Neuropsychological Outcomes After Psychosocial Intervention for Depression in Parkinson's Disease

Roseanne D. Dobkin, Ph.D.
Alexander I. Tröster, Ph.D.
Jade Tiu Rubino, Psy.D.
Lesley A. Allen, Ph.D.
Michael A. Gara, Ph.D.
Margery H. Mark, M.D.
Matthew Menza, M.D.

The authors describe neuropsychological outcomes in people with Parkinson's disease (PD) after their participation in an NIH-sponsored, randomized, controlled trial of cognitive-behavioral treatment for depression. Improvements in mood were associated with modest gains in verbal memory and executive functioning over the 10-week treatment period and accounted for greater variance in neuropsychological outcomes at the end of treatment than other known correlates of cognitive functioning in PD, such as disease severity, age, and education. Baseline working memory and executive skills were also associated with depression improvement over time.

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Depression affects approximately 50% of people with Parkinson's disease (PD).[1] This high rate of depression in PD (dPD) is of great clinical concern because dPD is associated with faster physical and cognitive deterioration,[2] poorer quality of life,[3] greater impairment in activities of daily living,[4] more rapid initiation of dopaminergic-replacement treatment,[4] and heightened levels of caregiver distress.[5] In particular, the negative impact that depression has on cognitive functioning in PD has received substantial attention in the literature.

Depression has been identified as a risk factor for dementia in PD in both longitudinal and cross-sectional investigations.[6,7] Depression may also exacerbate the wide range of cognitive deficits observed in PD, including impaired global cognition, executive functions, memory, attention, and language.[8–11] These cognitive deficits may be most profound in depressed PD patients with lower levels of education,[9,12] higher levels of apathy,[11,13] more severe depression,[14] and a history of depression that predates the onset of the movement disorder.[15] Depression may also be a more robust

Received December 3, 2012; accepted February 1, 2013. From the Depts. of Psychiatry and Neurology, Robert Wood Johnson Medical School, University of Medicine & Dentistry of New Jersey, and the Barrow Neurological Institute, Arizona (AIT). Send correspondence to Dr. Dobkin; e-mail: dobkinro@umdnj.edu

predictor of cognitive impairment in PD than disease severity, age at PD onset, and PD treatment regimen.[16]

Nonetheless, the extent to which cognition in PD improves after successful treatment of depression remains to be elucidated. Although some dPD treatment studies have documented pre–post improvements in global cognitive functioning,[17,18] executive skills, and visual-spatial ability,[19] others have found treatment to be associated with neither negative cognitive effects nor cognitive changes of any kind.[20–22] In some instances, baseline cognition (i.e., better memory, executive functions) was found to predict improved depression treatment response, although cognitive improvement did not coincide with the amelioration of depression.[23,24] These limited data stem largely from pharmacological (antidepressant, dopamine-agonist) and rTMS (repetitive transcranial magnetic stimulation) trials. To the best of our knowledge, cognitive functioning has yet to be investigated as a secondary endpoint in psychosocial treatment studies for dPD.

The purpose of this article is to describe neuropsychological outcomes in people with PD after their participation in a cognitive-behavioral treatment (CBT) trial for depression.[25] We hypothesized a priori that reduction of depressive symptoms would be associated with improvements in verbal memory (primary outcome) and executive functions (secondary outcome) after the psychosocial treatment of dPD (as these specific cognitive domains have been most consistently associated with treatment response in past treatment trials of dPD.[19,23,24] Exploratory analyses also addressed 1) the impact of depressive symptom reduction on attention, working memory, and verbal fluency; 2) the effect of improved secondary anxiety (a psychiatric complication highly comorbid with dPD that may complicate its course and treatment and itself affect cognition in a variety of domains[26]); and 3) the extent to which better performance on individual neuropsychological tests over the course of the trial predicts improved mood after psychosocial intervention.

Overview

A randomized, controlled trial of CBT-plus clinical monitoring versus clinical monitoring-only for the treatment of dPD was conducted from April 2007 until July 2010 in the departments of Psychiatry and Neurology at Robert Wood Johnson Medical School (RWJMS). Treatment was provided for 10 weeks. The CBT protocol incorporated behavioral activation, cognitive restructuring, sleep hygiene, anxiety management, and caregiver psychoeducation. Clinical monitoring encompassed six in-depth discussions with study staff about mood and motor functioning. Participants continued on all stabilized (≥6 weeks) treatment regimens under the supervision of their personal physicians. Randomization was stratified by antidepressant use at baseline, such that participants taking antidepressant medications were equally represented in both treatment groups. Medication use for all purposes and mental health care utilization was tracked throughout the study. Post-enrollment changes in depression treatment (other than the study interventions) were a criterion for early termination; 90% of participants completed the trial.

The study had full RWJMS IRB approval. Written informed consent was obtained before the initiation of any study procedures. Participant characteristics, recruitment strategies, flow of participants through the trial, study procedures, sample size, and power calculations are detailed in the main outcome paper.[25] Key aspects of the experimental design are highlighted below.

Participants

Participants were recruited from the Richard E. Heikkila Movement Disorders Clinic at RWJMS. Enrollment criteria included: PD per NINDS Criteria,[27] a primary psychiatric diagnosis of Major Depressive Disorder (MDD), Dysthymia, or Depression Not Otherwise Specified (per the SCID for DSM-IV), a Clinical Global Impression Severity Scale (CGI–S) score of ≥4 (at least moderately ill),[28] age 35–85 years, stable medication regimen for ≥6 weeks, and a caregiver willing to participate in treatment. Significant motor fluctuations (≥50% of the day), suicidality, psychosis, or possible dementia (operationally defined as a score below the 5th percentile for age on memory and at least one other subscale on the Mattis Dementia Rating Scale)[29] were exclusionary.

Measures

Neuropsychological tests and mood and disability ratings were administered at baseline and Week 10 (end of treatment) by masters- or doctoral-level psychologists (or the study neurologist, who completed PD symptom ratings) who were blind to treatment assignment. The primary outcome of verbal memory was assessed by the Total Recall, Delayed Recall, and Recognition scores of the Hopkins Verbal Learning

Test–Revised (HVLT–R).[30] The secondary outcome of executive functioning was assessed by the time taken to complete the inhibition task from the Delis-Kaplan Executive Function System (D–KEFS) Color–Word Interference Test.[31] Exploratory outcomes included measures of attention and working memory (Digit Span, Letter-Number Sequencing, Spatial Span scores from the Wechsler Memory Scales),[32] and verbal fluency (D–KEFS letter fluency, category fluency, category switching scores). Alternative versions of the HVLT–R and D–KEFS verbal fluency test were administered at Baseline and Week 10. Mood and disability measures included the Hamilton Depression Rating Scale (Ham–D 17; depression),[33] Hamilton Anxiety Rating Scale (Ham–A),[34] and Unified Parkinson's Disease Rating Scale (UPDRS; for PD symptom severity).[35]

Statistical Analysis Data were analyzed with SPSS Version 18. We used an intent-to-treat approach. In order to determine the impact of improved mood on cognition, a median split was conducted on the Ham–D change score between Baseline and Week 10 for the entire sample. Individuals with a change score at or above the median were classified as More Improved. Those with a change score below the median were classified as Less Improved. Raw neuropsychological scores were converted to standard scores, using accepted normative data, before data analysis. Baseline neuropsychological data are presented in Table 1.

Data were first analyzed with mixed-models, repeated-measures analysis of variance. Group assignment (Depression Improvement: More/Less), assessment point (Baseline/Week 10), and their interaction were fixed effects. The Group × Time interaction was the fixed effect of interest. Results were adjusted for multiple comparisons via the Bonferroni correction within each specific hypothesis. The main effect of depression improvement was also examined to determine whether higher scores on specific cognitive measures over the course of the trial were associated with a stronger likelihood of improved mood after treatment. Compound symmetry was used to model the covariance structure for all analyses.

When the Group × Time interaction was significant, follow-up stepwise linear-regression analyses were conducted to determine the relative contribution of depression improvement on Week-10 cognition, controlling for other relevant variables such as baseline performance on the respective neuropsychological measure, PD severity (UPDRS total score), age, and education. All available participant data, coupled with a multiple-imputation approach to missing data, was used in computing all regression statistics. When the main effect of "depression improvement" was significant, follow-up discriminant-function analysis was conducted to determine whether baseline scores on these measures (collectively) predicted improved mood over time, and the extent to which each respective cognitive test contributed to the improved outcome.

Mixed models followed by stepwise linear regression were also used for exploratory analyses regarding anxiety improvement and cognition. If both anxiety and depression improvement predicted the same aspect of Week 10 cognition in separate analyses, additional stepwise linear-regression models were conducted in order to determine the relative contribution of each psychiatric complication, controlling for the other, (i.e., depression improvement was entered first, followed by anxiety improvement; the order was then reversed) to the neuropsychological domain of interest.

TABLE 1. Means and Standard Deviations (SD) for Baseline Neuropsychological Measures

Measure	Mean	(SD)
HVLT–R Total Recall	37.06	(10.95)
HVLT–R Delayed Recall	35.96	(11.58)
HVLT–R Recognition	40.64	(11.38)
Digit Span	10.20	(3.10)
Letter–Number Sequencing	9.01	(3.59)
Letter Fluency	10.91	(3.94)
Category Fluency	10.13	(3.57)
Category Switching	9.75	(4.08)
Spatial Span	9.37	(3.24)
D–KEFS Inhibition	8.16	(4.08)

HVLT–R: Hopkins Verbal Learning Test–Revised; D–KEFS: Delis–Kaplan Executive Function System. All data presented are standardized scores (HVLT–R: mean: 50; SD: 10; all other measures, mean: 10, SD: 3).

RESULTS

Characteristics of the Sample

Eighty people with PD (60% men) were enrolled. On average, participants were 64.56 (SD: 10.53) years old (range: 40–83) and had had PD for 6.34 (SD: 5.51) years; 89% had mild-to-moderate PD, based on the Hoehn & Yahr Scale. The majority of the sample was highly educated (68% had a college degree or higher), had

TABLE 2. Stepwise Linear-Regression Models: Depression, Memory, and Executive Skills in Parkinson's Disease

	Variables	Mean (SD)	β (95% CI)	β	p	R^2 Change
Week 10 Total Recall	Baseline HVLT–R Total Recall	37.06 (10.95)	0.60 (0.38 – 0.82)	0.56	0.000	27%
	Baseline UPDRS Total Score	46.86 (17.71)	0.03 (–0.11 – 0.17)	0.05	NS	0%
	Education (highest level)		–0.45 (–1.74 – 0.843)	–0.07	NS	0%
	Age, years	64.56 (10.53)	–0.13 (–0.36 – 0.10)	–0.09	NS	2%
	Depression improved (more/less)		6.21 (1.57 – 10.84)	0.27	0.009	6%
Week 10 Recognition	Baseline HVLT–R Recognition	40.64 (11.38)	0.38 (0.13 – 0.63)	0.34	0.003	13%
	Baseline UPDRS Total Score	46.86 (17.71)	0.13 (–0.04 – 0.30)	0.15	NS	0%
	Education (highest level)		0.78 (–0.76 – 2.32)	0.12	NS	1%
	Age, years	64.56 (10.53)	–0.09 (–0.36 – 0.18)	–0.07	NS	2%
	Depression improved (more/less)		9.40 (3.82 – 14.97)	0.36	0.001	11%
Week 10 Inhibition	Baseline D–KEFS Inhibition	8.16 (4.08)	0.81 (0.66 – 0.95)	0.80	0.000	68%
	Baseline UPDRS Total Score	46.86 (17.71)	0.00 (–0.04 – 0.33)	0.00	NS	0%
	Education (highest level)		0.00 (–0.30 – 0.31)	0.00	NS	0%
	Age, years	64.56 (10.53)	–0.02 (–0.07 – 0.04)	–0.05	NS	0%
	Depression improved (more/less)		1.29 (0.20 – 2.38)	0.15	0.021	2%

SD: standard deviation; CI: confidence interval; HVLT–R: Hopkins Verbal Learning Test–Revised; UPDRS: Unified Parkinson's Disease Rating Scale; Inhibition: Delis-Kaplan Executive Function System Color–Word Interference Subtest.

TABLE 3. Stepwise Linear-Regression Models: Anxiety and Memory in Parkinson's Disease

	Variables	Mean (SD)	β (95% CI)	β	p	R^2 Change
Week 10 Total Recall	Baseline HVLT–R Total Recall	37.06 (10.95)	0.61 (0.39 – 0.83)	0.56	0.000	28%
	Baseline UPDRS Total Score	46.86 (17.71)	0.02 (–0.12 – 0.17)	0.04	NS	0%
	Education (highest level)		–0.09 (–1.47 – 1.28)	–0.01	NS	1%
	Age, years	64.56 (10.53)	–0.16 (–0.39 – 0.71)	–0.12	NS	2%
	Anxiety improved (more/less)		5.45 (0.52 – 10.38)	0.24	0.030	5%
Week 10 Delayed Recall	Baseline HVLT–R Delayed Recall	35.96 (11.58)	0.60 (0.38 – 0.82)	0.56	0.000	30%
	Baseline UPDRS Total Score	46.86 (17.71)	0.03 (–0.12 – 0.17)	0.03	NS	0%
	Education (highest level)		0.85 (–0.59 – 2.29)	0.10	NS	0%
	Age, years	64.56 (10.53)	–0.18 (–0.42 – 0.05)	–0.14	NS	2%
	Anxiety improved (more/less)		6.93 (1.83 – 12.03)	0.28	0.008	6%

SD: standard deviation; CI: confidence interval; HVLT–R: Hopkins Verbal Learning Test–Revised; UPDRS: Unified Parkinson's Disease Rating Scale.

Major Depressive Disorder (81%; N=65) and a secondary anxiety disorder diagnosis (56.3%; N=45).

Mixed-Models Analyses

There was a significant Group (depression improvement) × Time interaction on Week 10 Total Recall (F[1,74]=7.15; p=0.009; Cohen's d=0.58) and Recognition (F[1,73]=7.08; p=0.007; Cohen's d=0.72) scores (for primary outcome Verbal Memory). There was a significant Group (depression improvement) × Time interaction on Week 10 Inhibition scores (F[1,72]=5.58; p=0.02; Cohen's d=0.31) for Executive Functioning (secondary outcome) No significant effects of depression improvement on Delayed Recall, Attention, Working Memory, or Verbal Fluency were observed.

There was a significant Group (anxiety improvement) × Time interaction on Week 10 Total Recall (F[1,74]=6.63; p=0.01; Cohen's d=0.56) and Delayed Recall scores (F[1,74]=8.48; p=0.008; Cohen's d=0.62; Verbal Memory, exploratory outcome). There were no significant effects of improved anxiety on Recognition, Executive Functioning, Attention, Working Memory, or Verbal Fluency.

Stepwise Regression Models

Depression improvement contributed unique variance to Verbal Memory (Total Recall: 6%, p=0.009; Recognition: 11%, p=0.001) and Executive Functioning (Inhibition: 2%, p=0.021) at Week 10, controlling for baseline scores on PD severity, education, and age (Table 2). Anxiety improvement contributed unique variance to Verbal Memory (Total Recall: 5%, p=0.030; Delayed Recall: 6%, p=0.008) at Week 10, in the stepwise linear-regression model (Table 3).

Both depression and anxiety improvement were implicated in HVLT−R Total and Delayed Recall scores at end of treatment. (There was trend for the Group

(depression improvement) × Time interaction on Week 10 Delayed Recall scores (p=0.09), so this was included in combined analyses in order to be conservative.) Results indicated that neither depression (p=0.08), nor anxiety (p=0.37), contributed unique variance to Total Recall, controlling for the other, at Week 10 (when added to the stepwise regression model described above). Moreover, depression did not contribute unique variance to Delayed Recall, controlling for anxiety. However, anxiety improvement contributed unique variance to Delayed Recall scores at Week 10 (5%; p=0.03), even when controlling for depression.

Exploratory Discriminant-Function Analysis

Main effects of the grouping variable "depression improvement" were observed on the following tests: Inhibition/Switch (F[1,77]=4.24; p=0.04), Recognition (F[1,76]=4.43; p=0.04), Spatial Span (F[1,76]=4.09; p=0.05), Digit Span (F[1,78]=6.21; p=0.02), and Letter Number Sequencing (F[1,78]=6.47; p=0.01). When baseline scores on these tests were entered as independent variables in a discriminant-function analysis (DFA) to predict depression improvement over time, the overall model was nonsignificant (p=0.10). Closer inspection of data revealed that Spatial Span and Recognition subtests had the lowest individual loadings with the overall function, and these were thus removed from a follow-up DFA. Results from this follow-up DFA were significant (χ^2[3]=9.25; p=0.026). Pooled within-group correlations between discriminating variables and standardized canonical discriminant functions were as follows: Letter−Number Sequencing (0.894), Digit Span (0.786), and Inhibition Switch (0.772).

DISCUSSION

This is the first article to describe the impact of psychosocial intervention for depression on neuropsychological functioning in PD. Results indicate that improvements in depression were associated with small gains in verbal memory and executive functioning after the psychosocial treatment of dPD. Moreover, higher baseline scores on measures of working memory and executive functioning were able to reliably discriminate between participants who derived greater benefits from treatment, and those who did not, over 10 weeks. Although effect sizes were modest, improvements in depression accounted for more variance in neuropsychological outcomes at the end of treatment than other known correlates of cognitive functioning in PD, such as disease severity, age, and education. Finally, changes in both depression and anxiety were implicated in gains in select aspects of verbal memory. The impact of anxiety on cognition was shared with depression for immediate recall, and a small but significant amount of unique variance was explained by anxiety only for the Delayed Recall measure.

There are no additional psychosocial treatment studies for dPD with which to compare these results. However, the present findings are consistent with the published literature regarding pharmacologic and rTMS approaches for the treatment of dPD. For example, baseline verbal memory and executive functions have been associated with better antidepressant response in PD, and memory and executive skills have been found to improve after longer-term antidepressant treatment (i.e., 6 months) and short-term rTMS of the left dorsolateral prefrontal cortex, respectively.[19,23,24] The finding of improved cognition with the amelioration of depression and anxiety is also consistent with the biological substrates of anxiety and depression in PD. Medial prefrontal cortex and cingulate cortex, in particular, although not exclusively, have been implicated in mood disturbance and fluctuation in PD[36,37]. Because both PD and depression can reduce frontal cortical blood flow, it is plausible that amelioration of such metabolic changes with treatment improves executive functions and aspects of memory. However, future studies would need to show that psychosocial treatment produces lasting or even transiently significant changes in cerebral metabolism in PD.

Also, the relationship between anxiety and both immediate and delayed recall, suggest an effect on encoding. This is also consistent with the shared biological substrate of depression and mood fluctuation, including anxiety, as described above.

Clinical Implications

Because baseline executive and working memory were predictive of treatment response, it is tempting to speculate whether attempts to improve executive functioning might improve the odds of depression treatment response in PD. Such speculation is premature, given that there is only very limited evidence that remediation of executive and working-memory deficits can be accomplished in PD,[38] and there are no data regarding cognitive remediation in PD patients with depression.

However, the present data do suggest that successful depression treatment may be associated with cognitive improvements. Thus, it may be beneficial for depression treatment to be initiated before cognitive remediation attempts, so that lesser cognitive deficits need to be addressed in cognitive remediation.

Another issue that arises is whether cognitively impaired PD patients can benefit from psychosocial treatment of depression. There are no data addressing this issue, but extant literature on patients with Alzheimer's disease indicate that manualized psychosocial treatments for depression can be effective, although cognitive-behavioral treatments are more apt to be successful in mildly impaired patients, and more behavioral strategies may need to be used in persons with moderate cognitive compromise.[39]

Limitations

The study was not of sufficient duration (10 weeks) to assess the long-term clinical significance of the observed findings. Results also might not generalize to all dPD patients. The majority of the sample had MDD, was highly educated (possibly due to a strong preference among this subgroup for psychotherapy as a primary intervention for depression[40]), and had a supportive caregiver. The cognitive effects of treatment may be less profound in a mildly depressed sample (with perhaps lesser cognitive dysfunction) or a sample with lower levels of education and less social support. The restricted range on variables, such as education and disease severity, observed in the sample, may also have resulted in their minimal correlation with cognition in stepwise regression analyses. Finally, sample size was modest per clinical-trial standards. Additional cognitive effects may have been observed with larger numbers.

Summary and Conclusions

This study provides preliminary evidence to suggest that memory and executive functioning may improve after the successful psychosocial treatment of dPD. Anxiety, a common correlate of depression, may also influence cognitive changes in PD and may be most relevant to the assessment of delayed recall. Although a median split on depression-change scores was used to define the degree of mood improvement for study participants, 78% of the "more improved" group was randomized to CBT. Thus, we believe that these results generalize to both psychosocial treatment in general and CBT in particular. Further research is needed to replicate and extend these findings.

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References

1. Reijnders JS, Ehrt U, Weber WEJ, et al: A systematic review of prevalence studies of depression in Parkinson's disease. Mov Disord 2008; 23:183–189, quiz 313
2. Starkstein SE, Mayberg HS, Leiguarda R, et al: A prospective longitudinal study of depression, cognitive decline, and physical impairments in patients with Parkinson's disease. J Neurol Neurosurg Psychiatry 1992; 55:377–382
3. Forsaa EB, Larsen JP, Wentzel-Larsen T, et al: Predictors and course of health-related quality of life in Parkinson's disease. Mov Disord 2008; 23:1420–1427
4. Ravina B, Camicioli R, Como PG, et al: The impact of depressive symptoms in early Parkinson disease. Neurology 2007; 69:342–347
5. Carter JH, Stewart BJ, Lyons KS, et al: Do motor and non-motor symptoms in PD patients predict caregiver strain and depression? Mov Disord 2008; 23:1211–1216
6. Marder K, Tang MX, Cote L, et al: The frequency and associated risk factors for dementia in patients with Parkinson's disease. Arch Neurol 1995; 52:695–701
7. Riedel O, Heuser I, Klotsche J; GEPAD Study Group, et al: Occurrence risk and structure of depression in Parkinson disease with and without dementia: results from the GEPAD Study. J Geriatr Psychiatry Neurol 2010; 23:27–34
8. Fernandez HH, See RH, Gary MF, et al: Depressive symptoms in Parkinson disease correlate with impaired global and specific cognitive performance. J Geriatr Psychiatry Neurol 2009; 22:223–227
9. Kummer A, Harsányi E, Dias FM, et al: Depression impairs executive functioning in Parkinson disease patients with low educational level. Cogn Behav Neurol 2009; 22:167–172
10. Kuzis G, Sabe L, Tiberti C, et al: Cognitive functions in major depression and Parkinson disease. Arch Neurol 1997; 54:982–986
11. Santangelo G, Vitale C, Trojano L, et al: Relationship between depression and cognitive dysfunctions in Parkinson's disease without dementia. J Neurol 2009; 256:632–638
12. Klepac N, Trkulja V: Education effect on depression and quality of life in nondemented Parkinson's disease patients. J Neuropsychiatry Clin Neurosci 2009; 21:314–322
13. Butterfield LC, Cimino CR, Oelke LE, et al: The independent influence of apathy and depression on cognitive functioning in Parkinson's disease. Neuropsychology 2010; 24:721–730
14. Costa A, Peppe A, Carlesimo GA, et al: Major and minor depression in Parkinson's disease: a neuropsychological investigation. Eur J Neurol 2006; 13:972–980

15. Klepac N, Hajnsek S, Trkulja V: Cognitive performance in nondemented, nonpsychotic Parkinson disease patients with or without a history of depression prior to the onset of motor symptoms. J Geriatr Psychiatry Neurol 2010; 23:15–26
16. Stefanova E, Potrebic A, Ziropadja L, et al: Depression predicts the pattern of cognitive impairment in early Parkinson's disease. J Neurol Sci 2006; 248:131–137
17. Fregni F, Santos CM, Myczkowski ML, et al: Repetitive transcranial magnetic stimulation is as effective as fluoxetine in the treatment of depression in patients with Parkinson's disease. J Neurol Neurosurg Psychiatry 2004; 75:1171–1174
18. Weintraub D, Mavandadi S, Mamikonyan E, et al: Atomoxetine for depression and other neuropsychiatric symptoms in Parkinson disease. Neurology 2010; 75:448–455
19. Boggio PS, Fregni F, Bermpohl F, et al: Effect of repetitive TMS and fluoxetine on cognitive function in patients with Parkinson's disease and concurrent depression. Mov Disord 2005; 20:1178–1184
20. Devos D, Dujardin K, Poirot I, et al: Comparison of desipramine and citalopram treatments for depression in Parkinson's disease: a double-blind, randomized, placebo-controlled study. Mov Disord 2008; 23:850–857
21. Menza M, Dobkin RD, Marin H, et al: A controlled trial of antidepressants in patients with Parkinson disease and depression. Neurology 2009; 72:886–892
22. Rektorová I: Effects of dopamine agonists on neuropsychiatric symptoms of Parkinson's disease. Neurodegener Dis 2010; 7:206–209
23. Dobkin RD, Menza M, Bienfait KL, et al: The impact of antidepressant treatment on cognitive functioning in depressed patients with Parkinson's disease. J Neuropsychiatry Clin Neurosci 2010; 22:188–195
24. Weintraub D, Taraborelli D, Morales KH, et al: Escitalopram for major depression in Parkinson's disease: an open-label, flexible-dosage study. J Neuropsychiatry Clin Neurosci 2006; 18:377–383
25. Dobkin RD, Menza M, Allen LA, et al: Cognitive-behavioral therapy for depression in Parkinson's disease: a randomized, controlled trial. Am J Psychiatry 2011; 168:1066–1074
26. Ryder KA, Gontkovsky ST, McSwan KL, et al: Cognitive function in Parkinson's disease: association with anxiety but not depression. Neuropsychol Dev Cogn B Aging Neuropsychol Cogn 2002; 9:77–84
27. Gelb DJ, Oliver E, Gilman S: Diagnostic criteria for Parkinson disease. Arch Neurol 1999; 56:33–39
28. Guy W: ECDEU Assessment Manual for Psychopharmacology. Washington, DC, U.S. Department of Health, Education, and Welfare, 1976
29. Mattis S: Dementia Rating Scale. Odessa, FL, Psychological Assessment Resources, 1988
30. Benedict RHB, Schretlen D, Groninger L, et al: Hopkins Verbal Learning Test–Revised: normative data and analysis of interform and test–retest reliability. Clin Neuropsychol 1998; 12:43–55
31. Delis D, Kaplan E, Kramer J: Delis-Kaplan Executive Function System. San Antonio, TX, Psychological Corporation, 2001
32. Wechsler D: Wechsler Memory Scale, 3rd Edition. San Antonio, TX, Psychological Corporation, 1997
33. Hamilton M: A rating scale for depression. J Neurol Neurosurg Psychiatry 1960; 23:56–62
34. Hamilton M: The assessment of anxiety states by rating. Br J Med Psychol 1959; 32:50–55
35. Fahn S, Elton RL, members of the UPDRS Development Committee: Unified Parkinson's Disease Rating Scale, in Recent Developments in Parkinson's Disease. Edited by Fahn S, Marsden CD, Calne DB, et al. Florham Park, NJ, Macmillan Health Care Information, 1987, pp 53–64
36. Black KJ, Hershey T, Hartlein JM, et al: Levodopa challenge neuroimaging of levodopa-related mood fluctuations in Parkinson's disease. Neuropsychopharmacology 2005; 30: 590–601
37. Ring HA, Bench CJ, Trimble MR, et al: Depression in Parkinson's disease: a positron emission study. Br J Psychiatry 1994; 165:333–339
38. Calleo J, Burrows C, Levin H et al. M. Cognitive rehabilitation for executive dysfunction in Parkinson's disease: application and current directions. Parkinson Dis 2012; Article ID 512892, 6 pages; *doi:10.1155/2012/512892*
39. Teri L, Gallagher-Thompson D: Cognitive-behavioral interventions for treatment of depression in Alzheimer's patients. Gerontologist 1991; 31:413–416
40. Houle J, Villaggi B, Beaulieu MD: Treatment preferences in patients with first episode major depression. J Affect Disord 2013; 147:94–100; available at *doi: 10.1016/j.jad.2012.10.016*