Article

Cognitive-Behavioral Therapy for Depression in Parkinson's Disease: A Randomized, Controlled Trial

Roseanne D. Dobkin, Ph.D.

Matthew Menza, M.D.

Lesley A. Allen, Ph.D.

Michael A. Gara, Ph.D.

Margery H. Mark, M.D.

Jade Tiu, Psy.M.

Karina L. Bienfait, Ph.D.

Jill Friedman, Ph.D.

Objective: Despite the negative effects of depression in Parkinson's disease, there is currently no evidence-based standard of care. The purpose of this study was to examine the efficacy of individually administered cognitive-behavioral therapy (CBT), relative to clinical monitoring (with no new treatment), for depression in this medical population.

Method: Eighty depressed (based on DSM-IV criteria) patients with Parkinson's disease participated in a randomized, controlled trial of CBT relative to clinical monitoring (1:1 ratio) in an academic medical center from April 2007 to July 2010. All patients continued to maintain stable medication regimens under the care of their personal physicians. The 17-item Hamilton Depression Rating Scale (HAM-D) total score was the primary outcome. CBT was modified to meet the unique needs of the Parkinson's disease population and provided for 10 weeks. Assessments were completed by blind raters at baseline and 5 (midpoint), 10 (end of treatment), and 14 weeks (follow-up evaluation) postrandomization.

Results: The CBT group reported greater reductions in depression (change in HAM-D score) than the clinical monitoring group. At week 10, the mean HAM-D score change was 7.35 for CBT relative to 0.05 for clinical monitoring. CBT was also superior to clinical monitoring on several secondary outcomes (i.e., Beck Depression Inventory scores, anxiety, quality of life, coping, Parkinson's disease symptom ratings). There were more treatment responders in the CBT group than the clinical monitoring group (56% versus 8%, respectively).

Conclusions: CBT may be a viable approach for the treatment of depression in Parkinson's disease. Further research is needed to replicate and extend these findings.

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Parkinson's disease, the second most common neurodegenerative disorder in the United States, is defined by the motor triad of tremor, rigidity, and bradykinesia. The majority of patients also experience nonmotor complications (1), which are more closely associated with rates of disability and distress than the motor symptoms of the disease (2). Depression, the most prevalent nonmotor concern (3), affects approximately 50% of Parkinson's disease patients (4). Depression in Parkinson's disease is characterized by high rates of psychiatric comorbidity (5) and executive dysfunction (6) and is linked to faster physical and cognitive decline (7), poorer quality of life (8), and increased caregiver burden (9). Despite these negative effects, there is currently no evidence-based standard of care.

Pharmacological interventions have received the most empirical attention to date. Antidepressants (10, 11), dopamine agonists (12), and alternative treatments, such as omega-3 fatty acids (13), have demonstrated beneficial effects in preliminary controlled studies. Psychotherapeutic approaches, such as cognitive-behavioral therapy (CBT), have been the focus of fewer scientific investigations, despite demonstrated efficacy among the aged (14) and in other debilitating medical conditions (15). Only small pilot studies have examined the utility of CBT for depression in Parkinson's disease, with promising results (16–21). In other patient groups, CBT has shown effects comparable to those of antidepressants for mild depression, with combination treatment appearing most effective for moderate-to-severe forms of depression (22). Additional research is needed to inform the development of specific treatment recommendations for this medical population.

The purpose of the present study was to conduct the first randomized, controlled trial of CBT for depression in Parkinson's disease. We hypothesized that CBT would result in greater decreases in depressive symptoms, anxiety, negative thoughts, sleep disturbance, and caregiver burden, as well as greater improvements in quality of life, coping, and social support, than clinical monitoring (with no new treatment). Furthermore, we hypothesized that there would be more treatment responders in the CBT group. The effect of CBT on Parkinson's disease symptom ratings was also examined.

Method

This study received full approval by the Robert Wood Johnson Medical School Institutional Review Board. After complete description of the study to participants, written informed consent was obtained (prior to the initiation of any study procedures). Participants received the study treatment at no cost and were

This article is featured in this month's AJP Audio, is discussed in an editorial by Dr. Black (p. 1015), and is the subject of a CME course (p. 1127)

compensated $20.00 for each in-person assessment and $10.00 for each telephone assessment. Treatment and evaluation occurred at the Robert Wood Johnson Medical School. Participants enrolled in the study with a caregiver.

One-half of the participants received CBT plus clinical monitoring. The other half received clinical monitoring only. This additive design has been recommended for use when exploring the relative efficacy of a new psychotherapy intervention (23).

All participants continued to maintain stable medical regimens under the care of their personal physicians. Depression was addressed in the same manner in which it was handled prior to the study (e.g., antidepressant medication at a stable dose). No new depression treatment (other than CBT in the experimental condition) was provided to study participants. Those assigned to the comparison group (clinical monitoring only) had the option to receive the CBT treatment package after week 14.

Participants

Patients were recruited from the Richard E. Heikkila Movement Disorders Clinic, local newspapers, and the New Jersey Chapter of the American Parkinson's Disease Association between April 2007 and March 2010. The final follow-up evaluation occurred in July 2010. Patients were eligible for participation in the study if they 1) had a diagnosis of Parkinson's disease per research criteria (24); 2) had a diagnosis of primary major depression, dysthymia, or depression not otherwise specified per DSM-IV criteria; 3) had a Clinical Global Impression–Severity scale score ≥4 (at least moderately ill [25]); 4) were between 35 and 85 years old; 5) were receiving a stable medication regimen for a duration of ≥6 weeks; and 6) had a family member or friend willing to participate.

Expert panel guidelines were followed regarding the diagnosis of depression in Parkinson's disease (26). Patients with comorbid anxiety disorders were eligible to enroll as long as their depressive disorder was primary.

Participants in both study groups (CBT plus clinical monitoring and clinical monitoring only) continued with mental healthcare (other than CBT) that was stabilized (≥6 weeks) prior to baseline. Medication use and mental healthcare utilization were tracked throughout the study. New depression treatment was a criterion for early termination.

Exclusion criteria were 1) dementia (a score below the 5th percentile for age on memory and on at least one other subscale of the Mattis Dementia Rating Scale [27]); 2) off-time (time when medication is not effective and symptoms return) ≥50% of the day; 3) suicidal ideation; 4) unstable medical conditions; 5) bipolar, schizophrenia spectrum, or substance abuse disorders (as determined by DSM-IV criteria); and 6) receiving CBT elsewhere.

Caregiver inclusion criteria were 1) ages 25–85 years, 2) daily contact with the study participant, and 3) no unstable medical or psychiatric conditions (as determined via clinical interview).

Randomization and Masking

Appropriate candidates were allocated to receive CBT plus clinical monitoring or clinical monitoring only (1:1 ratio) by computer-generated random assignment (run by the statistical consultant [M.A.G.]). Randomization was stratified by antidepressant use at screening (yes/no) and conducted in blocks of six consecutive participants within each stratum.

All follow-up (i.e., postbaseline) assessments were conducted by independent evaluators without knowledge of the treatment condition. Participants were instructed not to reveal their group assignment to raters. Participants and therapists were not blind given the nature of the treatment.

Procedure

Potential participants called our office to receive information about the study and to complete preliminary screening (see Figure 1 in the data supplement accompanying the online version of this article). Appropriate individuals were scheduled for a face-to-face appointment, where a statement of informed consent (for both patient and caregiver) was reviewed and signed, demographic information was obtained, inclusion/exclusion criteria were assessed (by R.D.D., M.H.M., and M.M.), and baseline evaluations were completed. Those who met eligibility criteria were enrolled and randomly assigned to one of the two aforementioned treatment arms. Participants were reassessed at 5 (midpoint), 10 (end of treatment), and 14 weeks postrandomization (1-month follow-up evaluation). Telephone calls to participants were made at weeks 2 and 7 to assess patient safety.

Raters received extensive training from the first author (R.D.D.) in administration of the Structured Clinical Interview for DSM-IV, the 17-item Hamilton Depression Rating Scale (HAM-D [28]), and the Hamilton Anxiety Rating Scale (HAM-A [29]). Interviews for both Hamilton rating scale measures were standardized (by R.D.D.) at the outset of the trial, and a coding dictionary was developed to facilitate accurate scoring of participant responses.

Change in the HAM-D total score was the primary outcome. HAM-D interrater reliability was >0.95 (intraclass correlation coefficient, based on 234 interviews [with 50 participants] selected by computer-generated random numbers). Secondary outcomes were 1) responder status (defined a priori as depression much improved or very much improved based on Clinical Global Impression–Improvement scale ratings or a reduction of at least 50% from baseline in the HAM-D total score [30]); 2) depression (measured by the Beck Depression Inventory [BDI] [31]); 3) anxiety (based on the HAM-A score); 4) negative thoughts (measured by the Inference Questionnaire [32]); 5) sleep (measured by the Pittsburgh Sleep Quality Index [33]); 6) quality of life (measured by the social functioning, physical role limitations, and physical disability subscales of the Medical Outcomes Study Short-Form Health Survey [34]); 7) coping (measured by the positive reframing and problem-focused subscales of the brief COPE scale [35]); 8) social support (measured by the Social Feedback Questionnaire [36]); 9) caregiver burden (measured by the Caregiver Distress Scale [37]); and 10) Parkinson's disease symptoms (based on the Unified Parkinson's Disease Rating Scale total score [38]).

All scales were completed at baseline, week 5, endpoint (week 10), and the week 14 follow-up evaluation except the Unified Parkinson's Disease Rating Scale, which was given only at baseline and endpoint.

Intervention

CBT. The CBT employed in this trial was tailored to the unique needs of the Parkinson's disease population and is described in detail elsewhere (19, 39). In brief, specific modifications included 1) a stronger emphasis on behavioral and anxiety management techniques than what is traditionally integrated into CBT protocols for depression and 2) inclusion of a supplemental caregiver educational program. These changes were intended to address the psychiatric complexity and executive dysfunction that characterize this patient population.

Participants received 10 weekly individual sessions (60–75 minutes) of manualized CBT. Treatment incorporated exercise, behavioral activation, thought monitoring and restructuring, relaxation training, worry control, and sleep hygiene and was augmented with four separate individual caregiver educational sessions (30–45 minutes) that were intended to provide caregivers with the skills needed to facilitate participants' home-based practice of CBT techniques. For example, caregivers were taught to help participants identify negative thoughts and replace them with more balanced alternatives and were given tools to assist them in completing therapy goals (i.e., exercise, socializing). The primary focus was not to address the caregivers' own personal concerns. (The treatment manual is available upon request from the first author.)

Therapist Training and Treatment Fidelity

The first author (R.D.D.) and two doctoral-level psychologists (K.L.B. and J.F.) conducted CBT. Prior to treating the study participants, the latter two authors received extensive training in CBT for depression in Parkinson's disease, which included treating two nonstudy patients each, with audiotape review of all their sessions by the first author (N=40). Throughout the trial, the first author and an independent expert in CBT in medical populations (L.A.A.) reviewed audiotapes from the therapy sessions (N=150), based on training and supervision needs, and assessed therapist skill and treatment fidelity, on the Cognitive Therapy Scale (40), a widely used and validated CBT competence measure (with a score ≥40 reflecting proficiency; mean score=55.74 [SD=6.52]).

Clinical Monitoring

All participants received close clinical monitoring of their depressive symptoms by study personnel via follow-up telephone calls (at weeks 2 and 7 [30 minutes at each timepoint]) and evaluations (at weeks 5, 10, and 14 [60–90 minutes at each timepoint]). All participants remained on stable treatment regimens under the care of their personal physicians, who also monitored their medical and psychiatric status. No new depression treatment (other than CBT in the experimental condition) was provided.

Statistical Analyses

Data were analyzed using SAS, version 9.1 (SAS Institute, Cary, N.C.). An intent-to-treat approach was employed in all analyses, which included all 80 randomly assigned participants. The primary outcome (change in HAM-D total score) was evaluated at baseline and weeks 5, 10, and 14 using mixed-models repeated-measures analysis of variance (SAS PROC MIXED) with restricted maximum likelihood estimation. Treatment group (CBT plus clinical monitoring and clinical monitoring only), assessment point (baseline and weeks 5, 10, and 14), and their interaction were fixed effects. The randomly assigned participant was treated as a random effect. The group-by-time interaction was the fixed effect of interest. Spatial power (a function of the square root of days that a given assessment occurred for a given participant) was used to model the covariance structure for all analyses, since this model yielded the best fit for the data among all covariance structures examined. Gender, block, strata (antidepressant use), and baseline cognition (based on the Dementia Rating Scale total score) were examined as covariates. Because there was no significant effect for any of these variables, they were removed from the final model.

Responder status was examined separately at weeks 10 and 14 and cross-tabulated with treatment group. The Fisher's exact test was used to compare the rate of response between CBT plus clinical monitoring and clinical monitoring only. The aforementioned mixed-models analyses were used to explore all other secondary outcomes. Because multiple tests capitalize on chance, all p values for these secondary outcomes were adjusted for multiple tests by the Holm method using permutation-type resampling (100,000 resamples; two-tailed) in SAS PROC MULTTEST. Effect sizes were calculated for all primary and secondary outcomes. Planned contrasts to examine changes specific to a particular timepoint (i.e., week 10) were only conducted if the overall omnibus statistical test remained significant after adjustment for multiple comparisons. Least squared means are presented.

Sample size was determined a priori based on power analyses. Power calculations were based on the HAM-D total score, an alpha set at 0.05, power set at 0.80, a predicted effect size of Cohen's d (0.70), based on a previous CBT pilot investigation in Parkinson's disease conducted by the first author (19) as well as published literature on CBT for depression (41), and the potential for 20% attrition. These parameters indicated that 40 participants per group were needed to obtain the desired effect.

Results

Eighty individuals with Parkinson's disease, along with their caregivers, were enrolled in the study. Forty-one patients (51%) were randomly assigned to receive CBT plus clinical monitoring and 39 (49%) were assigned to receive clinical monitoring only. Ninety percent of participants (N=72) completed the study (see the data supplement). The mean number of CBT sessions attended was 9.17 ([SD= 2.32]). The mean number of caregiver sessions completed was 2.90 ([SD=1.43]). Forty-three participants (54%) were receiving a stable dose of antidepressant medication at baseline and reported compliance with their prescribed regimen throughout the trial. Baseline clinical and demographic characteristics are presented in Table 1.

Overall Treatment-by-Time Effects

Primary outcome. As seen in Table 2, the CBT plus clinical monitoring group reported significantly greater reductions in depression (HAM-D total score) compared with the clinical monitoring only group ($F=30.74$, df=3, 215, $p<0.0001$).

Secondary outcomes. Notable effects were also observed on depression (BDI scores), anxiety, social functioning, positive reframing, and Parkinson's disease symptom ratings for those in the experimental group relative to the comparison group (Table 2). No significant group-by-time improvements were noted for sleep, inferences, problem-focused coping, physical disability, physical role limitations, social support, or caregiver burden.

End of Treatment (Week 10)

Primary outcome. The mean HAM-D score was 13.58 (95% confidence interval [CI]=12.12–15.03) for CBT plus clinical monitoring and 19.33 (95% CI=17.89–20.77) for clinical monitoring only (Table 2). Mean change from baseline was 7.35 for CBT plus clinical monitoring compared with 0.05 for clinical monitoring only ($F=76.34$, df=1, 215, $p<0.0001$; Cohen's d=1.59) (Figure 1).

Secondary outcomes. The mean BDI score was 9.74 (95% CI=7.46–12.02) for CBT plus clinical monitoring relative to 17.45 (95% CI=15.19–19.72) for clinical monitoring only. Mean change from baseline was 9.44 for CBT plus clinical monitoring and 1.60 for clinical monitoring only ($F=27.25$, df=1, 210, $p<0.0001$; Cohen's d=1.1). Significant improvements were also observed on measures of anxiety ($F=25.83$, df=1, 214, $p<0.0001$), social functioning ($F=14.27$, df=1, 209, $p<0.001$), and positive reframing ($F=10.69$, df=1, 204, $p=0.001$) for CBT plus clinical monitoring relative to clinical monitoring only (Table 2). Although there was no significant group-by-time interaction on negative inferences, exploratory analyses suggested that treatment responders exhibited greater decreases in negative thoughts than nonresponders ($F=4.70$, df=2, 77, $p=0.01$).

Moreover, exploratory subscale analysis of the Unified Parkinson's Disease Rating Scale (significant group-by-

TABLE 1. Baseline Demographic and Clinical Characteristics Among Depressed Parkinson's Disease Patients Randomly Assigned to Receive CBT Plus Clinical Monitoring or Clinical Monitoring Alone

Characteristic	Participants (N=80)		Treatment: CBT Plus Clinical Monitoring (N=41)		Treatment: Clinical Monitoring Only (N=39)		Analysis[a]
	N	%	N	%	N	%	p
Gender							0.86
Male	48	60	25	61	23	59	
Female	32	40	16	39	16	41	
Primary DSM-IV diagnosis							0.74
Major depressive disorder	65	81	33	81	32	82	
Dysthymia	8	10	5	12	3	8	
Depression not otherwise specified	7	9	3	7	4	10	
Comorbid anxiety disorder	45	56.3	26	63	19	49	0.19
Antidepressant use[b]	43	54	22	54	21	54	0.99
Race							0.39
Caucasian	74	93	38	93	36	91	
African American	1	1	0	0	1	3	
Asian	4	5	3	7	1	3	
Pacific Islander	1	1	0	0	1	3	
Ethnicity							0.57
Hispanic	3	4	2	5	1	3	
Non-Hispanic	77	96	39	95	38	97	
Marital status							0.28
Married	57	71	32	78	25	64	
Divorced	12	12	6	15	6	15	
Widowed	9	11	3	7	6	16	
Never married	2	3	0	0	2	5	
Education							0.60
High school diploma	12	15	7	17	5	13	
Some college	14	17	7	17	7	17	
College degree	19	24	7	17	12	31	
Graduate degree	35	44	20	49	15	39	
Receiving disability	27	34	16	39	11	28	0.31
Deep brain stimulation	3	4	2	5	1	3	0.59
History of psychotherapy	50	62	27	66	23	59	0.53
Current supportive counseling	7	9	3	7	4	10	0.64
	Mean	SD	Mean	SD	Mean	SD	p
Age (years)	64.56	10.53	63.73	9.89	65.44	11.23	0.47
Parkinson's disease duration (years)	6.34	5.51	6.53	5.53	6.13	5.56	0.74
Age of Parkinson's disease onset (years)	58.21	11.78	57.12	11.22	59.36	12.39	0.40
Depression duration (current episode [years])	2.84	3.06	3.13	3.36	2.54	2.72	0.39
Clinical Global Impression Scale–Severity score	4.41	0.57	4.44	0.63	4.38	0.49	0.67
Hamilton Depression Rating Scale score	20.18	4.27	20.93	4.56	19.38	4.56	0.11
Beck Depression Inventory score	19.30	7.97	19.18	7.47	19.05	7.37	0.90
Hamilton Anxiety Rating Scale score	18.95	4.33	19.32	4.41	18.49	4.35	0.36
Dementia Rating Scale score[c]	138.24	4.9	139.44	3.8	136.97	5.5	0.02
Parkinson's disease stage (based on the Hoehn and Yahr scale)	2.14	0.77	2.12	0.90	2.16	0.83	0.81
Number of comorbid medical conditions	2.50	1.81	2.20	1.55	2.82	2.02	0.13
Number of current axis I diagnoses	1.80	0.92	1.88	0.81	1.72	1.03	0.44
Number of Parkinson's disease medications	1.75	1.04	1.80	1.23	1.69	0.80	0.63
Number of psychotropic medications	1.25	1.15	1.20	1.15	1.31	1.17	0.67
Number of total medications	7.64	3.99	7.17	3.40	8.13	4.53	0.29
Number of past depression medication trials	1.29	1.67	1.17	1.36	1.41	1.96	0.53
Time (weeks) to week-10 evaluation	11.79	2.75	11.70	3.40	11.90	1.87	0.76
Time (weeks) to week-14 evaluation	15.90	4.03	15.74	4.85	16.08	3.00	0.71

[a] CBT and clinical monitoring were compared at baseline on relevant demographic and clinical variables to determine group equivalence, using t or chi-square tests as appropriate.
[b] For participants receiving antidepressant medications, the average length of treatment with the stable regimen was 2 years; this did not differ between treatment groups.
[c] A nominal baseline difference was observed for the Dementia Rating Scale total score; the baseline score was added as a covariate in the analysis of the primary outcome (change in Hamilton Depression Rating Scale score); this was not a significant covariate and thus was removed from the final analysis. No significant differences emerged for any other variable.

TABLE 2. Outcome Variables Among Depressed Parkinson's Disease Patients Randomly Assigned to Receive CBT Plus Clinical Monitoring or Clinical Monitoring Alone

Outcome and Timepoint	Treatment				Analysis			
	CBT Plus Clinical Monitoring (N=41)		Clinical Monitoring Only (N=39)					
	Mean[a]	SD	Mean[a]	SD	F	df	p[b]	Cohen's d (Effect Size)[c]
Primary								
Hamilton Depression Rating Scale score[d]					30.74	3, 215	<0.0001	1.59
Baseline	20.93	4.56	19.38	4.56				
Midpoint	14.92*	4.73	19.71	4.56				
Endpoint	13.58*	4.72	19.33	4.55				
Follow-up evaluation	14.52*	4.75	19.31	4.63				
Secondary								
Beck Depression Inventory score[d]					9.77	3, 210	0.001	1.10
Baseline	19.18	7.47	19.05	7.37				
Midpoint	13.29	7.59	16.33	7.31				
Endpoint	9.74*	7.40	17.45	7.17				
Follow-up evaluation	11.18*	7.58	16.20	7.39				
Hamilton Anxiety Rating Scale score[d]					11.65	3, 214	0.001	0.98
Baseline	19.32	4.41	18.49	4.35				
Midpoint	15.41*	4.55	18.88	4.35				
Endpoint	14.73*	4.54	18.21	4.35				
Follow-up evaluation	15.36*	4.60	18.30	4.43				
Unified Parkinson's Disease Rating Scale score[d]					17.51	1, 68	0.001	0.41
Baseline	45.69	17.42	48.03	17.21				
Endpoint	40.11*	17.73	49.59	17.28				
Brief COPE scale score[e]								
Reframing subscale					4.25	3, 204	0.05	0.80
Baseline	4.59	1.63	4.23	1.61				
Midpoint	4.82	1.72	4.30	1.64				
Endpoint	5.78*	1.70	4.09	1.67				
Follow-up evaluation	5.16	1.75	4.33	1.68				
Problem-focused subscale					3.32	3, 204	0.12	0.61
Baseline	15.87	3.87	16.10	3.84				
Midpoint	16.55	4.05	14.86	3.90				
Endpoint	17.28	4.01	15.14	3.95				
Follow-up evaluation	16.69	4.11	16.20	3.96				
Medical Outcomes Study Short-Form Health Survey score[e]								
Social functioning subscale					5.07	3, 209	0.02	0.81
Baseline	58.44	22.05	54.17	21.78				
Midpoint	72.30*	23.07	54.13	22.03				
Endpoint	73.51*	22.82	51.32	21.71				
Follow-up evaluation	70.92*	23.34	53.64	22.37				
Physical disability subscale					2.60	3, 208	0.27	0.31
Baseline	54.00	27.46	49.30	27.12				
Midpoint	55.13	28.26	51.73	27.28				
Endpoint	63.15	27.99	49.89	27.08				
Follow-up evaluation	54.84	28.32	48.00	27.49				
Physical role limitations subscale					3.43	3, 209	0.12	0.58
Baseline	23.75	33.18	21.80	32.77				
Midpoint	40.99	34.95	17.47	33.35				
Endpoint	37.54	34.50	16.42	32.73				
Follow-up evaluation	32.45	35.59	24.86	33.96				
Social Feedback Questionnaire score[d]					1.33	3, 208	0.60	0.01
Baseline	4.68	4.25	5.54	4.20				
Midpoint	3.77	4.47	4.83	4.25				
Endpoint	4.05	4.40	4.62	4.20				
Follow-up evaluation	4.18	4.50	6.42	4.32				

continued

TABLE 2. Outcome Variables Among Depressed Parkinson's Disease Patients Randomly Assigned to Receive CBT Plus Clinical Monitoring or Clinical Monitoring Alone (*continued*)

Outcome and Timepoint	Treatment				Analysis			
	CBT Plus Clinical Monitoring (N=41)		Clinical Monitoring Only (N=39)					
	Mean[a]	SD	Mean[a]	SD	F	df	p[b]	Cohen's d (Effect Size)[c]
Pittsburgh Sleep Quality Index score[d]					1.06	3, 206	0.60	0.24
Baseline	10.93	4.02	11.20	4.02				
Midpoint	9.92	4.20	11.10	4.06				
Endpoint	9.56	4.14	10.82	4.09				
Follow-up evaluation	10.16	4.24	10.31	4.11				
Inference Questionnaire score[d]					0.63	3, 205	0.60	0.35
Baseline	6.92	3.41	6.92	3.37				
Midpoint	6.00	3.70	6.65	3.50				
Endpoint	4.97	3.56	6.19	3.38				
Follow-up evaluation	5.57	3.64	6.37	3.50				
Caregiver Distress Scale score[d]								
Baseline	24.26	14.88	22.45	14.88	1.31	3, 178	0.60	0.21
Midpoint	23.24	15.61	20.92	15.43				
Endpoint	21.08	15.34	22.41	15.20				
Follow-up evaluation	20.92	15.71	21.34	15.41				

[a] Data indicate least squares means.
[b] All p values for secondary outcomes have been adjusted using the Holm method. Raw p values are not reported.
[c] Data were calculated for the acute treatment period of baseline to endpoint.
[d] Lower scores indicate symptom improvement.
[e] Higher scores indicate symptom improvement.
* p≤0.01 (change significant from baseline).

time effect noted for the total score) indicated statistically significant change for mood (F=39.75, df=1, 68, p<0.0001) and motor functioning (F=5.90, df=1, 68, p=0.02) favoring CBT. Specifically, the mean motor score was 21.10 (95% CI=17.95–24.26) for CBT plus clinical monitoring and 25.38 (95% CI=22.26–28.50) for clinical monitoring only. Mean motor change was 1.11 (improvement) for CBT plus clinical monitoring compared with –2.16 (worsening) for clinical monitoring only.

One-Month Follow-Up Evaluation (Week 14)

Planned contrasts (baseline to week 14) demonstrated that improvements in depression (HAM-D score: F=55.62, df=1, 215, p<0.0001; BDI score: F=11.14, df=1, 210, p=0.001), anxiety (F=18.88, df=1, 214, p<0.0001), and social functioning (F=7.09, df=1, 209, p=0.008) were maintained at the follow-up evaluation (Table 2). Treatment responders continued to exhibit larger decreases in negative thoughts than nonresponders (F=3.04, df=3, 76, p=0.03). Parkinson's disease symptom ratings were not conducted at week 14.

Treatment Response

At week 10, 23/41 (56%) participants receiving CBT plus clinical monitoring and 3/39 (8%) receiving clinical monitoring only met criteria for treatment response (Fisher's exact test: p<0.0001). At week 14, 21 (51%) participants in the CBT plus clinical monitoring group and none in the clinical monitoring only group met criteria for response (Fisher's exact test: p<0.0001).

Number Needed to Treat

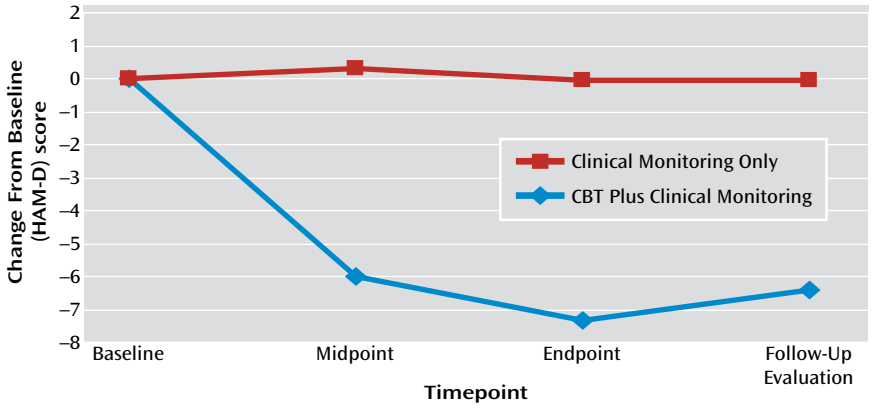
The number needed to treat based on responders for CBT plus clinical monitoring compared with clinical monitoring only was 2.1, with an absolute risk reduction of 48%.

Discussion

The results of this first randomized, controlled trial suggest that CBT may be a feasible and possibly efficacious approach for treating depression in Parkinson's disease. Ninety percent of the sample completed the study, and 88% of participants randomly assigned to CBT plus clinical monitoring attended all 10 treatment sessions. CBT was associated with significant improvements on all clinician-rated and self-reported measures of depression. Gains were observed by the end of treatment (week 10) and maintained during the follow-up evaluation (week 14). Effect sizes were large for both the HAM-D (1.59) and BDI (1.1). Response rates favored CBT plus clinical monitoring relative to clinical monitoring only at weeks 10 (56% versus 8%, respectively) and 14 (51% versus 0%, respectively).

The CBT plus clinical monitoring group also reported greater improvements in quality of life, coping, and anxiety as well as less motor decline. These results underscore several points. First, CBT participants reported less avoidance of and greater enjoyment from social activities as well as the use of positive reframing as a coping strategy in response to daily stress. Second, treatment effects may generalize to the negative thoughts and avoidance behaviors that maintain anxiety. Third, the incorporation of anxiety management

FIGURE 1. Hamilton Depression Rating Scale (HAM-D) Change Scores Among Parkinson's Disease Patients Randomly Assigned to Receive CBT Plus Clinical Monitoring or Clinical Monitoring Alone



strategies, such as worry control and relaxation, into a CBT program for primary depression in Parkinson's disease may be useful. Lastly, consistent with previous findings, suboptimally treated depression may accelerate Parkinson's disease-related physical disability (7, 42).

Although there was no significant group-by-time interaction on inferences, treatment responders exhibited larger decreases in negative thinking compared with nonresponders. Since negative thoughts are a primary target of CBT, it follows that people who did not respond to treatment would not exhibit changes in thinking patterns. Despite moderate effect sizes, the effect of CBT on problem-focused coping and perceptions of role limitations and physical disability was no longer significant after controlling for multiple comparisons. CBT also had no substantial effects on sleep, social support, or caregiver burden.

There are no controlled trials, to our knowledge, of CBT for depression in Parkinson's disease with which to compare these results. However, completion and response rates, as well as effect sizes, are comparable to those observed in randomized trials of CBT in other populations (41). For example, the literature suggests that the average effect size of CBT for depression relative to a comparison condition similar to the one utilized in this study (i.e., no new treatment) is 0.67 (41). Thus, this initial randomized, controlled trial offers preliminary data to suggest that the beneficial effects of CBT observed in other patient groups might not be attenuated by the disease process (i.e., neurodegeneration, neurotransmitter changes, dysfunction in brain regions/pathways).

This study has several limitations related to the interpretation of efficacy. First, the study design did not include an attention-matched control or alternative psychosocial intervention. Although the additive approach and comparison condition employed did control for threats to internal validity (i.e., time, spontaneous remission, regression to the mean, treatment history, effects of repeated testing) and are appropriate for use in early-phase psychotherapy trials (23, 43), the role of nonspecific factors, such as the increased attention and social contact received by the CBT group, cannot be adequately explored. It is also not possible to isolate which aspects of the CBT package (e.g., caregiver sessions, exercise) were most helpful. Related to this, we cannot rule out the placebo effect as a partial explanation for differences between groups. However, several factors make this explanation less likely. Throughout the trial, it was emphasized that the effects of both study treatments (CBT plus clinical monitoring and clinical monitoring only) on depression in Parkinson's disease were not yet known and that there may not be any personal benefit from participation. Additionally, the chronic nature of depression in the sample, progressive nature of Parkinson's disease (i.e., not an acute stressor), durability of CBT gains exhibited over 14 weeks, changes in negative cognition that accompanied treatment response, minimal improvement observed in the clinical monitoring only condition, and comparability of results with CBT trials in other populations suggest that the effect of CBT may be larger than that which can be explained by placebo response alone. Of note, a CBT effect size of 0.75 is obtained when comparing CBT data from this study with pill-placebo data from our recent double-blind placebo-controlled antidepressant trial for depression in Parkinson's disease (10).

Second, despite an average reduction of 7.35 points, the mean HAM-D score of 13.58 for the CBT group at week 10 still reflects moderate depressive symptoms. This finding may be in part a result of the high rate of somatic complaints experienced by Parkinson's disease patients, independent of depression, as well as the inclusive scoring approach employed (44). For example, all reported symptoms were counted toward HAM-D ratings, despite potential overlap with the physical symptoms of Parkinson's disease (i.e., psychomotor slowing, fatigue). Importantly, the BDI emphasizes cognitive symptoms of depression (i.e., guilt, hopelessness), and the mean week-10 BDI score of 9.7 for the CBT group indicates minimal symptoms of depression. Third, given the psychiatric comorbidity in the sample and the inclusion of two anxiety management modules in the CBT package, it is possible that reduced anxiety could have influenced depression treatment re-

Patient Perspective

A 64-year-old man with an 11-year history of Parkinson's disease was experiencing significant depression. Despite only mild motor symptoms, he rarely left the house because he believed that he would be viewed as frail. He stated, "People will view me as weak if I tremor in public." In order to test the accuracy of this belief, the patient and therapist walked around the medical school where the therapist worked, and 25 people were approached at random and asked what they think when they see someone in public who is struggling with a physical handicap. Twenty-four expressed that they would view the person as "strong or admirable" for living a full life despite physical limitations while only one indicated that she might view the person with pity. This experiment was a turning point for the patient, who learned that it is important to evaluate evidence for his negative thoughts before assuming they are true. Based on this new information, he changed his thought to: "While some people might view me as weak if I tremor in public, the majority will see me as strong." The patient's activity level increased, and his mood improved following this change in his thinking.

sponse. Because the depression effect remained robust ($p<0.0001$) when controlling for change in the HAM-A score (exploratory analyses), it is unlikely that improved anxiety was a main mechanism of action. Fourth, motor functioning results warrant prudent interpretation. Although the group-by-time interaction on motor scores at week 10 was statistically significant, the effect size was small (0.13) and may be an artifact of the sample.

It is also necessary to acknowledge that our results may not generalize to those in more advanced stages of disease or with severe depression, dementia, suboptimal social supports, inability to travel to weekly therapy, and limited access to specialized mental health resources. In addition, we could not explore the longer-term durability of treatment gains because the follow-up period was limited to 1 month for ethical reasons (protocol restrictions regarding changing depression treatment). Lastly, treatment side effects were not assessed prospectively. Collectively, these limitations suggest that the results should be viewed as a preliminary first step in the establishment of an evidence base for CBT in the treatment of the psychiatric complications of Parkinson's disease.

The precise cause of depression in Parkinson's disease is unclear, with both biological and psychosocial factors implicated in its onset and maintenance (45). As a whole, the results of this trial suggest that CBT for depression in patients with Parkinson's disease may be beneficial, independent of etiology. Further research is needed to replicate and extend these findings.

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