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Subthreshold depression in Parkinson's disease

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SUMMARY

Objective—It is estimated that 40% of patients with Parkinson's disease (PD) are clinically depressed, however, little is known about the frequency and associated features of subthreshold depression in PD. The current study sought to determine the prevalence of subthreshold depression (sD) and to further characterize the associated features in a sample of 111 nondemented patients with moderate to severe PD.

Methods—Patients were classified into the following groups: diagnostic depression (DD), subthreshold depression (sD), or nondepressed (ND) by applying the Diagnostic and Statistical Manual, 4th edn criteria for depression and previously reported criteria for sD to items from the Beck Depression Inventory, 2nd edn. These groups were compared on clinical and demographic variables. The symptom profile of the sD group is also described.

Results—Fifty participants (45.0%) were classified as ND, 32 (28.8%) as sD, and 29 (26.1%) as DD. Patients with sD were younger (~5 yrs) than nondepressed patients, but did not differ in disease stage or any other demographic variables. Patients with sD tended to endorse mood symptoms that overlap with PD, including fatigue, sleep difficulties, appetite dysfunction, and concentration difficulties. These symptoms were also endorsed with high frequency by the other groups.

Conclusions—These findings suggest that sD is not uncommon in PD and may be more prevalent among younger patients. The finding that sD patients report mood symptoms that overlap with the PD symptomatology suggests that these two entities share common features and may be difficult to disentangle.

Keywords

subthreshold depression; subsyndromal depression; Parkinson's disease

INTRODUCTION

Depression is a common neuropsychiatric comorbidity in Parkinson's disease (PD) (McDonald *et al.*, 2003) and has been shown to negatively impact quality of life, motor function, and disability (Schrage *et al.*, 2000; Weintraub *et al.*, 2004; Papapetropoulos *et al.*, 2006). The high prevalence of depression in these patients is partially due to direct disruption of subcortical circuitry as a result of the ongoing neurodegenerative process. Another factor influencing

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CONFLICT OF INTEREST None known.

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prevalence estimates for depression in this population is the similarity between somatic mood symptoms and other neurological symptoms in PD. The etiology of PD related depression is unknown, but has been shown to occur in approximately 40% of patients. Depression in PD is linked to advanced age, early age of onset, female gender, past history of depression, more severe functional disability (Cummings, 1992).

A major challenge to identifying depression in PD is the extensive overlap between mood symptoms and PD symptoms (Shulman *et al.*, 2002). This may be particularly true for patients with more subtle depressive symptoms that do not meet criteria for a formal diagnosis of depression. Research on the elderly in primary care settings suggests that low level mood symptoms are at least as common as depression and may be of clinical significance (Lyness *et al.*, 1999). These low level mood symptoms, have recently been termed 'subsyndromal' or 'subthreshold' depression and may represent a modifiable risk factor for the development of major depression (Chopra *et al.*, 2005). Studies examining subthreshold depression (sD) differ in how they define and operationalize the construct. In general, sD has been described as depressive symptoms that do not meet criteria for major depression, minor depression, or dysthymia based on the duration, frequency, intensity, or type of symptoms present (Pincus *et al.*, 1999).

The NINDS/NIMH conducted a working group on depression and PD that recommended more careful delineation of criteria for diagnosing sD in this population (Marsh *et al.*, 2006). Judd and colleagues initially introduced the concept of sD in 1994 and defined the syndrome by the presence of two or more symptoms of depression at levels below the threshold for diagnosis (Judd *et al.*, 1994). This definition is designed to capture patients experiencing depressive symptoms that are not necessarily present 'most of the day, nearly every day', as required for the diagnosis of major depressive disorder (MDD) by the Diagnostic and Statistical Manual for Mental Disorders, 4th edn (DSM-IV). Another study conducted by Lyness and colleagues (2007) in an elderly primary care population defined sD as either: (1) two or more threshold level symptoms; or (2) one threshold level symptom with at least subthreshold levels of sadness or anhedonia. These criteria were specifically designed to be used in an elderly primary care setting in which numerous general medical conditions may increase the frequency of somatic symptoms of depression. This problem is particularly important in PD patients due to the extensive overlap of other neurological sequelae with somatic symptoms of depression.

To date, only one study has examined sD in PD (Ehrt *et al.*, 2007). They found that approximately 20% of PD patients with dementia met criteria for sD. No specific depressive symptoms were reported, precluding a detailed characterization of the disorder's symptomatology. The current study sought to determine the prevalence of sD in more advanced PD patients without dementia and to further characterize its associated features and symptom profile. We utilized the sD criteria derived by Lyness and colleagues (2007). This approach was chosen due to the fact that these criteria effectively identified patients with clinically significant mood symptoms in elderly primary care patients, a population similar to our PD group. Other commonly used criteria for sD may lead to overdiagnosis in these populations due to the high prevalence of overlapping somatic symptoms (Lyness *et al.*, 1999).

METHODS

Participants and measures

We identified 111 PD patients from the movement disorders clinic at the University of Miami, Miller School of Medicine. All patients had moderate to severe disease and were undergoing a pre-surgical evaluation for possible deep brain stimulation (DBS) surgery. Data from the neurological examination, clinical interview and neuropsychological evaluation were collected and analyzed. Information regarding gender, age, years of education, age of PD onset, PD

duration, and antidepressant treatment were obtained during the patient interview. A movement disorders specialist evaluated degree of motor impairment, side of symptom onset, and provided a modified Hoehn and Yahr rating as part of a comprehensive neurological examination. All patients were screened for possible dementia using the Mini Mental State Examination (MMSE) (Folstein *et al.*, 1983) and patients with a score below 24 were excluded from the present analyses. In addition, all patients underwent a clinical neuropsychological evaluation as part of their diagnostic work-up for DBS. No patient in the current study was found to show evidence of dementia based on the results of their neuropsychological evaluation.

Depressive symptomatology was assessed during the clinical interview and was measured with the Beck Depression Inventory, 2nd edn (BDI-II), a 21-item self-report questionnaire of depressive symptoms (Beck *et al.*, 1996). The instrument requires patients to rate depressive symptoms present over the last 2 weeks from 0–3, with increasing scores reflecting greater severity. A score of 0 on a given item indicates the complete absence of the symptom (e.g. 'I have as much energy as ever'), a score of 1 suggests the symptom may be present to some degree (e.g. 'I have less energy than I used to have'), a 2 indicates the symptom is clearly present (e.g. 'I don't have enough energy to do very much'), and a 3 indicates the symptom is present to a severe degree (e.g. 'I don't have enough energy to do anything'). The total possible score can range from 0–63. The BDI has been validated for use in PD (Levin *et al.*, 1988; Visser *et al.*, 2006) and compares favorably with other depression screening measures used in this population (Schrage *et al.*, 2007). An advantage of the BDI-II is that it is consistent with DSM-IV criteria for major depression since it includes questions assessing the presence of each symptom of depression over the last 2 weeks (American Psychiatric Association, 2000).

Depression groups

DSM-IV criteria were used to categorize patients into one of the following three groups: NonDepressed (ND), Subthreshold Depression (sD), Diagnostic Depression (DD). Each of the nine depressive symptoms listed in the DSM-IV was defined by one or two related questions from the BDI-II. Depressed mood was defined by items related to 'sadness' and 'crying' (items 1 and 10), anhedonia by 'loss of pleasure' and 'loss of interest' (items 4 and 12), appetite dysfunction by 'changes in appetite' (item 18a and 18b), sleep disturbance by 'changes in sleeping pattern' (item 16a and 16b), psychomotor agitation by 'agitation' (item 11), fatigue by 'loss of energy' and 'fatigue' (items 15 and 20), feelings of worthlessness by 'guilty feelings' and 'worthlessness' (items 5 and 14), diminished ability to concentrate by 'indecisiveness' and 'concentration difficulty' (items 13 and 19), and suicidal ideation by 'suicidal thoughts or wishes' (item 9).

Patients were determined to have a specific depressive symptom at threshold level (meeting DSM-IV criteria) if they endorsed any of the items addressing that symptom with a score greater than or equal to 2 (clearly present) and at subthreshold level with scores of 1 (present to some degree). Consistent with DSM-IV criteria, the DD group was composed of patients meeting criteria for either minor or major depression, with two or more threshold level symptoms, at least one of which must be either sadness or anhedonia.

Criteria similar to those utilized by Lyness and colleagues (2007) were employed to define sD. Patients were identified as having sD if they did not meet criteria for major or minor depression and had either: (1) two or more threshold level symptoms; or (2) one threshold level symptom with at least subthreshold levels of sadness or anhedonia. All remaining participants were categorized as ND.

Statistical analyses

Groups (ND, sD, DD) were compared on basic demographic and clinical characteristics. Analysis of variance (ANOVA) was used to compare groups on continuous variables and chi-square tests were employed for categorical variables. Where significant overall group differences were found, post-hoc Tukey tests were used to determine which groups differed.

Descriptive statistics were calculated and examined to specify the profile of depressive symptomatology in each group.

RESULTS

One hundred and eleven PD patients (77 men and 34 women) were included in the analyses. Fifty participants (45.0%) were classified as ND, 32 (28.8%) as sD, and 29 (26.1%) as DD. Mean age and age of PD onset for the entire sample were 64.1 ± 9.7 years and 52.7 ± 10.9 years, respectively. Mean years of education was 14.4 ± 3.8 . Sixty-two (59.6%) had right-side PD onset, mean PD duration was 11.8 ± 5.5 years, mean Hoehn and Yahr disease stage was 2.7 ± 0.7 , mean MMSE was 27.4 ± 1.7 , and 27 (24.5%) were taking antidepressant medications.

Demographic and disease related variable

Patients in the sD group were younger than those in the ND group ($p < 0.05$). Individuals in the DD group had fewer years of education than those in the ND or sD group ($p < 0.05$ for both). The groups did not differ in terms of gender, age at PD onset, side of PD onset, PD duration, disease stage, MMSE scores, or use of antidepressants (Table 1).

Profile of depressive symptomatology

Examination of the frequency of depressive symptoms reported at any level of intensity (BDI-II item score ≥ 1) revealed that the most commonly endorsed symptom in the sD group was fatigue (93.8%), followed by anhedonia, sleep and concentration difficulties (87.5% for all), appetite dysfunction (65.6%), agitation (59.4%), sadness (50.0%), guilt (46.9%), and suicidality (12.5%) (Figure 1A).

A similar response pattern was also observed among the DD and ND groups, with fatigue, sleep, concentration difficulties, and appetite dysfunction being among the five most commonly reported symptoms. As with the sD group, suicidal ideation was the least commonly reported symptom within the DD and ND groups (2.0% and 31.0%, respectively).

Threshold depressive symptomatology

In terms of threshold level symptoms (BDI-II item score ≥ 2), the most commonly endorsed symptom in the sD group was sleep difficulties (71.9%), followed by fatigue (40.6%), appetite dysfunction (21.9%), concentration difficulties (18.8%), and agitation and guilt (both 9.4%) (Figure 1B). For patients in the ND group, only four symptoms were reported at threshold levels in a small number of patients, including sleep difficulties (12.0%), fatigue and appetite dysfunction (both 4.0%), and concentration difficulties (2.0%). For the DD group the order of reported symptoms was as follows: fatigue and anhedonia (both 79.3%), sleep difficulties (69.0%), sadness, guilt, and concentration difficulties (48.3% for all), agitation (44.8%), and appetite (31.0%). Threshold levels of suicidality were not reported by patients in any of the three groups.

DISCUSSION

Our findings indicate that sD is not uncommon in the middle to late stages of PD, being present in approximately 30% of our nondemented sample. This is consistent with previous work

demonstrating 35% of elderly primary care patients are identified as having sD (Lyness *et al.*, 2007). One other study conducted by Ehrt and colleagues (2007) examined sD in PD and reported a slightly lower prevalence (approximately 20%), but this is likely due to differences in methodology and clinical sample. This prior study focused on demented patients and utilized one item from the Neuropsychiatric Inventory, a caregiver questionnaire, to classify patients as depressed. The current study centered on nondemented PD patients and applied more specific criteria for the diagnosis of sD by assessing self-reported DSM-IV symptoms.

Patients with sD were similar to those with depression and those without mood symptoms in terms of gender, age of onset, disease duration, disease stage, side of onset, and overall mental status. Statistical comparisons indicated that the sD group was younger than the ND group, which is consistent with results presented by Ehrt and colleagues (2007) indicating that patients with sD are younger than those without mood symptoms. This prior study also found that patients with sD developed the disease at an earlier age. While the sD group in our sample was almost five years younger at onset than the ND group, this difference was not statistically significant in our sample.

The current study found that patients in the DD group had fewer years of education than those in either the sD or ND group, but sD patients had a level of education similar to that of the ND group. This is consistent with previous studies showing that PD patients with depression tend to be less educated than nondepressed patients (Cohen *et al.*, 2007), but this is the first study to examine education in PD patients with sD. These data suggest that fewer years of education may represent an important risk factor for the development of major depression in PD patients and could contribute to the exacerbation of depressive symptoms from subthreshold levels to a more diagnostic symptom profile. Future prospective studies should more carefully examine the ability of education to predict the progression of depressive symptomatology from a minimal or subthreshold stage to a major depressive episode.

An important concern regarding the clinical significance of low level mood symptoms in PD is that many symptoms intrinsic to the disease itself could be mistaken for depressive symptoms. Patients classified as having sD according to our criteria frequently reported symptoms potentially related to PD itself, including fatigue, difficulty concentrating, appetite and sleep dysfunction. It can be argued that these symptoms reflect PD symptoms and do not necessarily indicate low level mood symptoms, which would justify concerns regarding how to classify somatic symptoms when diagnosing mood disorders in PD patients. These concerns are further supported by the fact that these symptoms were also the only threshold level symptoms reported by nondepressed patients in our sample. Given their frequency in nondepressed patients and their substantial overlap with PD symptomatology, fatigue, difficulty concentrating, and appetite and sleep dysfunction should be carefully scrutinized in studies attempting to identify sD in this population.

This interpretation of the present study is complicated by the fact that depression associated with PD may be a direct result of the ongoing neurodegenerative process within frontal-subcortical systems (Cummings, 1992; Lemke, 2008). Support for this hypothesis comes from numerous neuropathological and neuroimaging studies showing differences between depressed and nondepressed PD patients in the structure and function of monoaminergic systems known to be important in the pathophysiology of depression. For example, a recent study comparing depressed and nondepressed PD patients found that depressed patients showed increased neuronal loss and gliosis in areas rich in catecholamines, such as the locus coeruleus (Frisina *et al.*, 2008). Other studies have found that PD patients with depression display increased neuropathological changes in areas responsible for indolamine system functioning, such as the dorsal raphe nuclei (Paulus and Jellinger, 1991). It is well established that these monoaminergic systems modulate frontal-subcortical system function and disruption of these

systems has been implicated in the pathophysiology of depression even in patients with no known neurodegenerative condition (Konarski *et al.*, 2008). Consequently, many authors have concluded that the overlap of symptomatology between depression and PD is a direct result of the overlapping neurophysiological basis of the diseases, suggesting that depression is an integral part of the PD syndrome (Mayberg and Solomon, 1995; Frisina *et al.*, 2008). This view is further supported by evidence that depression is associated with more extensive neuropathology within the substantia nigra itself (Frisina *et al.*, 2008), more severe motor and nonmotor symptoms (Reijnders *et al.*, 2008), and a more malignant course (Post *et al.*, 2007). This suggests that somatic symptoms may continue to be important features of depressive mood in PD, despite the fact that they are a direct result of the same underlying pathophysiological process. In support of this notion, there is some evidence that specific types of appetite and sleep dysfunction, namely reduced appetite and early morning insomnia, may be related to depression in PD patients (Leentjens *et al.*, 2003). Furthermore, measures of depression known to emphasize somatic symptoms, such as the BDI, have repeatedly been shown to be valid measures of depression in PD patients (Levin *et al.*, 1988; Visser *et al.*, 2006; Schrag *et al.*, 2007).

It has been argued that the subtle mood symptoms thought to characterize sD represent prodromal manifestations of an imminent mood disorder or residual symptoms of a waning depressive episode (Forsell, 2007). The fact that our data show no differences in use of antidepressants between groups suggests that sD is not merely major depression partially resolved with pharmacotherapy. A substantial number of nondepressed patients from our sample were taking antidepressants. This is likely due to a number of factors, including the use of some antidepressants to treat insomnia, or other symptoms potentially unrelated to mood, and the tendency to falsely attribute certain PD symptoms (e.g. apathy) to depression (Kirsch-Darrow *et al.*, 2006).

Two other notable findings regarding depressive symptomatology include the high rates of anhedonia in patients in the sD and DD groups and low rates of suicidality. Increased reporting of anhedonia could be due to high levels of apathy that is not necessarily related to depressive symptomatology, lending empirical support to theoretical concerns regarding the distinction between anhedonia and apathy in PD. None of the patients in our sample displayed suicidal ideation at threshold levels. This supports previous research suggesting suicide in PD is a relatively uncommon occurrence (Merschdorf *et al.*, 2003).

The use of self-report measures of depression are limited and future research incorporating caregiver and clinician rating scales as well as other objective measures of depression are warranted. The use of the BDI-II in medically ill populations has been criticized over concerns that it asks many questions related to somatic symptoms of depression (Schrag *et al.*, 2007). This was addressed in an earlier study in which an item analysis of the BDI was conducted to examine the internal consistency and validity of this measure in PD. In this study, the BDI, including the somatic items, was shown to be a valid and reliable measure of depression in this population (Levin *et al.*, 1988). In addition, the current study only used BDI-II questions that directly address DSM-IV symptoms, avoiding any potential confounding symptoms due to a general medical condition. As only one other study has examined sD in this population, the current study was primarily intended to be a qualitative description of sD symptomatology in our sample of nondemented PD patients. Future studies should take into consideration the significant overlap between mood symptoms and those intrinsic to PD itself. Longitudinal studies are also needed to determine whether patients with sD may go on to develop diagnostic depression.

KEY POINTS

- Parkinson's disease patients with subthreshold depression frequently endorse depressive symptoms that overlap with disease.

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Figure 1.

Self-reported depressive symptoms taken from select BDI-II items are displayed. A) Frequency of symptoms endorsed at any level (BDI-II score ≥ 1) are displayed for all three groups. Note that the sD group endorsed a pattern of depressive symptomatology similar to those of the other two groups. Fatigue, anhedonia, sleep difficulties, appetite dysfunction, and concentration difficulties were the most frequently reported symptoms, even in patients that were not depressed. B) Frequency of symptoms endorsed at threshold levels (BDI-II score ≥ 2) are shown. Note that for the sD group, the same four symptoms were most commonly reported, including fatigue, sleep difficulties, appetite dysfunction, and concentration difficulties. These were the only symptoms reported by any patients in the ND group.

Table 1

Demographic and Clinical Data by Group

	ND	sD	DD	p	Post-hoc
N (%)	50 (45.0%)	32 (28.8%)	29 (26.1%)		
Age (yrs)	66.4 ± 9.1	61.4 ± 9.7	63.0 ± 10.1	p = 0.023	sD < ND
% Male	70.0%	78.1%	78.6%	n.s.	—
Age PD onset (years)	54.6 ± 11.5	50.0 ± 9.4	52.4 ± 11.1	n.s.	—
PD duration	12.0 ± 5.6	12.0 ± 5.2	11.2 ± 5.4	n.s.	—
% Right side onset	66.0%	51.7%	57.1%	n.s.	—
MMSE	27.4 ± 1.6	27.6 ± 1.5	27.0 ± 1.8	n.s.	—
Education	15.1 ± 3.8	15.0 ± 3.1	12.6 ± 3.9	p = 0.008	DD < ND; DD < sD
% Antidepressant tx	24.0%	19.4%	31.0%	n.s.	—
Hoehn and Yahr	2.6 ± 0.7	2.6 ± 0.7	2.8 ± 0.7	n.s.	—

The three patient groups were compared on basic clinical and demographic data. Patients in the sD group were significantly younger than those in the ND group. Patients in the DD group had fewer years of education than those in the sD and ND groups. No other significant differences were observed among groups in terms of gender, age of onset, disease duration, side of onset, mental status, use of antidepressants, or disease stage.

Mean ± Standard Deviation.

n.s. = not significant.