

# Anxiety, depression, and quality of life in Parkinson's disease: the implications of multidisciplinary treatment

<https://doi.org/10.4103/1673-5374.293151>

Received: January 10, 2020

Peer review started: January 20, 2020

Accepted: May 12, 2020

Published online: September 22, 2020

Viviana Lo Buono, Rosanna Palmeri, Simona De Salvo, Matteo Berenati, Agata Greco, Rosella Ciurleo, Chiara Sorbera, Vincenzo Cimino, Francesco Corallo\*, Placido Bramanti, Silvia Marino, Giuseppe Di Lorenzo, Lilla Bonanno

## Abstract

Anxiety and depression in Parkinson's disease (PD) reduce well-being of the patients. Emotional alterations influence motor skills and cognitive performance; moreover, they contribute significantly and independently to worsen rehabilitative treatment response. We investigated anxiety, depression, and quality of life in PD patients subjected to multidisciplinary rehabilitative training. The self-controlled study included 100 PD patients (49 males and 51 females with the mean age of 64.66 years) admitted to 60 days hospitalization rehabilitative program, between January 2017 and December 2018. Motor, cognitive, linguistic abilities, and functional independence were evaluated at admission (T0 baseline visit) and 60 days after (T1) the multidisciplinary rehabilitation including motor exercises, speech therapies, and cognitive intervention. The multidisciplinary rehabilitation improved functional status in PD patients and exerted its positive effects on mood, motor abilities, autonomy in the activities of daily life, perception of quality of life, cognitive performance and speech skills. Non-motor symptoms may worsen severe disability and reduce quality of life. They are often poorly recognized and inadequately treated. Nonetheless, multidisciplinary rehabilitative training represents an optimal strategy to improve disease management. The study was approved by Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Centro Neurolesi "Bonino-Pulejo" Ethical Committee (approval No. 6/2016) in June 2016.

**Key Words:** anxiety; depression; multidisciplinary rehabilitation; Parkinson's disease

Chinese Library Classification No. R493; R741; R749

## Introduction

Parkinson's disease (PD) is a neurodegenerative disorder related to dopaminergic innervation loss in the substantia nigra. PD is characterized by motor symptoms including tremor, postural instability, muscle rigidity and bradykinesia (Bhat et al., 2018) and non-motor symptoms such as cognitive impairment, olfactory dysfunctions and mood alterations (Van Laar and Jain, 2004).

Non-motor symptoms in PD represent one of the major challenges faced in the management of disease. These symptoms are often underdiagnosed and do not respond adequately to dopaminergic therapy (Fabbri et al., 2017; Ztaou et al., 2018). Non-motor symptoms, like depression or anxiety (Palmeri et al., 2017) may impair patient's quality of life (QoL), worsen daily living activities, reduce the opportunities of leisure and a normal social life and compromise psychological well-being (D'lorio et al., 2017; Ciurleo et al., 2018; Lerman et al., 2019). Several studies also showed the influence of emotional disturbances on motor skills, in particular on walking speed and gait initiation reaction time (Avanzino et al., 2018; Jazaeri et al., 2018). Episodic anxiety has been associated with motor fluctuations (Chen and Marsh, 2014)

and freezing episodes are highly correlated with the presence of panic disorders (Lauterbach et al., 2003).

PD patients frequently present mild cognitive impairment (MCI). MCI indicates a syndrome of cognitive decline greater than expected based on age and the level of education, however, does not interfere with the ability to perform daily life activities (Petersen et al, 2014).

This decreased cognitive performance in multiple domains represents a risk factor for the increase of anxiety and depression (Corallo et al., 2017; Petkus et al., 2019). It has been shown that depressive mood affects language performance in PD patients (Starkstein et al., 1989). Numerous language problems manifest in PD, such as vocal articulation. In particular, PD patients showed dysarthria, spontaneous speech reduction and verbal fluency deficits (Liu et al., 2015).

Mood alterations in PD patients are also associated with a worse response to rehabilitation treatment and a great functional impairment (Dissanayaka et al., 2015; Schrag and Taddei, 2017). In addition to the basic pharmacological treatment, non-pharmacological treatment, such as

Department of Neurobioimaging, Istituto di Ricovero e Cura a Carattere Scientifico IRCCS Centro Neurolesi Bonino-Pulejo, Messina, Italy

\*Correspondence to: Francesco Corallo, francesco.corallo80@yahoo.it.

<https://orcid.org/0000-0003-4862-3832> (Francesco Corallo)

**Funding:** This study was supported by a grant from the Italian Health Minister, No. GR-2013-02359069.

**How to cite this article:** Lo Buono V, Palmeri R, De Salvo S, Berenati M, Greco A, Ciurleo R, Sorbera C, Cimino V, Corallo F, Bramanti P, Marino S, Di Lorenzo G, Bonanno L (2021) Anxiety, depression, and quality of life in Parkinson's disease: the implications of multidisciplinary treatment. *Neural Regen Res* 16(3):587-590.

## Research Article

multidisciplinary rehabilitation treatment, is also generally recommended because it is able to treat both the motor and non-motor aspects of PD.

Neurorehabilitative training is an important approach to improve functional status in PD, in particular, multidisciplinary care program showed positive effect on motor and non-motor symptoms (Dockx et al., 2016; Biundo et al., 2017; Kaseda et al., 2017). In this study, we investigated changes in anxiety and depressive symptoms and quality of life in PD patients under multidisciplinary rehabilitative training.

## Subjects and Methods

### Subjects

One hundred PD patients hospitalized at our neurorehabilitative unit were admitted to 60 days hospitalization rehabilitative program; the recruitment time was between January 2017 and December 2018.

All subjects signed informed consent in accordance with the Declaration of Helsinki. The study was approved by Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Centro Neurolesi "Bonino-Pulejo" Ethical Committee (approval No. 6/2016) in June 2016.

Inclusion criteria were: diagnosis of idiopathic PD according to the UK Brain Bank criteria (Lyons and Pahwa, 2011), Hoehn and Yahr stages (Hoehn and Yahr, 1996) 2–3 and stable pharmacological treatment (dopaminergic therapy: dopamine agonists and Levo-dopa both) in the last 6 weeks. Exclusion criteria were: atypical Parkinsonisms, PD with dementia according to Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria (American Psychiatric Association, 2013); other neurological or psychiatric disorders.

The mean age of included patients was  $64.66 \pm 6.85$  years, the mean time of education was  $10.33 \pm 4.45$  years, and the mean disease duration was  $7.57 \pm 3.46$  years. The assessments were performed at the date of admission (T0 baseline visit) and 60 days later (T1).

### Anxiety, depression and quality of life evaluations

Motor conditions of PD patients were evaluated by means of unified Parkinson's disease rating scale-Part III (UPDRS) (Fahn et al., 1987) The Barthel Index rating scale (Hobart and Thompson, 2001) was used to measure performance in activities of daily living and functional independence (ADL). The neuropsychological evaluation was assessed using Addenbrooke's Cognitive Examination-Revised (ACE-R) (Mioshi et al., 2006), a brief battery that provides evaluation of six cognitive domains: orientation and attention, memory, verbal fluency, language and visuospatial ability.

Beck Depression Inventory (BDI-II) and Hamilton Anxiety Rating Scale (HAM-A) (Hamilton, 1959) were used for evaluation of depressive and anxiety symptoms, respectively. Quality of life was evaluated by means of Parkinson's Disease Quality of Life Questionnaire (PDQ-39) (Jenkinson et al., 1997). Speech language was assessed using the Clinical Bedside Swallowing examinations (Carnaby-Mann and Lenius, 2008) for dysphagia and Robertson dysarthria profile, clinical-perceptual methods exploring all components potentially involved in speech difficulties.

### Rehabilitative program

Rehabilitative program included motor, cognitive, and speech language training. Motor training was based on task-oriented

exercises; balance exercises and gait training have been carried out as they improve mobility. The cognitive training included specific exercises, paper-and-pencil or computerized tasks oriented to attention/working memory, psychomotor speed, executive functions, visuo-spatial abilities, and calculation skills. Speech language training included an intensive stimulation of speech intensity, exercises to improve verbal intelligibility, treatment of limitations to swallowing choking and slowness of chewing. Every day rehabilitative program was organized according to a predefined scheme: motor exercises (60 minutes), language exercises (60 minutes), cognitive exercises (60 minutes). The rehabilitation program lasted 8 weeks. Rehabilitation also included psychoeducation intervention once a week (60 minutes) in group setting, focused on information and explanations about the disease and the possible effects on patients' psychological wellbeing. Four main areas were targeted: disease awareness, adherence to treatment, detection of motor and non-motor symptoms, and lifestyle regularity.

### Statistical analysis

The Shapiro normality test was used to verify the distribution of variables. Data that do not follow a normal distribution are presented in median and first-third quartile.

The Mann-Whitney *U* test was used to compare clinical variables between two time points, while correlations between demographic characteristics and clinical variables were analyzed by Spearman's coefficient.

For analysis, we used an open source R3.0 software package considering a confidence level of 95%, a 5% alpha error and statistical significance at  $P < 0.05$ .

## Results

### Clinical variables

The Mann-Whitney *U* test showed significant differences in almost all clinical variables between T0 and T1 (**Table 1**). No significant difference was found in cognition ( $P = 0.82$ ), sub-item PDQ-39. Moreover, memory, verbal fluency, and visuospatial abilities, sub-items of ACE-R, remained unchanged between T0 and T1.

### Correlations of anxiety, depression and quality of life with clinical features

UPDRS-III scores were significantly positively correlated with education ( $r_s = 0.21, P = 0.03$ ) and BDI-II scores were negatively correlated with and disease duration (DD) ( $r_s = -0.28, P = 0.004$ ). Significant correlations between Barthel Index and education ( $r_s = -0.19, P = 0.06$ ), UPDRS and education ( $r_s = 0.18, P = 0.07$ ), HAM-A and DD ( $r_s = -0.18, P = 0.07$ ) were found.

### Predictors

Results in **Table 2** showed the significant impact of BDI-II, HAM-A and UPDRS-III scores on sub-item of PDQ-39. BDI-II and HAM-A were significant predictors of mobility, while UPDRS-III was a significant predictor of communications.

## Discussion

Emotional disturbances are frequently observed in PD patients and aggravate their motor symptoms, thereby leading to increased disability, high healthcare costs, and poor quality of life. In some cases, depression and anxiety may precede the diagnosis of PD; however, the under-recognition and side effects of the pharmacological management of

**Table 1 | Clinical scores to assess motor, cognition, dysphagic and quality of life features at the date of admission (T0 baseline) and after 60 days (T1)**

	T0	T1	P-value
Barthel Index	65(65–75)	85(75–90)	< 0.001**
UPDRS_III	50(40–62)	35(29–48)	< 0.001**
UPDRS	99(86–123)	75(63–92)	< 0.001**
ACE-R			
Attention and Orientation	16(13–18)	18(16–18)	< 0.001**
Memory	17(12–22)	17(12–22)	–
Verbal fluency	9(7–12)	9(7–12)	–
Language	23(19–25)	24(22–25)	< 0.001**
Visuospatial abilities	11(8–13)	11(8–13)	–
TOT	81(74–88)	82(75–90)	0.004*
MMSE	27(25–28)	28(26–30)	< 0.001**
BDI-II	24(18–29)	15(12–21)	< 0.001**
HAM-A	21(17–27)	14(10–18)	< 0.001**
Dysarthria	216(192–245)	240(213–255)	< 0.001**
BEDSIDE SWALLOW	8(8–9)	8(8–8)	< 0.001**
WATER SWALLOW TEST_STEP1	8(8–8)	8(8–8)	0.0001**
WATER SWALLOW TEST_STEP2	5(5–5)	5(5–5)	0.003*
PDQ-39			
Mobility	50(30–75)	35(29.2–50)	< 0.001**
Activities of daily living	45(25–65)	41(25–50)	0.0005**
Emotional well being	50(29–58)	37(25–50)	< 0.001**
Stigma	54(25–68)	25(15–43)	< 0.001**
Social support	25(0–52)	20(0–35)	0.0007**
Cognitions	37(18–50)	35(25–50)	0.820
Communication	25(9–50)	25(8–33)	0.007*
Bodily discomfort	42(25–50)	33(25–50)	< 0.001**

Data are expressed as median (I–III quartile). \* $P < 0.01$ , \*\* $P < 0.001$  (Mann-Whitney  $U$  test). ACE-R: Addenbrooke's Cognitive Evaluation-Revised; BDI-II: Beck Depression Inventory; HAM-A: Hamilton Anxiety Rating Scale; I: First quartile; III: third quartile; MMSE: Mini Mental State Examination; PDQ-39: Parkinson Disease Questionnaire-39; UPDRS: Unified Parkinson Disease Rating Scale. "–": In memory, verbal fluency, and visuospatial abilities, the median was the same at T0 and T1, so the  $P$ -value cannot be calculated.

psychopathologic symptoms in the PD population are considerable. Mood alterations in PD may be a consequence of interactions between the neurodegeneration of neurochemical pathways involved with regulating depression and anxiety, in particular of the specific loss of dopaminergic and noradrenergic innervation in the limbic system (Wee et al., 2016). In addition, mood disorders could onset as a psychological response to the physical symptoms and side effects of dopaminergic treatments (Pachana et al., 2013). Anxiety or depressive symptoms have important clinical implications; their recognition and correct management are essential in the rehabilitative training. A multidisciplinary approach has been frequently proposed for rehabilitation both in motor and in non-motor symptoms in PD (Ellis et al., 2008; van der Marck et al., 2013; Ferrazzoli et al., 2018). The important effect of high intensity multidisciplinary treatment on motor symptoms severity, physical function and quality of life persist also after 1 year (Abbruzzese et al., 2016). In addition, rehabilitation treatment demonstrated some efficacy against cognitive decline in PD patients (Diez-Cirarda et al., 2018).

Our findings showed improvements in functional status in patients following specialized multidisciplinary rehabilitation. In our patients, the items which showed a remarkable improvement were those related to motor function, balance and gait. After rehabilitative treatment, patients showed improvements in attention and language performance, especially in prosody and vocal articulation. Cognitive

**Table 2 | Backward linear regression: significant predictors on each subscale of PDQ-39**

Dependent variables	Predictors	$\beta$	Std $\beta$	P-value	Adjusted $R^2$
Mobility	BDI-II	0.55	0.22	0.02	0.05
	HAM-A	–0.52	–0.17	0.08	
Communications	UPDRS III	–0.63	–0.37	< 0.001	0.12

BDI-II: Beck Depression Inventory; HAM-A: Hamilton Anxiety Rating Scale; PDQ-39: Parkinson's Disease Questionnaire; Std  $\beta$ : standardized regression coefficient; UPDRS-III: Unified Parkinson's disease rating scale;  $\beta$ : regression coefficient.

strategies resulted in reinforcement of attention in patients that learned to better manage their disease and enhance empowerment skills also using compensatory strategies or external cues. The improvement of symptoms was associated with a mood increase and subjective sense of well-being. Moreover, the participation in the psychoeducational groups decreased the level of self-stigma and improved perception of quality of life.

This study has several limitations that should be considered. First, the sample size is small, and the important data must be addressed by studies involving a larger sample size. Second, we cannot determine whether the benefit from the rehabilitative treatment was maintained for a long time after discharge. Further studies with a larger population and a longer-term follow-up can allow us to confirm these results.

## Conclusion

Although traditionally considered a pure motor disorder, PD is increasingly recognized as a complex disease process. Anxiety and depression are the most common non-motor symptoms in PD with a potential negative impact on motor disability and quality of life. Multidisciplinary rehabilitative training has potential to improve PD management.

**Author contributions:** Study design: VLB; study implementation: VLB, RP, PB, SM, GDL; data collection and analysis: SDS, MB, AG, RC, CS, VC, FC, LB; manuscript preparation: VLB, RP, LB, FC; approval of final version of this manuscript for publication: all authors.

**Conflicts of interest:** The authors declare no conflicts of interest.

**Financial support:** This study was supported by a grant from the Italian Health Minister, No. GR-2013-02359069.

**Institutional review board statement:** The study was supported by approved by Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Centro Neurolesi "Bonino-Pulejo" Ethical Committee (approval No. 6/2016) in June 2016.

**Declaration of patient consent:** The authors certify that they have obtained all appropriate patient consent forms. In the forms, the patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity.

**Reporting statement:** This study followed the Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals developed by the International Committee of Medical Journal Editors.

**Biostatistics statement:** The statistical methods of this study were reviewed by the biostatistician of Istituto di Ricovero e Cura a Carattere Scientifico IRCCS Centro Neurolesi Bonino-Pulejo, Messina, Italy.

**Copyright license agreement:** The Copyright License Agreement has been signed by all authors before publication.

**Data sharing statement:** Datasets analyzed during the current study are available from the corresponding author on reasonable request.

**Plagiarism check:** Checked twice by iThenticate.

**Peer review:** Externally peer reviewed.

**Open access statement:** This is an open access journal, and articles are distributed under the terms of the Creative Commons Attribution-Non-

# Research Article

*Commercial-ShareAlike 4.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as appropriate credit is given and the new creations are licensed under the identical terms.*

## References

- Abbruzzese G, Marchese R, Avanzino L, Pelosin E (2016) Rehabilitation for Parkinson's disease: current outlook and future challenges. *Parkinsonism Relat Disord* 22 Suppl 1:S60-64.
- American Psychiatric Association (2013) *Diagnostic and Statistical Manual of Mental Disorders*. 5<sup>th</sup> ed. Washington, DC: APA.
- Avanzino L, Lagravinese G, Abbruzzese G, Pelosin E (2018) Relationships between gait and emotion in Parkinson's disease: A narrative review. *Gait Posture* 65:57-64.
- Bhat S, Acharya UR, Hagiwara Y, Dadmehr N, Adeli H (2018) Parkinson's disease: Cause factors, measurable indicators, and early diagnosis. *Comput Biol Med* 102:234-241.
- Biundo R, Weis L, Fiorenzato E, Antonini A (2017) Cognitive rehabilitation in Parkinson's disease: is it feasible? *Arch Clin Neuropsychol* 32:840-860.
- Carnaby-Mann G, Lenius K (2008) The bedside examination in dysphagia. *Phys Med Rehabil Clin N Am* 19:747-768.
- Chen JJ, Marsh L (2014) Anxiety in Parkinson's disease: identification and management. *Ther Adv Neurol Disord* 7:52-59.
- Ciurleo R, Corallo F, Bonanno L, Lo Buono V, Di Lorenzo G, Versaci R, Allone C, Palmeri R, Bramanti P, Marino S (2018) Assessment of Duodopa® effects on quality of life of patients with advanced Parkinson's disease and their caregivers. *J Neurol* 265:2005-2014.
- Corallo F, De Cola MC, Lo Buono V, Di Lorenzo G, Bramanti P, Marino S (2017) Observational study of quality of life of Parkinson's patients and their caregivers. *Psychogeriatrics* 17:97-102.
- Diez-Cirarda M, Ibarretxe-Bilbao N, Peña J, Ojeda N (2018) Efficacy of cognitive rehabilitation in Parkinson's disease. *Neural Regen Res* 13:226.
- D'Iorio A, Vitale C, Piscopo F, Baiano C, Falanga AP, Longo K, Amboni M, Barone P, Santangelo G (2017) Impact of anxiety, apathy and reduced functional autonomy on perceived quality of life in Parkinson's disease. *Parkinsonism Relat Disord* 43:114-117.
- Dissanayaka NNW, White E, O'Sullivan JD, Marsh R, Silburn PA, Copland DA, Mellick GD, Byrne GJ (2015) Characteristics and treatment of anxiety disorders in Parkinson's disease. *Mov Disord Clin Pract* 2:155-162.
- Dockx K, Bekkers EM, Van den Bergh V, Ginis P, Rochester L, Hausdorff JM, Mirelman A, Nieuwboer A (2016) Virtual reality for rehabilitation in Parkinson's disease. *Cochrane Database Syst Rev* 12:CD010760.
- Ellis T, Katz DI, White DK, DePiero TJ, Hohler AD, Saint-Hilaire M (2008) Effectiveness of an inpatient multidisciplinary rehabilitation program for people with Parkinson disease. *Phys Ther* 88:812-819.
- Fabbri M, Coelho M, Guedes LC, Chendo I, Sousa C, Rosa MM, Abreu D, Costa N, Godinho C, Antonini A, Ferreira JJ (2017) Response of non-motor symptoms to levodopa in late-stage Parkinson's disease: Results of a levodopa challenge test. *Parkinsonism Relat Disord* 39:37-43.
- Fahn S, Elton RL; the members of the UPDRS Development Committee (1987) The Unified Parkinson's Disease Rating Scale. In: *Recent developments in Parkinson's disease*. Vol. 2 (Fahn S, Marsden CD, Calne DB, Goldstein M, eds), pp153-163. Florham Park, NJ: Macmillan Healthcare.
- Ferrazzoli D, Ortelli P, Zivi I, Cian V, Urso E, Ghilardi MF, Maestri R, Frazzitta G (2018) Efficacy of intensive multidisciplinary rehabilitation in Parkinson's disease: a randomised controlled study. *J Neurol Neurosurg Psychiatry* 89:828-835.
- Hamilton M (1959) The assessment of anxiety states by rating. *Br J Med Psychol* 32:50-55.
- Hobart JC, Thompson AJ (2001) The five item Barthel index. *J Neurol Neurosurg Psychiatry* 71:225-230.
- Hoehn M, Yahr M (1996) Parkinsonism: onset progression and mortality. *Neurology* 17:427-442.
- Jazaeri SZ, Azad A, Mehdizadeh H, Habibi SA, Najafabadi MM, Saberi ZS, Rahimzadegan H, Moradi S, Behzadipour S, Parnianpour M, Taghizadeh G, Khalaf K (2018) The effects of anxiety and external attentional focus on postural control in patients with Parkinson's disease. *PLoS One* 13:e0192168.
- Jenkinson C1, Fitzpatrick R, Peto V, Greenhall R, Hyman N (1997) The Parkinson's Disease Questionnaire (PDQ-39): development and validation of a Parkinson's disease summary index score. *Age Ageing* 26:353-357.
- Kaseda Y, Ikeda J, Sugihara K, Yamawaki T, Kohriyama T, Matsumoto M (2017) Therapeutic effects of intensive inpatient rehabilitation in advanced Parkinson's disease. *Neurol Clin Neurosci* 5:18-21.
- Lauterbach EC, Freeman A, Vogel RL (2003) Correlates of generalized anxiety and panic attacks in dystonia and Parkinson disease. *Cogn Behav Neurol* 16:225-233.
- Lerman SF, Bronner G, Cohen OS, Elinx-Benizri S, Strauss H, Yahalom G, Hassin-Baer S (2019) Catastrophizing mediates the relationship between non-motor symptoms and quality of life in Parkinson's disease. *Disabil Health J* 12:673-678.
- Liu L, Luo XG, Dy CL, Ren Y, Feng Y, Yu HM, Shang H, He ZY (2015) Characteristics of language impairment in Parkinson's disease and its influencing factors. *Transl Neurodegener* 4:2.
- Lyons KE, Pahwa R (2011) Diagnosis and initiation of treatment in Parkinson's disease. *Int J Neurosci* 121 Suppl 2:27-36.
- Mioshi E, Dawson K, Mitchell J, Arnold R, Hodges JR (2006) The Addenbrooke's Cognitive Examination Revised (ACE-R): a brief cognitive test battery for dementia screening. *Int J Geriatr Psychiatry* 21:1078-1085.
- Pachana NA, Egan SJ, Laidlaw K, Dissanayaka N, Byrne GJ, Brockman S, Marsh R, Starkstein S (2013) Clinical issues in the treatment of anxiety and depression in older adults with Parkinson's disease. *Mov Disord* 28:1930-1934.
- Palmeri R, Lo Buono V, Corallo F, Foti M, Di Lorenzo G, Bramanti P, Marino S (2017) Nonmotor symptoms in parkinson disease: a descriptive review on social cognition ability. *J Geriatr Psychiatry Neurol* 30:109-121.
- Petersen RC, Caracciolo B, Brayne C, Gauthier S, Jelic V, Fratiglioni L (2014) Mild cognitive impairment: a concept in evolution. *J Intern Med* 275:214-228.
- Petkus AJ, Filoteo JV, Schiehser DM, Gomez ME, Petzinger G (2019) Worse cognitive performance predicts increased anxiety and depressive symptoms in patients with Parkinson's disease: A bidirectional analysis. *Neuropsychology* 33:35.
- Schrag A, Taddei RN (2017) Depression and anxiety in Parkinson's disease. *Int Rev Neurobiol* 133:623-655.
- Starkstein SE, Preziosi TJ, Berthier ML, Bolduc PL, Mayberg HS, Robinson RG (1989) Depression and cognitive impairment in Parkinson's disease. *Brain* 112:1141-1153.
- van der Marck MA, Bloem BR, Borm GF, Overeem S, Munneke M, Guttman M (2013) Effectiveness of multidisciplinary care for Parkinson's disease: a randomized, controlled trial. *Mov Disord* 28:605-611.
- Van Laar AD, Jain S (2004) Non-motor symptoms of Parkinson disease: update on the diagnosis and treatment. *Neurologist* 10:185.
- Wee N, Wen MC, Kandiah N, Chander RJ, Ng A, Au WL, Tan LC (2016) Neural correlates of anxiety symptoms in mild Parkinson's disease: A prospective longitudinal voxel-based morphometry study. *J Neurol Sci* 371:131-136.
- Ztaou S, Lhost J, Watabe I, Torromino G, Amalric M (2018) Striatal cholinergic interneurons regulate cognitive and affective dysfunction in partially dopamine-depleted mice. *Eur J Neurosci* 48:2988-3004.

*C-Editor: Zhao M; S-Editor: Li CH; L-Editor: Song LP; T-Editor: Jia Y*