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Depression in Parkinson's disease: Symptom Improvement and Residual Symptoms Following Acute Pharmacological Management

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Abstract

Objective—Parkinson's disease is frequently complicated by depression (dPD) and there is a paucity of controlled research that can inform the management of this disabling non-motor complaint. A randomized controlled trial of nortriptyline, paroxetine, and placebo for the treatment of dPD was recently completed. The purpose of this paper is to describe the baseline pattern of depressive symptom presentation in PD, the specific symptoms of dPD that improve with pharmacotherapy, and the residual symptoms which remain in patients who meet *a priori* criteria for response or remission after acute treatment (8-weeks).

Setting—The Departments of Psychiatry and Neurology at Robert Wood Johnson Medical School.

Participants—Fifty-two depressed patients (Major Depression or Dysthymia based on DSM-IV criteria) with Parkinson's disease (by research criteria).

Design/Intervention—A randomized controlled trial of nortriptyline, paroxetine, and placebo.

Measurement—The four subscales (core mood, anxiety, insomnia, somatic) and individual items from the Hamilton Rating Scale for Depression (HAM-D-17) were the focus of the current study. These measures were assessed at baseline and week 8.

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Results—Baseline depressive symptoms were unrelated to motor functioning. Treatment response was associated with significant improvements in the core mood, anxiety, insomnia, and somatic symptoms seen in dPD. Residual symptoms, like sadness and loss of interest, persisted in treatment responders in a milder form than was initially present.

Conclusions—Antidepressants may influence all symptoms of dPD, including those which share great overlap with the physical disease process. Additional research regarding adjunctive interventions is needed to help optimize the management of dPD.

Keywords

Parkinson's disease; depression; antidepressants; residual symptoms

Introduction

Depression is one of the most common psychiatric complications of Parkinson's disease (PD)^{1,2}, affecting up to 50% of patients³. Depression in PD (dPD) is important due to its detrimental effects on quality of life, self-care, family relationships, cognition, and physical functioning^{4,5,6,7}. Despite the negative impact of dPD on both patients and families, there is a paucity of controlled research that can inform the management of this disabling non-motor complaint.

Accordingly, there is also a dearth of information regarding the specific symptoms of dPD that respond well to antidepressant medication (ADM) and the residual symptoms that remain prime targets for further treatment optimization. In treatment trials of late-life depression in non-PD populations, residual symptoms have been shown to predict both relapse and re-occurrence of future depressive episodes^{8, 9}. Moreover, residual symptoms have been linked with increased rates of suicidality, functional impairment, medical comorbidity, mortality, and resource utilization^{10, 11, 12}. Clinically significant residual symptoms may require vigorous and longer than usual courses of ADM and may benefit from adjunctive and/or combination therapies¹³.

In an NIH-funded, randomized, double-blind trial of nortriptyline, paroxetine, and placebo, we recently showed that nortriptyline was superior to placebo for the acute treatment (8-weeks) of dPD¹⁴. The purpose of this paper is to describe the baseline pattern of depressive symptom presentation in PD, the specific symptoms of dPD that improved with short-term pharmacological management, and the residual symptoms which remained in patients who met *a priori* criteria for response or remission after 8-weeks. This information may be useful in the delineation of future treatment recommendations for dPD.

Method

Participants

Patients were recruited from the Movement Disorders Clinic at Robert Wood Johnson Medical School, the New Jersey chapter of the APDA and advertisements in local papers. All participants were paid \$20 for each study evaluation, and received free medication and psychiatric assessments. Inclusion criteria were as follows: 1). PD by research criteria¹⁵; 2). a primary diagnosis of depression or dysthymia based on the Structured Clinical Interview (SCID)¹⁶ for the Diagnostic and Statistical Manual of Mental Disorders 4th edition (DSM-IV)¹⁷; and 3). aged 35–80. Exclusion criteria included: 1). cognitive impairment defined as an MMSE¹⁸ less than 26; 2). “off” time greater than 50% of the day; 3). any comorbid DSM-IV Axis I diagnosis other than anxiety disorders; and 4). failure of two or more trials of an approved antidepressant of adequate dose and length. Patients were required to

maintain a stable dose of their PD medication(s) and could not use any additional psychotropic medications other than the study drug while enrolled. All assessments were performed during “on time”.

Fifty-two patients (27 male, 25 female) met all inclusion/exclusion criteria and were entered into the acute phase of the trial. Thirteen additional patients signed consent and were screened, but failed to meet all inclusion/exclusion criteria. The study was approved by UMDNJ-Robert Wood Johnson Medical School’s IRB. All participants provided written, informed consent prior to any study procedures.

Measures

Depression (Hamilton Rating Scale for Depression, HAM-D19, Clinical Global Impression Improvement Scale, CGI-I20), anxiety (Hamilton Anxiety Rating Scale, HAM-A21), sleep (Pittsburgh Sleep Quality Index- PSQI22), quality of life (Medical Outcome Study Short Form - SF-3623; Parkinson's Disease Questionnaire- PDQ-824), motor functioning (Unified Parkinson's Disease Rating Scale- UPDRS25) and cognition (verbal fluency²⁶, Stroop²⁷, digit span²⁸, word list recall and recognition²⁹, naming³⁰) were assessed at baseline and week 8.

The total score from the HAM-D 17 was the main measure of depression employed in the work stemming from this NIH trial described to date ^{14, 31, 32}. While the HAM-D 17 is often conceptualized as a global measure of depression, meta-analyses have suggested that four separate factors or subscales (Core Mood, Anxiety, Insomnia, and Somatic) comprise the total score³³. The individual items contained within each subscale are as follows: **Core Mood**: #1 depressed mood, #2 guilt, #3 suicidal thinking, #7 lack of interest, #8 psychomotor retardation; **Insomnia**: #4 early insomnia, #5 middle insomnia, #6 late insomnia; **Anxiety**: #9 Agitation, #10 Psychic Anxiety, #11 Somatic Anxiety, #15 Hypochondriasis, #17 Insight; **Somatic**: #12 Appetite, #13 Energy, #14 Sexual Interest, #16 Loss of Weight.

Changes in the HAM-D subscales and individual items are the focus of the current study. The effect of treatment on the additional outcome measures noted above has been detailed in prior publications ^{14, 31, 32} and is beyond the scope of the current paper.

Procedure

Participants were first screened by telephone. Participants who met phone screening criteria were invited for an in-person evaluation. The initial evaluation included a detailed medical and psychiatric history, along with an assessment of motor functioning, depression, anxiety, sleep, quality of life, and cognition. Eligible individuals were randomized, in variable length blocks, to equivalent-appearing drug groups (i.e., nortriptyline, paroxetine CR, or placebo). Medication dosing was flexible and based on ranges typical for a geriatric population. Dosing decisions were made at each visit based on efficacy and tolerability. The dosage range for each study drug was as follows: nortriptyline 25 mg to 75 mg; paroxetine CR 12.5 mg to 37.5 mg; and placebo 1 to 3 pills. Patients took a single daily dose of the study drug in the evening. Assessments of depression, anxiety, motor function, sleep, quality of life, and cognition were re-administered at the end of the acute phase (week 8) by study personnel who were blind to group assignment.

Overview of statistical analyses

Clinical response was defined *a priori* as a 50% reduction in baseline to endpoint score on the HAM-D-17. Remission was defined as a HAM-D score of less than 8. Participants who met criteria for either response or remission after 8 weeks of treatment were collapsed into

one group (RESPONDERS) and those who did not meet these criteria were classified as NONRESPONDERS. Only patients who took at least one dose of study drug and completed at least one follow-up evaluation were included in the analyses regarding treatment response, symptom improvement and residual symptoms. Sixteen patients (3 paroxetine, 4 placebo, 9 nortriptyline) met criteria for RESPONSE after acute treatment and 36 (15 paroxetine, 13 placebo, 8 nortriptyline) met criteria for NONRESPONSE.

Data was analyzed using SAS version 9.1 First, we examined the frequencies of the specific depressive symptoms reported at baseline and explored the relationship between different clusters of baseline depressive symptoms (as assessed by HAM-D subscales) and patient characteristics using a series of t-tests. Second, we explored which specific depressive symptoms improved for RESPONDERS (vs. NONRESPONDERS), as assessed by t-tests on difference scores (baseline to week 8) for each HAM-D subscale. Third, we explored pre-post changes in individual HAM-D item scores as a function of RESPONSE/NONRESPONSE. In these analyses, a non-parametric test was used because of distributional anomalies in change scores for individual items. For any given patient, improvement was scored as '1' for any improvement from baseline to endpoint, 'zero' otherwise. The Cochran-Armitage test was used to compare RESPONDERS and NONRESPONDERS with respect to these binary change scores. Lastly, we report on the residual symptoms endorsed by RESPONDERS after 8 weeks of treatment.

Given the fact that multiple tests capitalize on chance, raw p-values are not reported below for any given statistical test; rather p-values are adjusted for multiple tests by the Holm method using permutation-type re-samplings (100,000 re-samples; two-tailed) in SAS PROC MULTTEST.

Results

Sample Characteristics

Forty-eight patients met criteria for Major Depressive Disorder (10 single episode, 38 recurrent). Two patients were diagnosed with Dysthymia, and two patients were diagnosed with both. Thirty-four patients (65%) also met criteria for a comorbid anxiety disorder (2 for Specific Phobia, 7 for Social Phobia, 15 for Generalized Anxiety Disorder, 10 Not Otherwise Specified). Thirty-four patients (65%) had previously taken antidepressants and 13 (25%) had previously used sedative-hypnotics. Thirty-five (67%) were currently taking carbidopa/levodopa, 34 (65%) were using a dopamine agonist, and eight (15%) were prescribed a COMT inhibitor.

Patients had PD an average of 6.6 years (SD= 5.9), with a mean age of onset at 56 years old (SD= 9.5). The majority of patients were in stage 2 (Hoehn and Yahr³⁴) of PD. The average age of the sample was 62.2 (SD= 8.7). The average dose of drug was 28.4 mg of paroxetine CR, 48.5 mg of nortriptyline (average nortriptyline level of 74.88), and 3 pills of placebo. The mean baseline score on the HAM-D was 19.81(SD=4.7).

Baseline Symptoms

The most frequently reported baseline symptoms (endorsed by more than 75% of the sample) included depressed mood, guilt, middle insomnia, early awakening, lack of interest, psychic anxiety, fatigue, and low sexual interest. Suicidal thinking, early insomnia, poor appetite, and loss of weight were the least frequently reported complaints (described by less than 50% of the sample). See Table 1.

The nature of baseline depressive symptoms was unrelated to motor aspects of PD such as duration, stage, and baseline UPDRS motor score. Moreover, gender, age, age of onset, and

concomitant medications (i.e., use of a COMT inhibitor, carbidopa/levodopa, dopamine agonist, prior antidepressant or sedative hypnotic use) were not associated with the type of baseline depressive symptoms endorsed. No significant baseline differences were found between RESPONDERS and NONRESPONDERS on the HAM-D subscales.

Symptom Improvement

Treatment RESPONDERS demonstrated significant improvement on the core mood { $t(50)=4.52$, adjusted $p<.0001$; Cohen's $d=1.52$ }, anxiety { $t(50)=2.59$, adjusted $p=.009$; Cohen's $d=.96$ }, insomnia { $t(50)=3.61$, adjusted $p=.01$; Cohen's $d=.94$ }, and somatic subscales { $t(50)=5.90$, adjusted $p=.0003$; Cohen's $d=1.30$ }, compared to NONRESPONDERS. A post-hoc examination of change on each individual HAM-D 17 item indicated that RESPONDERS significantly improved (compared to NONRESPONDERS) on the following items: depressed mood, middle insomnia, interest, and somatic anxiety (Table 2). Bar graphs depicting percentage change for each individual HAM-D-17 item for RESPONDERS and NONRESPONDERS can be seen in Figure 1.

Residual Symptoms

Despite the gains described above, some level of depressed mood, lack of interest, psychic anxiety, and low energy continued to be reported by more than 50% of RESPONDERS (Table 2). However, an inspection of means indicated that the residual symptoms endorsed by RESPONDERS at week 8 were milder in severity compared to their initial presentation at baseline. Correcting for multiple tests (Holm method) suggests that the improvements in depressed mood, guilt, middle insomnia, late insomnia, interest, somatic anxiety, and energy that were reported by RESPONDERS over the course of treatment were statistically significant at adjusted $p<.05$. Of note, suicidal thinking is the only symptom (albeit an important one) that completely resolved for 100% of RESPONDERS.

Discussion

This is the first study to describe which depressive symptoms in PD respond best to antidepressant treatment and which residual symptoms remain after acute pharmacological management. Consistent with past research¹, patients reported high levels of somatic symptoms, anxiety, fatigue, and sleep disturbance at baseline, in addition to the traditional symptoms of depressed mood and lack of interest. Suicidal thinking was less frequently endorsed, while feelings of guilt, thought to be less common in this population¹, were noted by the majority of the sample. Sixty-five percent of the sample also met criteria for a comorbid anxiety disorder, in line with previous findings³⁵.

Treatment RESPONDERS (vs. NONRESPONDERS) demonstrated significant improvements in all four HAM-D subscales, with the largest effect size (descriptively) emerging for core mood symptoms. RESPONDERS made the largest gains (compared to NONRESPONDERS) on the following individual items: depressed mood, middle insomnia, interest, and somatic anxiety. Moreover, as shown in Figure 1, RESPONDERS demonstrated a 50% improvement (indicative of treatment response) on 15 out of the 16 HAM-D items under study (only 45% change noted in sexual interest), while NONRESPONDERS only experienced a 50% improvement on one item (weight loss). These results suggest that successful antidepressant treatment may influence all symptoms of dPD to some extent, including somatic symptoms such as fatigue, which may share great overlap with the physical disease process. The potential for ADMs to affect the broad range of depressive symptoms experienced by PD patients is further underscored by the fact that baseline depressive symptom presentation was unrelated to motor functioning. These findings are particularly noteworthy given that somatic depressive complaints have been

associated with the onset of future depressive episodes in medically ill older adults,³⁶ while anxiety³⁷ and co-occurring depressive and anxious symptoms³⁸ have been linked with the experience of great disability and reduced quality of life in the aged.

The most common residual symptoms for RESPONDERS at week 8 were depressed mood, lack of interest, psychic anxiety, and low energy. This data is consistent with other studies that have also found low mood, anxiety, loss of interest, fatigue, and insomnia to persist despite successful treatment of depression in late-life.^{8, 39} However, it is important to note that many of the residual symptoms endorsed by RESPONDERS following acute treatment (i.e., mood, guilt, interest, fatigue) were less frequent in duration, milder in severity, and associated with less functional impairment than those reported at baseline.

Several factors may be implicated in the rates of residual symptoms observed in the current sample. It has been suggested that the high prevalence of residual symptoms in geriatric depression may in part be due to the strong presence of comorbid anxiety and medical illness (two factors with great relevance to this study) in the population.⁴⁰ It is also possible that the neurophysiological changes inherent in both PD and natural aging may cause medications to be less effective than would be expected⁴⁰, or that residual symptoms may be related to the chronicity of depression found in our sample. For example, the majority of the sample met criteria for a chronic depressive disorder (e.g., Recurrent MDD, Dysthymia, Double Depression). Thus, it is possible that depression remained a persistent life-long problem that perhaps never fully resolved between episodes for many of these patients.

In addition, there are some limitations to this study which are important to note. First, the small sample size and short length of treatment may limit the generalizability of study results. Furthermore, since the majority of patients presented with mild to moderate levels of chronic depression, our findings may not extend to patients with more severe symptomatology or first-time episodes. Thus, the results of this study should be viewed as preliminary. Future research in larger, more diverse samples over a longer period of time is needed to replicate and extend these findings. Further study is also needed to investigate if improvements in comorbid anxiety mediate the changes observed in depressive disorders following pharmacological intervention in the PD population.

In sum, this is the first study to report that antidepressant treatment significantly improved the core mood, anxiety, somatic, and insomnia symptoms seen in dPD, including those with great overlap with the disease process. Residual symptoms did persist despite successful pharmacological management, but to a lesser degree than were initially present. Additional research investigating adjunctive interventions, such as cognitive-behavioral therapy (which may incorporate techniques such as relaxation training, sleep hygiene, and worry control), adding a second antidepressant, psychostimulants, anti-anxiety medication, or sedative hypnotic, and/or utilizing a longer duration and/or higher dosages of ADM therapy, is needed to help optimize the treatment of dPD.

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Figure 1.
Percent change at Week 8

Table 1**Baseline Symptom Means and Frequencies**

Symptom	Baseline	
	WHOLE SAMPLE (N=52)	
	M(SD)	N(%)
Depressed mood	2.50 (0.67)	52 (100.0)
Guilt	1.27 (0.93)	39 (75.0)
Suicidal thinking	0.40 (0.54)	20 (38.5)
Early insomnia	0.63 (0.86)	20 (38.5)
Middle insomnia	1.40 (0.80)	42 (80.8)
Early awakening	1.21 (0.70)	44 (84.6)
Lack of interest	2.40 (0.82)	51 (98.0)
Retardation	0.60 (0.66)	27 (52.0)
Agitation	1.19 (1.12)	33 (63.5)
Psychic anxiety	1.85 (1.00)	47 (90.4)
Somatic anxiety	1.33 (1.08)	34 (65.4)
Poor appetite	0.54 (0.70)	22 (42.3)
Low energy	1.65 (0.60)	49 (94.2)
Genital symptoms	1.15 (0.80)	39 (75.0)
Hypochondriasis	1.17 (1.06)	32 (61.5)
Loss of weight	0.48 (0.75)	17 (32.7)
Insight	0 (0.0)	0 (0.0)

Key: M = mean; SD= standard deviation; N(%) = number and percentage of patients reporting the symptom

Table 2

Week 8 Symptom Means and Frequencies

Symptom	WHOLE SAMPLE (N=52)		RESPONSE (N=16)		NO RESPONSE (N=36)		p value*
	M(SD)	N(%)	M(SD)	N(%)	M(SD)	N(%)	
Depressed mood	1.85 (1.13)	44 (84.6)	0.81 (0.91)	9 (56.2)	2.31 (0.89)	35 (97.2)	0.0008
Guilt	0.85 (0.96)	27 (52.0)	0.38 (0.62)	5 (31.2)	1.06 (1.01)	22 (61.1)	0.7142
Suicidal thinking	0.35 (0.59)	15 (28.8)	0.00 (0.00)	0 (0.0)	0.50 (0.66)	15 (41.7)	0.7000
Early insomnia	0.50 (0.75)	18 (34.6)	0.25 (0.58)	3 (18.8)	0.61 (0.80)	15 (41.7)	1.0000
Middle insomnia	0.83 (0.90)	26 (50.0)	0.31 (0.70)	3 (18.8)	1.09 (0.90)	15 (65.2)	0.0190
Early awakening	0.77 (0.76)	30 (57.7)	0.25 (0.45)	4 (25.0)	1.00 (0.76)	26 (72.2)	0.5635
Lack of interest	1.69 (1.09)	44 (84.6)	0.81 (0.91)	9 (56.2)	2.08 (0.94)	35 (97.2)	0.0033
Psychomotor retardation	0.48 (0.61)	22 (42.3)	0.19 (0.40)	3 (18.8)	0.61 (0.65)	19 (52.8)	1.0000
Agitation	0.98 (1.16)	26 (50.0)	0.31 (0.60)	4 (25.0)	1.28 (1.23)	22 (61.1)	0.5465
Psychic anxiety	1.46 (1.11)	42 (80.8)	0.75 (0.78)	9 (56.2)	1.78 (1.10)	33 (91.6)	0.9982
Somatic anxiety	0.81 (1.05)	22 (42.3)	0.38 (0.62)	5 (31.2)	1.00 (1.15)	17 (47.2)	0.0108
Poor appetite	0.52 (0.70)	21 (40.4)	0.25 (0.45)	4 (25.0)	0.64 (0.76)	17 (47.2)	0.5854
Low energy	1.31 (0.78)	42 (80.8)	0.81 (0.75)	10 (62.5)	1.53 (0.70)	32 (88.8)	0.0716
Genital symptoms	1.00 (0.86)	33 (63.5)	0.69 (0.87)	7 (43.8)	1.14 (0.83)	26 (72.2)	0.9995
Hypochondriasis	1.00 (0.97)	30 (57.6)	0.25 (0.58)	3 (18.8)	1.33 (0.93)	27 (75.0)	0.9995
Loss of weight	0.19 (0.49)	7 (15.4)	0.13 (0.50)	1 (6.30)	0.22 (0.49)	7 (19.4)	1.0000
Insight	0.00 (0.00)	0 (0.00)	0.00 (0.00)	0 (0.00)	0.00 (0.00)	0 (0.0)	**

Key: M = mean; SD= standard deviation; N(%) = number and percentage of patients reporting the symptom; RESPONSE- responders (50% or greater reduction in baseline to endpoint HAMDD) plus remitters (HAMDD < 8)

* Exact permutation based p-values from Cochran-Armitage tests of symptom improvement by RESPONSE status

** Insight item not included in analyses as all patients were rated as 0 at all time points