a convenience sample of PD patients who were assessed as part of an ongoing study at a movement disorders center.

METHOD

Subjects
The study sample consisted of 100 outpatients—99 males and 1 female—with idiopathic PD at the Parkinson’s Disease Research, Education and Clinical Center (PADRECC) at the Philadelphia Veterans Affairs Medical Center (PVAMC). They were participants in an ongoing study assessing depression and possible correlates of depression in PD. The institutional review boards at the PVAMC and the University of Pennsylvania approved the study, and only patients able to provide their own informed consent were included. Subjects were a convenience sample of new or established clinic patients, were approached or referred for evaluation for the aforementioned study, and were not selected on the basis of any clinical features or as part of routine psychiatric care. A diagnosis of “possible” or “probable” PD was rendered by a movement disorders specialist based on established guidelines.21

Procedures

General
A research psychiatrist (DW) or trained research assistant administered clinician-rated psychiatric instruments. Neurological, cognitive, and functional assessments were completed or supervised by a neurology attending physician with expertise in PD. All assessments were completed at the same time, the exceptions being that neurological and cognitive examinations completed within 3 months of the psychiatric assessment were allowed if there had been no reported change in PD pharmacotherapy or clinical status in the interim (in which case, the assessments were repeated as part of routine clinical care to be concurrent with the psychiatric assessment). PADRECC patients routinely provide the following information: age, gender, duration of PD, and side predominance of PD symptoms. Subjects were asked about current medication use, and antidepressant use was defined as taking an FDA-approved antidepressant for the treatment of depressive symptoms. Additional information about history of psychiatric treatment for antidepressant users was obtained during a separate telephone call, which occurred up to 1 year after the patient’s initial study assessment. These subjects were queried about psychiatric treatment prior to and since being diagnosed with PD, and currently, including specifics about antidepressant treatment (starting dosage, maximum dosage, and total duration of treatment), use of adjunctive psychotropic medication (eg, benzodiazepines), engagement in psychosocial treatment (eg, psychotherapy), and attendance at support groups. Adequacy of dosage and duration of antidepressant treatment was based on the recommendations of experts in late-life depression.22

Psychiatric and Other Nonmotor Assessments
The Geriatric Depression Scale–Short Form (GDS-SF)23 is a 15-item (range = 0-15, higher scores indicating greater depression severity) self-report or clinician-administered depression-screening questionnaire. A GDS-SF cutoff of ≥ 5, which has demonstrated good sensitivity and specificity for a diagnosis of major depression in primary care,24 was used to indicate clinically significant depression.

The Hamilton Depression Rating Scale–24 Item (HDRS),25 which has demonstrated validity in PD,26 was added after study initiation as part of an expanded assessment battery to provide a measure of depression severity. In conjunction with the HDRS, subjects were interviewed with the depression module of the Structured Clinical Interview for DSM-IV (SCID),27 and subjects were given a DSM-IV diagnosis of no depressive disorder, major depression, or minor depression (minor depression or dysthymia). An inclusive scoring approach (ie, counting items irrespective of presumed etiology) was used for the HDRS and SCID.
The presence of psychosis was determined by asking subjects about current visual/auditory perceptual disturbances or delusions. Global cognitive status was assessed with the Mini-Mental State Examination (MMSE). The Epworth Sleepiness Scale (ESS) is an 8-item (range = 0-24, higher scores indicating greater somnolence) scale measuring daytime sleepiness. The Apathy Scale is a 14-item (range = 0-42, higher scores indicating greater apathy) instrument that was developed specifically to assess apathy in PD.

As the HDRS and SCID were not administered at the initiation of the study, a subset (77.0% [77/100]) of patients was assessed with these instruments. MMSE scores were available for 92% (92/100) of subjects.

Neurological Assessments

An attending neurologist at the PADRECC (either MBS or JED) reviewed a patient’s history and conducted a neurological examination. Severity of PD was assessed with Unified Parkinson’s Disease Rating Scale (UPDRS) (range = 0-108) and the Hoehn and Yahr Scale (range 0-5, higher scores indicating greater overall PD severity). Function was assessed with the Schwab and England Activities of Daily Living (ADL) Scale.

Statistical Analysis

All statistical procedures were performed with SPSS 11.0 for Windows. Categorical variables were compared using the chi-square statistic. Student’s t test was used to compare means, and Levene’s test for equality of variances was used. P < .05 was considered to be significant for all analyses.

RESULTS

Subject Characteristics

Mean (SD) values for all subjects were as follows: age = 72.7 years (7.8), MMSE score = 27.1 (2.7), Apathy Scale score = 14.4 (6.1), ESS score = 10.1 (5.1), duration of PD = 7.5 years (5.5), UPDRS total motor score = 25.8 (12.3), Hoehn and Yahr stage = 2.4 (0.7), and Schwab and England ADL score = 76.6% (15.4). Thus, on average, subjects had mild, bilateral PD with little global cognitive impairment but significant apathy and daytime sleepiness. Forty-six percent (46/100) had predominately right-sided PD symptoms. Approximately one fifth (21.0% [21/100]) of study participants reported current psychotic symptoms.

Current Depression

Forty-two percent of subjects screened positive for clinically significant depression (ie, GDS-SF ≥ 5), and 33.8% interviewed with the SCID met criteria for a depressive disorder. The latter group consisted of 20.8% with major depression and 13.0% with minor depression. Mean (SD) HDRS scores based on DSM-IV diagnoses were as follows: no depression 6.1 (3.9), minor depression 12.8 (4.9), and major depression 19.2 (5.7).

Current Antidepressant Use

At the time of assessment, 23.0% (23/100) of subjects were currently being treated with an antidepressant. Two thirds (69.6%) were taking an SSRI, either sertraline (n = 6), citalopram (n = 6), or paroxetine (n = 4). Other prescribed antidepressants were bupropion (n = 2), venlafaxine (n = 2), mirtazapine (n = 2), and nefazodone (n = 1). No subjects were taking a TCA or selegiline for depression.

At follow-up, nearly all antidepressant users (91.3% [21/23]) remained on an antidepressant. Again, the overwhelming majority (71.4%) were taking an SSRI, either sertraline (n = 6), citalopram (n = 6), or paroxetine (n = 3). Other antidepressants at follow-up were bupropion (n = 2), venlafaxine (n = 2), and mirtazapine (n = 2).

Current Depression and Antidepressant Status

Examining subjects by depression status, 65.4% (17/26) of subjects meeting criteria for a depressive disorder were not currently receiving antidepressant treatment, including 56.3% of those with major depression. There were no differences on demographic or clinical variables between this group and subjects treated with an antidepressant.

Of those subjects currently taking an antidepressant, 47.4% (9/19) still met DSM-IV criteria for a depressive disorder, most (7/9) of whom were diagnosed with major depression. Among antidepressant users, there were no differences between those currently meeting criteria for a depressive disorder and nondepressed subjects on any demographic or clinical factors, psychosis excepted. Antidepressant users who still met criteria for a depressive disorder were more likely to have psychotic symptoms than treated patients without depression were (χ² = 4.6, df = 1, P < .05) (see Table 1).

Correlates of Antidepressant Use

Subjects treated with an antidepressant had higher GDS-SF, but not HDRS scores, and were more likely to have a diagnosis of major depression than untreated patients were. There were no differences between subjects treated with and those not treated with an antidepressant in terms of age, MMSE score, duration of PD, Schwab and England ADL score, UPDRS total motor score, Hoehn and Yahr stage, side predominance of PD, Apathy Scale Score, ESS Score, or presence of psychotic symptoms (see Table 2).

Adequacy of Antidepressant Treatment

A determination of duration of antidepressant treatment was not made at the time of initial assessment, but antidepressant dosages were recorded. Almost all (91.3%) subjects were receiving an antidepressant dosage within the recommended range, and 13.0% were at a dosage within
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the highest recommended range. Few subjects meeting criteria for a depressive disorder in spite of antidepressant treatment had received either an antidepressant dosage within the highest recommended range (11.1%) or more than one antidepressant trial (33.3%) at the time of initial assessment.

At follow-up, mean (SD; median) total duration of antidepressant treatment was 106.9 (104.7; 60) weeks. At that point, antidepressants had been prescribed for at least 9 weeks at a dosage within the recommended range in almost all (87.0%) subjects and at a dosage within the highest recommended range in 30.4%.

**Concurrent Treatment**
Approximately one quarter of antidepressant users (26.0%) were concurrently taking a benzodiazepine for anxiety. Two subjects (8.7%) were engaged in psychotherapy for the treatment of depression, and an additional 2 (8.7%) were attending a PD support group.

**Prior Psychiatric Treatment**
More than one third (34.8%) of subjects taking an antidepressant had received antidepressant treatment prior to being diagnosed with PD. Since being diagnosed with PD, three quarters (78.3%) had received 1 antidepressant trial, 13.0% had received 2 antidepressant trials, and 8.7% had been on a total of 3 or more antidepressants. Six subjects (26.0%) had engaged in psychotherapy since being diagnosed with PD, and 4 others (17.4%) had engaged in psychotherapy and attended a support group at one point.

**DISCUSSION**
This study estimated the frequency of depression and characteristics of antidepressant use for PD patients evaluated at a movement disorders center. We found a high frequency of depression in our population, which is consistent with previous epidemiological research for PD conducted in clinical settings.1

Also consistent with a previous report, we found that there is a high frequency of antidepressant use in PD, at least among patients seen in specialty care settings. Twenty-three percent of assessed patients were taking an antidepressant, which is similar to the 26% reported more than 5 years ago in a survey of practicing academic neurologists.20

The most notable change compared with the previous survey is the change in type of antidepressant currently being prescribed. We found that SSRIs were being prescribed in more than two thirds of patients, compared with approximately one half previously. Almost all of our subjects were taking an SSRI or other newer antidepressant, whereas almost half of patients were taking a TCA a little more than 5 years ago. This mirrors changes in antidepressant prescribing in general, although there is no controlled clinical research on efficacy or tolerability to support the use of newer antidepressants as first-line agents in PD. Finally, unlike previously, no one was currently taking fluoxetine or fluvoxamine, both of which have significant drug-drug interactions and are not routinely recommended for use in older patients with comorbid conditions.22

It was striking that of antidepressant users, approximately one half met criteria for a depressive disorder. Discounting minor forms of depression, for which antidepressant treatment benefits are less clear, 37% of subjects on an antidepressant still met criteria for major depression in spite of treatment. This finding suggests that a significant percentage of PD patients either do not receive optimal treatment for depression or do not respond to 1 or more trials of pharmacotherapy. Although the available data did not allow us to determine adequacy of antidepressant treatment, the majority of treated patients

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**Table 1. Current Depression and Antidepressant Status**

<table>
<thead>
<tr>
<th>Current Depression (n = 26)</th>
<th>No Current Depression (n = 51)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current antidepressant treatment</td>
<td>9</td>
</tr>
<tr>
<td>No current antidepressant treatment</td>
<td>17</td>
</tr>
</tbody>
</table>

Includes only patients interviewed with the Structured Clinical Interview for DSM-IV (n = 77).

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**Table 2. Demographic and Clinical Characteristics of Subjects by Current Antidepressant Status**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Currently on Antidepressant (n = 23)</th>
<th>Not Currently on Antidepressant (n = 77)</th>
<th>χ² or t Test (df)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>72.3 (8.8)</td>
<td>72.1 (7.4)</td>
<td>−0.1 (98)</td>
<td>.91</td>
</tr>
<tr>
<td>MMSE score</td>
<td>26.8 (2.9)</td>
<td>27.2 (2.6)</td>
<td>0.6 (92)</td>
<td>.56</td>
</tr>
<tr>
<td>Duration of Parkinson’s disease (years)</td>
<td>6.9 (5.2)</td>
<td>7.7 (5.7)</td>
<td>0.6 (98)</td>
<td>.55</td>
</tr>
<tr>
<td>ADL score (mean % [SD])</td>
<td>72.6 (20.0)</td>
<td>77.7 (13.6)</td>
<td>1.1 (28.3)</td>
<td>.26</td>
</tr>
<tr>
<td>UPDRS motor score</td>
<td>22.7 (13.7)</td>
<td>26.4 (11.8)</td>
<td>1.4 (98)</td>
<td>.18</td>
</tr>
<tr>
<td>Hoehn and Yahr stage</td>
<td>2.6 (0.6)</td>
<td>2.3 (0.7)</td>
<td>−1.6 (98)</td>
<td>.10</td>
</tr>
<tr>
<td>Overall predominance (% right-sided)</td>
<td>39.1</td>
<td>48.1</td>
<td>1.3 (2)</td>
<td>.52</td>
</tr>
<tr>
<td>Apathy Scale score</td>
<td>14.7 (5.9)</td>
<td>14.3 (6.1)</td>
<td>−0.3 (98)</td>
<td>.76</td>
</tr>
<tr>
<td>ESS score</td>
<td>10.6 (5.1)</td>
<td>10.0 (5.1)</td>
<td>−0.5 (98)</td>
<td>.59</td>
</tr>
<tr>
<td>Presence of psychosis (% yes)</td>
<td>26.1</td>
<td>19.5</td>
<td>0.5 (1)</td>
<td>.50</td>
</tr>
<tr>
<td>GDS score</td>
<td>5.9 (3.8)</td>
<td>4.1 (3.2)</td>
<td>−2.2 (98)</td>
<td>.03</td>
</tr>
<tr>
<td>HDRS score</td>
<td>11.6 (79)</td>
<td>9.1 (6.5)</td>
<td>−1.4 (75)</td>
<td>.17</td>
</tr>
<tr>
<td>DSM-IV any depression diagnosis (% yes)</td>
<td>47.4</td>
<td>29.3</td>
<td>2.1 (1)</td>
<td>.15</td>
</tr>
<tr>
<td>DSM-IV major depression diagnosis (% yes)</td>
<td>36.8</td>
<td>18.4</td>
<td>4.0 (1)</td>
<td>.05</td>
</tr>
</tbody>
</table>
had received only 1 antidepressant trial since being diagnosed with PD, including two thirds of those currently meeting criteria for a depressive episode. In addition, only 1 subject with depression in spite of treatment had received an antidepressant dosage within the highest recommended range, although our data did not allow us to determine if poor tolerability prevented the use of maximum dosages in other subjects.

Thus, nearly all persistently depressed subjects had received an adequate dosage of 1 antidepressant but had not been provided recommended treatment for resistant or partially responsive depression, which typically consists of maximizing antidepressant dosages, antidepressant augmentation (with pharmacotherapy or psychotherapy), or switching antidepressants.\(^\text{22,28}\) For instance, we recently reported that extending an SSRI trial and increasing the dosage to the maximum recommended offered benefit to some frail, elderly patients who did not respond to an acute trial at a moderate dosage.\(^\text{39}\)

On the other hand, approximately two thirds of subjects meeting diagnostic criteria for a depressive disorder were not currently receiving any antidepressant treatment. This is consistent with recent research reporting a low recognition of depressive symptoms in PD\(^\text{2}\) and suggests that a significant proportion of depressed PD patients are undiagnosed and untreated. However, there were no demographic or clinical correlates to help identify this group of patients.

Approximately one quarter of antidepressant users were also taking a benzodiazepine for anxiety, compared with 10.4% of subjects not currently on an antidepressant. Although this combination of psychotropic medication is understandable given the high comorbidity of depression and anxiety in PD, the possible negative impact of benzodiazepines on cognition, alertness, and gait call into question the safety of using these medications in PD.

Few subjects on an antidepressant were receiving a combination of pharmacotherapy and psychotherapy or support through attendance at a PD group. Given the lack of evidence for antidepressant efficacy in PD and the psychological impact of this illness, it is surprising that so few patients were incorporating psychosocial treatment or support.

The lack of a correlation between any demographic or clinical characteristics and antidepressant use suggests that depression is being diagnosed and treated in a broad range of PD patients. Current psychosis distinguished current antidepressant users with a depression diagnosis from those without depression, and examination of the entire sample found that patients with psychosis had higher HDRS scores (14.8 vs 8.5, \(t = –3.4, df = 75, P < .01\)) and were more likely to have a diagnosis of any depressive disorder (\(\chi^2 = 9.0, df = 1, P < .01\)) than were subjects without psychosis. These findings suggest that there is an association between psychosis and depression in PD and that the presence of psychosis may be associated with a poorer antidepressant response.

Approximately one third of subjects being treated with an antidepressant had received antidepressant treatment prior to being diagnosed with PD. Although we did not have a control group of non-PD elderly patients taking an antidepressant for comparison, the large number of treated patients with a pre-PD history of depression calls to mind recent research suggesting that depression may be a risk factor for or a prodromal phase of PD.\(^\text{40-42}\)

A limitation of this study was its use of a nonrandom, almost entirely male, veterans’ sample at a movement disorders center, limiting the generalizability of our findings. However, existing research does not support an association between gender and depression in PD.\(^\text{9,42}\) In addition, although our sample may have been biased toward patients with depression, those taking an antidepressant, or those nonresponsive to antidepressant treatment, the consistency of our findings with previous research on the frequencies of depression and antidepressant use suggests that our sample was representative of PD patients receiving specialty care. Another limitation was that all information concerning present and past psychiatric symptomatology and treatment was based on patient report and recall and not verified, which may have particularly hindered the validity of answers for subjects with mild cognitive impairment, although overall, subjects did not display significant global cognitive impairment based on mean MMSE score.

Depression is a significant cause of disability in PD\(^\text{44}\) and appears to be underrecognized and undertreated, although ongoing questions concerning the phenomenology of PD depression likely confound the issue. Further research is needed to improve diagnostic accuracy by modifying the criteria for depression in PD to more closely match clinical presentation, determine the efficacy of a variety of depression treatments, and develop treatment algorithms for nonresponsive patients. In the interim, given the high prevalence of depression in PD and the suggestion from our research of a high frequency of antidepressant use in clinical practice, it is suggested that routine screening for depression be implemented in PD and that outcomes of antidepressant treatment be closely monitored.

References


\(^\text{2}\) Starkstein SE, Preziosi TJ, Forrester AW, Robinson RG. Specificity of affective and autonomic symptoms of depression in Parkinson’s disease.


