Phenomenology of Atypical Anxiety Disorders in Parkinson's Disease

Am J of Geriatric Psychiatry 30:9 (2022) 1026–1050

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ajgponline.org

Clinical Review Article

Phenomenology of Atypical Anxiety Disorders in Parkinson's Disease: A Systematic Review

Nadeeka N. Dissanayaka, Ph.D., Elana J. Forbes, B.Sc. (Hons), Kate Perepezko, M.S., Albert F.G. Leentjens, Ph.D., Roseanne D. Dobkin, Ph.D., Kathy Dujardin, Ph.D., Gregory M. Pontone, M.D.

ARTICLE INFO

Article history:
Received November, 14 2021
Revised February, 3 2022
Accepted February, 10 2022

Key Words:
Parkinson's disease
anxiety
atypical
fluctuations
fear of falls

ABSTRACT

Objective: *Anxiety is a prominent concern in Parkinson's disease (PD) that negatively impacts quality of life, increases functional disability, and complicates clinical management. Atypical presentations of anxiety are under-recognized and inadequately treated in patients with PD, compromising global PD care.* ***Methods:*** *This systematic review focuses on the prevalence, symptomology and clinical correlates of atypical presentations of PD-related anxiety following PRISMA guidelines.* ***Results:*** *Of the 60 studies meeting inclusion criteria, 14 focused on 'Anxiety Not Otherwise Specified (NOS)' or equivalent, 31 reported on fluctuating anxiety symptoms, and 22 reported on 'Fear of Falling (FOF)'. Anxiety NOS accounted for a weighted mean prevalence of 14.9%, fluctuating anxiety for 34.19%, and FOF for 51.5%. These latter two exceeded the average reported overall prevalence rate of 31% for anxiety disorders in PD. We identified a diverse array of anxiety symptoms related to motor and non-motor symptoms of PD, to complications of PD medication (such as "on" and "off" fluctuations, or both), and, to a lesser extent, to cognitive symptoms.* ***Conclusion:*** *Atypical anxiety is common, clinically relevant, and heterogeneous in nature. A better understanding of the phenomenology, clinical course, and pathophysiology of varied forms of atypical anxiety in PD is needed to improve recognition, advance therapeutic development and ultimately optimize quality of life in PD.* (Am J Geriatr Psychiatry 2022; 30:1026–1050)

From the UQ Centre for Clinical Research, Faculty of Medicine (NND, EJF), The University of Queensland, Brisbane, Australia; School of Psychology (NND, EJF), University of Queensland, Brisbane, Australia; Department of Neurology (NND), Royal Brisbane & Women's Hospital, Brisbane, Australia; Department of Mental Health (KP), Johns Hopkins University Blomberg School of Public Health, Baltimore, USA; Department of Psychiatry (AFGL), Maastricht University Medical Center, Maastricht, the Netherlands; Department of Psychiatry (RDD), Rutgers University, Robert Wood Johnson Medical School, Piscataway, New Jersey, USA; Department of Neurology and Movement Disorders (KD), University Lille, Lille, France; Department of Psychiatry and Behavioral Sciences (GMP), Johns Hopkins University School of Medicine, Baltimore, USA; and the Department of Neurology (GMP), Johns Hopkins University School of Medicine, Baltimore, USA. Send correspondence and reprint requests to Nadeeka Dissanayaka, Ph.D., University of Queensland, UQ Centre for Clinical Research, Building 71/918, Royal Brisbane & Women's Hospital, Herston QLD4029, Brisbane, Australia. e-mail: n.dissanayaka@uq.edu.au

https://doi.org/10.1016/j.jagp.2022.02.004

Highlights

- **What is the primary question addressed by this study?**
  A systematic review was conducted to better define and describe the clinical presentation of atypical anxiety in Parkinson's disease in order to help improve recognition, advance therapeutic development and ultimately optimize routine PD care.
- **What is the main finding of this study?**
  Across the 60 studies meeting inclusion criteria, estimates of atypical anxiety ranged from 15%−51%. We identified a diverse array of anxiety symptoms related to motor and non-motor symptoms of PD, to complications of PD medications (such as "on" and "off" fluctuations), and, to a lesser extent, to cognitive symptoms.
- **What is the meaning of the finding?**
  Atypical anxiety is highly prevalent, clinically relevant, heterogeneous in nature, and a key target for intervention in multidisciplinary PD care.

INTRODUCTION

Anxiety is a prominent non-motor symptom in Parkinson's disease (PD) patients, with a global average prevalence of 31%. [1] The prevalence of anxiety in PD is three times higher than that in healthy adults of the same age and in patients with other neurological diseases.[2] On average, 13% of PD patients experience clinically significant anxiety that does not meet criteria for anxiety disorder as defined by the Diagnostic and Statistical Manual (DSM) of Mental Disorders and are typically classified as having unspecified anxiety according to the DSM criteria.[3] This category was previously known as 'Anxiety disorder not otherwise specified' (NOS) in earlier versions of the DSM.

In order to obtain a more complete view of the spectrum of anxiety in PD, as well as to increase the recognition of significant anxiety in routine clinical practice, there is a need to better define and describe the symptomatology of unspecified anxiety in PD. Indeed, the 'NOS' or 'unspecified' category is not circumscribed. It is a 'waste category' and an artifact of the inappropriateness of the DSM to categorize anxiety in PD. The aim of this systematic review is to examine the prevalence, symptomatology, and clinical correlates of atypical presentations of anxiety in PD patients.

METHODS

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[4] The study selection process is summarized in the PRISMA flow diagram (Fig. 1).

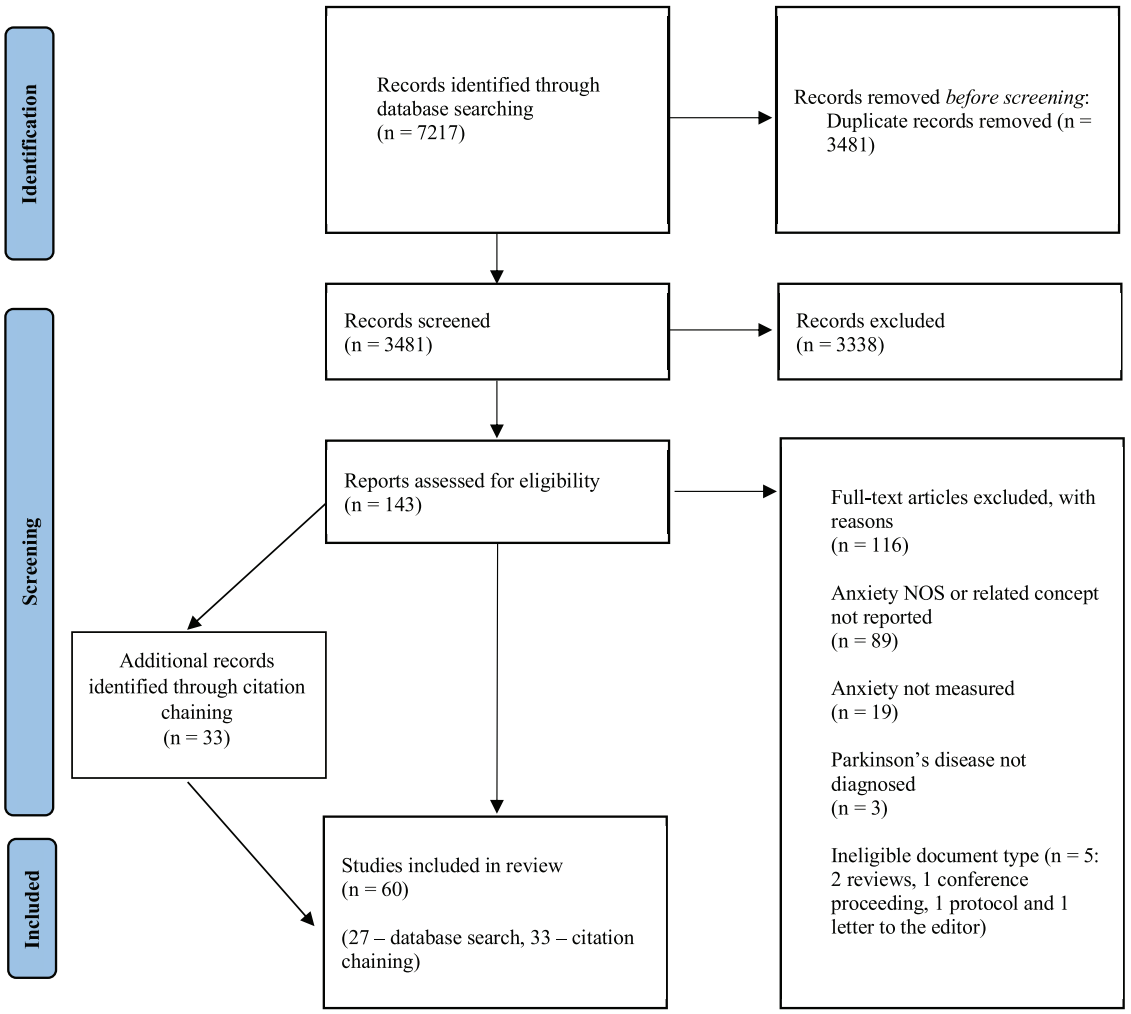
Search Strategy

A systematic review of research-based literature catalogued in PubMed, CINAHL, EMBASE, PsycINFO and Web of Science was performed. The entire available time range of databases was used until May 15, 2021. (Title OR Abstract OR Index Terms: (Parkinson Disease OR Parkinson)) AND ((Title OR Abstract: "Anxiety" OR "Anxiety Disorder" OR "Generalized Anxiety Disorder" OR "Social Anxiety" OR "Social Phobia" OR "Panic Disorder" OR "Panic Attack" OR "Fear" OR "Worry" OR "Avoidance" OR "Embarrassment" OR "atypical anxiety" OR (anxiety AND fluctuation) OR (anxiety AND wearing-off)) (see supplementary material for complete search strategy). Original articles that had an abstract available and were written in English were independently screened by two reviewers (EF and KP). Discrepancies were resolved by a third reviewer (ND). Articles meeting the inclusion criteria and not meeting exclusion criteria were selected for review. After duplicates were removed, the initial search yielded 3,481 papers to be screened. We also conducted the following additional search strategies: 1) references cited of all included studies, and 2) forward citation chaining using Google Scholar for all included studies to find more recent publications which have cited included studies.

Study Selection

Peer-reviewed studies analyzing the prevalence and factors associated with Anxiety NOS in persons

FIGURE 1. PRISMA flowchart of study selection.



with confirmed diagnoses of PD and anxiety were included. Articles were excluded if there was no reference to anxiety NOS or related concepts, as well as reviews, book chapters, abstracts only or conference proceeding and animal models.

Identified records were exported to EndNote for the removal of ineligible record types (e.g., books, conference proceedings) and duplicate records based on the document title, year of publication, and authors. Remaining titles and abstracts were then screened using the inclusion and exclusion criteria (Table 1). Records included during abstract screening progressed to full-text screening and were then also bench-marked against the inclusion and exclusion criteria.

In all, 3,338 articles were excluded due to the non-relevance of their titles and abstracts. Finally, 27 papers were included in this review after the application of inclusion and exclusion criteria to the full-text. An additional 33 articles were identified through a further search of references of the selected articles and forward citation searching as described above. A total of 60 studies comprised the review.

Quality Assessment

The quality of studies was assessed by adjusting a modified version of the Quality Assessment of Diagnostic Accuracy Studies (QUADAS[5] tool, which was previously used for a review of the prevalence of

TABLE 1. Inclusion and Exclusion Criteria of the Systematic Review

Inclusion Criteria	Exclusion Criteria
Article topic relates to Parkinson's disease and anxiety	Article topic does not related to Parkinson's disease and anxiety
Measured and reported at least one of: Anxiety NOS, Anxiety Not Otherwise Specified, Atypical Anxiety, Subsyndromal Anxiety, Unspecified Anxiety, persistent anxiety, episodic anxiety, avoidance anxiety, fluctuations, wearing-off or specific anxiety disorders not reaching the required number of symptoms or severity, wearing-off anxiety, fear of falling, social phobia characterized by shame of visible symptoms	Article does not make reference to: Anxiety NOS, Anxiety Not Otherwise Specified, Atypical Anxiety, Subsyndromal Anxiety, Unspecified Anxiety, persistent anxiety, episodic anxiety, avoidance anxiety, fluctuations, wearing-off or specific anxiety disorders not reaching the required number of symptoms or severity, wearing-off anxiety, fear of falling, social phobia characterized by shame of visible symptoms
Peer reviewed articles available in English.	Articles is not peer-review, not in English. Record type is a review, book, abstracts only/conference proceedings.
Included article types include case studies, caregiver/ family studies and treatment studies.	Animal studies

anxiety in PD.[1] Our modified QUADAS tool comprised eight criteria assessing the reliability of each study (Table 2). The score range was 0−16 points, with a cut-off value for methodological acceptability set at >12 points (75% of the total possible score). All of the articles were reviewed independently by two researchers (EF and KP), and a discussion and consensus approach was used to resolve discrepancies between the raters. The criteria and a complete list of included studies with item-by item quality scores are provided as supplementary information.

Data Extraction and Analysis

Anxiety NOS, fluctuating anxiety and fear of falling (FOF) were recorded in combination with the study aim, sample size and characteristics, country and setting, study design, identification method of anxiety, anxiety measures, diagnostic criteria, PD severity measures, other measures (e.g., depression, cognitive impairment, quality of life), prevalence, symptomatology, and characteristics (Tables 3-5). Anxiety was evaluated as a primary or secondary outcome measure. Using the prevalence, when reported, prevalence rates were calculated as weighted means across studies, that is, the prevalence rate per study was multiplied by the sample size of that study and then divided by the total sample size of all studies.

TABLE 2. Modified QUADAS Criteria

Section	Item	Criteria
A	1	At least 1 of the following should apply for the study (2 points): − An entire target population − Randomly selected sample − Sample stated to represent the target population
	2	At least one of the following (2 points) − Reasons for non-responders described − Non-responders described − Comparison of responders and non-responders − Comparison of sample and target population
	3	Response rate ≥ 90% (2 points) Response rate 70% to 90% (1 point) Response rate ≤ 70% (0 points)
B	4	The same mode of data collection should be used for all subjects (2 points), if not: 1 point
	5	− The data have been collected directly from the patient by means of a validated questionnaire/interview (3 points) − No validated questionnaire/interview patients (2 points) − Data have been collected from proxies or retrospectively from medical record (1 point).
C		General description of the method and results should include:
	6	Description of target population and setting where patients were found (2 points)
	7	Description of stage of disease, sex, age (all 2 points, 1 or 2: 1 point)
	8	Final sample size (1 point)

RESULTS

Overall, 53 studies were conducted in outpatient settings. One study included both inpatients and outpatients, two studies were conducted in inpatient settings, one was conducted with outpatients via postal survey and three studies did not explicitly report a setting. Forty-six studies excluded people with dementia, and four studies included participants with dementia, while 10 studies did not report the

TABLE 3. Studies Reporting a Diagnosis of Anxiety NOS (or Equivalent) in Parkinson's Disease According to Diagnostic Criteria

Study	Study Aim	Sample	Study design	Sample size	Quality Score	Cognitive status	Mean MMSE/ MoCA score	Anxiety Measures	Diagnostic Criteria	Prevalence	Disease Duration (years)	MDS UPDRS Total Score	Hoehn & Yahr	Characteristics /Markers / Symptomatology
Chen, 2010[9]	Assess anxiety disorders and their correlates in Chinese PD patients	Outpatient clinic	Cross-sectional	133	15	MMSE <15 excluded	25.3 (MMSE)	CB-SCID-DSM IV	CB-SCID-DSM IV	5.3%	-	-	-	Younger age of onset of PD, severity of depressive symptoms, and muscle cramps correlated with anxiety.Anxiety more frequent in PD patients with "on-off" motor symptoms, whereby anxiety symptoms worsened during the "off" state
Dissanayaka, 2015 [12]	Investigate demographic and PD-specific factors associated with DSM-IV anxiety disorders in PD	Outpatient clinic	Cross-sectional	90	12	MMSE <24 excluded	-	MINI-Plus	DSM-IV	26.67%	-	-	-	Compared to no anxiety: greater anxiety and depression severity, greater UPDRS-I and UPDRS-IV scores, younger age of PD onset, poorer quality of life, more likely to have current pharmacological treatment for anxiety or depressive disorder and lower quality of life Compared to DSM anxiety: lower UPDRS Total, UPDRS-I and UPDRS-II scores, lower depression, and anxiety severity. less likely to have a lifetime history of depression, less likely to have been treated for anxiety or depression and greater quality of life
Dissanayaka, 2016 [7]	Characterize PD-related anxiety symptoms	Outpatient clinic	Cross-sectional	90	12	MMSE <24 excluded	28.4 (MMSE)	MINI-plus PDAMCQ	DSM-IV	26.7%	6 years for total sample - 6.7 years for NOS	UPDRS total score 45.3 (15.4) 54.7 (19.0) 42.2 (9.6) (total, DSM, NOS) III Motor examination 24.1 (9.1) 24.2 (10.2) 22.2 (7.6) (total, DSM, NOS)	Hoehn & Yahr staging 2.3 (0.5) 2.5 (0.7) 2.2 (0.4) (total, DSM, NOS)	Onset after PD diagnosis PD-related anxiety symptoms include: psychological distress resulting from PD diagnosis, stress or worry, insecurity about future, worry related to motor symptoms and wearing-off medication, fear of losing control of motor/bodily functions due to disability, social embarrassment due to motor symptoms or "off" states, social withdrawal due to motor symptoms or "off" states, frustration or anger relating to cognitive problems, agitation, inner unrest, internal tremor or inability to relax
Ehgoetz Martens, 2016 [10]	Evaluate the relationship between movement, dopaminergic treatment, and gait in PD	Outpatient clinic	Cross-sectional	17	11	3MS (3MS; scored 0-100)	PD-GI: 96 (4.5); PD +GI: 95 (7.0)	STAI	-	-	-	UPDRS-III (off): PD without Gait Impaired 27 (9.8), PD with Gait Impaired 48 (18.5); UPDRS-III (on): PD-GI PD without Gait Impaired 20 (10.5), PD with Gait Impaired 34 (18.2)	-	Those with gait impairment reported greater anxiety levels. Higher levels of anxiety reported in the high threat, compared to the low threat condition. Greater levels of anxiety reported in those with gait impairment when walking compared to standing in the low threat environment. Reduced levels of anxiety reported in the on-state.

(*continued on next page*)

TABLE 3. (*continued*)

Study	Study Aim	Sample	Study design	Sample size	Quality Score	Cognitive status	Mean MMSE/ MoCA score	Anxiety Measures	Diagnostic Criteria	Prevalence	Disease Duration (years)	MDS UPDRS Total Score	Hoehn & Yahr	Characteristics /Markers / Symptomatology
Fleminger, 1991 [86]	Compare symptoms of PD patients with markedly asymmetric motor symptoms: RHP and LHP PD	Outpatient clinic	Cross-sectional	17	15	-	-	PSE	PSE	33%	7.2	-	-	-
Lauterbach, 2004 [87]	Identify prevalence of DSM-III psychiatric disorders in PD patients	Outpatient clinic	Cross-sectional	28	15	-	50.67 (mMMSE; scored 0-57)	DIS	DSM-III	21.43%	12.52	26.71	3.25	-
Leentjens, 2011 [88]	Identify markers of anxiety disorders in PD	Outpatient clinic	Cross-sectional	342	14	MMSE <23 excluded	28.5 (MMSE)	MINI HARS	DSM-IV	11.4%	8.2	8.2[a]	2	-
Menza, 1993 [89]	Assess comorbidity of anxiety and depression in PD	Outpatient clinic	Cross-sectional	42	14	MMSE <24 excluded	27.8 (MMSE)	DSM-III-R SAS	DSM-III-R	2%	-	-	2.4	-
Pontone, 2009 [8]	Determine prevalence and clinical correlates of DSM-IV-TR anxiety in PD patients	Outpatient clinic	Cross-sectional	127	14	MMSE <24 excluded	28.1 (MMSE)	SCID-DSM-IV-TR	DSM-IV-TR	Current prevalence: 25% Lifetime prevalence: 30%	7.9 years (total sample, 7.8 nonanxious and 8.0 anxiety disorder)	UPDRS-III = 18.0 (total sample), 18.5 nonaxious sample, 17.4 (anxiety disorder)	H-Y stages: 1 = 18 1.5 = 2 2 = 64 2.5 = 23 3 = 14 4 = 5 5 = 1	High comorbidity of anxiety NOS with depression and poorer quality of life Among disorder NOS manifested as: excessive and recurrent situational anxiety related to motor deficits, corresponding to ''wearing off'' of antiparkinsonian medications, panic attack-like episodes, persistent excessive anxiety and worry that did not meet DSM-IV-TR criteria for GAD, and combinations of these presentations of anxiety
Pontone, 2011 [13]	Determine whether anxiety in general or specific anxiety subtypes have independent effect on health status in PD	Outpatient clinic	Cross-sectional	249	16	MMSE <24 excluded	28.3 (MMSE)	SCID-DSM-IV-TR	DSM-IV-TR	22.09%	8.3	-	2.2	Anxiety disorder NOS subtypes compared to no anxiety group: (1) Anticipatory anxiety: higher daily levodopa dose (2) Fluctuation associated anxiety: higher proportion female, younger age of onset, longer PD duration, higher daily levodopa dose, greater complications of therapy (UPDRS-IV) scores, poorer quality of life (higher PDQ-8 scores) (3) Generalized worry: poorer global cognition (higher MMSE scores)

(*continued on next page*)

TABLE 3. (*continued*)

Study	Study Aim	Sample	Study design	Sample size	Quality Score	Cognitive status	Mean MMSE/ MoCA score	Anxiety Measures	Diagnostic Criteria	Prevalence	Disease Duration (years)	MDS UPDRS Total Score	Hoehn & Yahr	Characteristics /Markers / Symptomatology
Qureshi, 2012 [90]	Examine co-occurring anxiety and depression in veterans with PD	Male veteran outpatients	Cross-sectional using existing administrative data	273	13	44.69% of sample with dementia diagnosis	-	ICD-9-CM	ICD-9-CM	6.59%	-	-	-	Greater prevalence in those with depression (22.6%) compared to without (1.9%)
Stein, 1990 [91]	Study the prevalence and importance of anxiety disorders in patients with PD	Doesn't specify	Cross-sectional	24	12	MMSE <27 excluded	-	SADS-LA SAS	DSM-III-R	4.17%	Without anxiety disorders: 12.7 years; with anxiety disorders: 7.7 years	-	Without anxiety, H-Y= = 2.9; with anxiety disorders, H-Y = 2.7	-
Thordardottir, 2014 [6]	Understand participation for PD patients with varying disease severity	Outpatient clinic	Cross-sectional	29	11	Dementia excluded	-	Focus groups discussions	Stress identified (no specific anxiety measure)	-	11	-	-	Uncertainty of symptoms causes distress for those with moderate to severe PD. Planning helped individuals cope with internal (insecurity, fear of what might happen) and external stress (demanding environments, crowds, or social gatherings).
Tudoricca, 2009 [92]	Evaluate anxiety in PD	Admitted patients	Cross-sectional	37	12	MMSE <25 excluded	H&Y stage 1: 28.3 (MMSE) H&Y stage 2: 27.8 (MMSE)	DSM-IV SAS HARS	DSM-IV	10.81%	-	-	1 and 2	Associated with dysthymia and minor depression

Notes: Dashes indicate no data is available. CB-SCID-DSM IV: Chinese-Bilingual Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; STAI: State-Trait Anxiety Inventory; HARS: Hamilton Anxiety Rating Scale; SCID-DSM-IV-TR: Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision [93]; DSM-III-R: Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised [94]; ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification [95]; PSE: Present State Examination [96]; MINI: Mini-International Neuropsychiatric Interview [97]; PDAMCQ: Parkinson's disease Anxiety-Motor Complications Questionnaire [17]; SAS: Zung Self-Rating Anxiety Scale [98]; DIS: Diagnostic Interview Schedule [99]; SADS-LA: Schedule for Affective Disorders and Schizophrenia-Lifetime Version Modified for the Study of Anxiety Disorders [100]; UPDRS: Movement Disorder Society Unified Parkinson's Disease Rating Scale [101]; MMSE: Mini-Mental State Examination [102]; mMMSE: Modified Mini-Mental State Examination [103]; PDQ-8: 8-item Parkinson's disease Questionnaire [104]; PG-GI: Parkinson's disease without gait impairment; PD+GI: Parkinson's disease with gait impairment; 3MS: Modified Mini Mental State Exam [105]; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition;

[a] UPDRS III only reported.

TABLE 4. Studies Reporting Fluctuating Anxiety in Patients with Parkinson's Disease

Study	Study Aim	Sample	Study design	Sample size	Quality Score	Cognitive status	Mean MMSE/ MoCA score	Anxiety measures	Anxiety symptom/ type	Prevalence	Disease Duration (years)	MDS UPDRS Total Score	Hoehn & Yahr	Characteristics/ Markers/ Symptomatology
Broen, 2018 [34]	Investigate marker profiles for proposed anxiety subtypes in PD	Outpatient clinic	Cross-sectional	311	13	MMSE <23 excluded	28.5 (MMSE)	PAS	Episodic, persistent and avoidance behavior subtypes	-	9.8	UPDRS II = 12.4 UPDRS III = 24.7 UPDRS IV = 3.6	2.3	Persistent anxiety associated with: greater depression scores, history of anxiety, fewer years of education, lower MMSE scores, lower LIADL, female sex and complications of therapy Episodic anxiety associated with: PD-specific disturbances of activities of daily living, complications of therapy, higher depression scores, female sex and a history of anxiety. Avoidance behavior associated with: higher depression scores, a history of anxiety, complications of therapy and longer disease duration were associated with avoidance behavior
Brown, 2011 [33]	Identify the main anxiety and depression related subtype(s) in PD and their associated demographic and clinical features	Outpatient clinic	Cross-sectional	513	12	MMSE ≤24 excluded	27.9 (MMSE)	HADS GMS	Anxiety-related subtypes	22% had anxiety symptomatology	6.9	26.4[a]	HY1: 12.6% HY 2 or 3: 80.2% HY4 or 5: 7.2%	Anxiety predicted by: younger age, female gender, younger age of PD onset, higher LEDD and greater disability Combined depression and anxiety predicted by: younger age, PD onset less than 55 years, greater level of disability and higher UPDRS III score
Dissanayaka, 2016 [7]	Characterize PD-related anxiety symptoms	Outpatient clinic	Cross-sectional	90	12	MMSE <24 excluded	28.4 (MMSE)	MINI-plus PDAMCQ	DSM-IV anxiety-disorder	-	6 years for total sample - 6.7 years for NOS	Total MDS-UPDRS score of 45.3 (15.4) average for total sample III Motor examination 24.1 (9.1) average for total sample	2.3 (0.5) average for total sample	PD-related anxiety symptoms included worry related to motor symptoms and wearing-off medication, social embarrassment due to "off" states, and social withdrawal due to "off" states
Ehgoetz Martens, 2016 [10]	Evaluate the relationship between movement, dopaminergic treatment, and gait in PD	Outpatient clinic	Cross-sectional	17	11	3MS (3MS; scored 0-100)	PD-GI: 96 (4.5); PD +GI: 95 (7.0)	STAI	-	-	-	UPDRS-III (off): PD without GI 27 (9.8), PD with GI 48 (18.5); UPDRS-III (on): PD-GI PD without GI 20 (10.5), PD with GI 34 (18.2)	-	Reduced levels of anxiety reported in the on-state.

(*continued on next page*)

TABLE 4. (*continued*)

Study	Study Aim	Sample	Study design	Sample size	Quality Score	Cognitive status	Mean MMSE/ MoCA score	Anxiety measures	Anxiety symptom/ type	Prevalence	Disease Duration (years)	MDS UPDRS Total Score	Hoehn & Yahr	Characteristics/ Markers/ Symptomatology
Fanciulli, 2013 [82]	Report two cases of anxiety during wearing-off of rotigotine in PDD patients	Outpatient clinic	Case studies	2	12	PD dementia	19 (MMSE)	HARS	Wearing-off	100%	Case 1: 7 years; Case 2: 8 years	Case 1: 43[a] Case 2: 45[a]	Case 1: 3 Case 2: 4	Case 1: therapy with levodopa/carbidopa 100/ 25 mg, 5 daily doses, female, motor and non-motor symptoms of wearing-off, MMSE score of 18, with severe executive and visual-spatial deficits Case 2: visual hallucinations, depressed mood and anxiety, MMSE score of 20, neuropsychological examination in the on-state showed severe executive, visual-spatial and moderate verbal memory impairment
Fernie, 2019 [35]	Identify individual psychological factors contributing to the relationship between episodic distress and motor fluctuations	Outpatient clinic	Cross-sectional	20	11	-	-	PAS	Episodic distress	-	7.6	-	-	Time of day, cognitive processes and negative metacognitions predicted episodic distress independent of motor state
Ghielen, 2017 [83]	Investigate the feasibility and efficacy of a group intervention	Outpatient clinic	Randomized controlled trial	40	15	MMSE <24 excluded	28.1 (MMSE)	BAI	Wearing-off related anxiety	100% had wearing-off symptoms	TAU = 12.3 Intervention (BEWARE)= 10.5	-	2 or 3	-
Henderson, 1992 [24]	Determine the prevalence of anxiety and depression in PD	Outpatient clinic	Cross-sectional	164	12	Not reported	-	SAS STAI	Motor fluctuations and anxiety/ panic	41% with panic/anxiety during "off" state 31% with panic/anxiety during both "on" and "off" states	8.6	-	-	Patients with motor fluctuations were more likely to report depression and/or panic/anxiety
Kulisevsky, 2007 [30]	Explore whether wearing−off have more mood fluctuations than stable patients and whether a slower rise in plasma LD concentrations is associated with less marked mood swings	Outpatient clinic	Intrasubject randomized double-blind crossover design	14	16	MMSE ≤24 excluded	27.6 (MMSE)	STAI VAS	Levodopa effect on mood	-	7.15	24.8[a]	-	Anxiety was associated with motor status
Leentjens, 2012 [17]	Describe the relationship between anxiety and motor fluctuations in PD	Outpatient clinic	Cross-sectional	250	12	MMSE <26 excluded	Non-fluctuators: 28. Fluctuators: 29.1	HARS HADS	Fluctuation presence and anxiety severity	-	No fluctuations: 6.4 (4.9) years, fluctuations: 10.1 (5.6) years	No fluctuations − UPDRS-I: 2.1 (1.8), UPDRS II: 12.8 (6.1), UPDRS -II: 24.0	2	Fluctuators reported higher HARS scores compared to non-fluctuators. Six anxiety symptoms were more likely during the

(*continued on next page*)

TABLE 4. (*continued*)

Study	Study Aim	Sample	Study design	Sample size	Quality Score	Cognitive status	Mean MMSE/ MoCA score	Anxiety measures	Anxiety symptom/ type	Prevalence	Disease Duration (years)	MDS UPDRS Total Score	Hoehn & Yahr	Characteristics/ Markers/ Symptomatology
												(12.2), UPDRS-IV: 1.2 (1.5); Fluctuations – UPDRS-I: 2.7 (2.2), UPDRS II: 10.4 (7.2), UPDRS-III: 27.1 (11.0), UPDRS-IV: 5.4 (3.0)		"off" state: feeling anxious, feeling sad, avoiding situations, palpitations, dizziness, and chills or hot flushes.
Maricle, 1995a [31]	Describe the timing and nature of emotional fluctuations in relation to levodopa administration	Outpatient clinic	Cross-sectional	15	13	-	-	VAS	Mood and anxiety fluctuations associated with levodopa	-	10	-	3.6	Anxiety fluctuations were related to levodopa dosing and deemed a pharmacologic rather than placebo effect
Maricle, 1995b [58]	Examine the effect of levodopa on mood in PD patients with motor fluctuations	Outpatient clinic	Cross-sectional	8	14	Not measured	-	VAS	VAS		10.5	-	3.6	Anxiety decreased shortly after onset of the high-dose infusion but was delayed at least 1 hour with the low-dose infusion. The length of the anti-anxiety effect was also longer for the high dose infusion.
Mehdizadeh, 2016 [14]	Study the relationship between FOF and quality of life	Outpatient clinic	Cross-sectional	139	12	MMSE> 23	-	FES-I	FOF	-	-	UPDRS-ADL (off phase): 21.09; UPDRS-ADL (on phase): 12.80	stage 1 - 67.14%, stage 2-32.85%	In the drug "off" state, the strongest relation was observed between FOF and mobility as well as activities of daily living dimensions.
Mehdizadeh, 2019 [15]	Study the association between functional balance, FOF, and independence in activities of daily living based on medication state	Outpatient clinic	Cross-sectional	140	12	MMSE >21	-	FES-I	FOF	-	-	UPDRS-ADL (off phase): 21.09; UPDRS-ADL (on phase): 12.80	stage 1 - 67.14%, stage 2-32.85%	FOF moderately correlated with functional balance in both "on" and "off" states.
Melo, 2010 [106]	Verify if the presence of wearing-off phenomenon in patients with PD could be better identified by the administration of QC	Outpatient clinic	Cross-sectional	79	16	-	-	QC	Wearing-off	3.79% experience wearing-off	12.4	-	stage 1.5: 4, stage 2: 27, stage 2.5: 23, stage 3: 22, stage 4: 2	-
Menza, 1990 [29]	Examine changes in mood and anxiety states during "on" and "off" phases to determine how central nervous system dopaminergic activity may relate to mood and anxiety	Outpatients	Cross-sectional	10	16	Dementia excluded	-	VAS	Anxiety associated with "off" and "on with dyskinesia" states	-	-	-	2.4	Poorer mood and greater anxiety found during the "off" state compared to "on" state or "on with dyskinesia" state No effect of number of years ill, age, and dose of levodopa

(*continued on next page*)

TABLE 4. (*continued*)

Study	Study Aim	Sample	Study design	Sample size	Quality Score	Cognitive status	Mean MMSE/ MoCA score	Anxiety measures	Anxiety symptom/ type	Prevalence	Disease Duration (years)	MDS UPDRS Total Score	Hoehn & Yahr	Characteristics/ Markers/ Symptomatology
Nilsson, 2012 [16]	Evaluate the effect of motor, nonmotor, demographic factors and medications on FOF in PD	Postal Survey	Cross-sectional	131	14	Dementia or severe cognitive impairment (clinician-rated) excluded	-	FES	FOF	-	6	-	-	Fluctuations predicted FOF
Nissenbaum, 1987 [23]	Assess the nature of, and relationship between, mood and motor fluctuations in nine Parkinsonian patients with "on-off" motor swings	Study 1: in-patients Study 2: out-patients	Cross-sectional	Study 1: 9 Study 2: 136	12	-	-	Study 1: CAS Study 2: anxiety self-ratings	Mood swings associated with "on-off" fluctuations	Study 1: 44.44% with mood and anxiety changes in "off" state. Study 2: 21% anxiety fluctuated with "on-off" motor fluctuations.	10.1	-	On median = 2, off median = 3	Anxiety associated with "off" state More severe anxiety associated with more severe depression and worse motor state Anxiety was more prevalent in the elderly Depressive and anxiety swings were strongly related: more severe intensity of depressive changes associated with more severe the anxiety changes
Ossig, 2016 [26]	To evaluate circadian patterns and temporal connections of NMS and motor fluctuations in PD	Outpatient clinic	Cross-sectional	15 control 17 non-fluctuating 15 fluctuating	16	MoCA ≤26 excluded	Non-fluctuators: 27.1 (MoCA) Fluctuators: 27.5 (MoCA)	A novel non-motor symptom diary (rating of nine NMS)	Nonmotor fluctuations	-	Non-fluctuators: 4.3 years. Fluctuators: 10.5 years	UPDRS total (non fluctuators, fluctuators):: 37.3, 34.1 UPDRS I: 2.4, 1.9 UPDRS II: 8.5, 10.6 UPDRS III: 25.1, 14.8 UPDRS IV: 15.5, 33.2	H-Y (non fluctuators, fluctuators): 1−1.5: 0, 1 2: 6,8 2.5: 8, 4 3: 3, 2	Anxiety associated with motor "off" state
Pontone, 2009 [8]	Determine prevalence and clinical correlates of DSM-IV-TR anxiety in PD patients	Outpatient clinic	Cross-sectional	127	14	MMSE <24 excluded	28.1 (MMSE)	SCID-DSM-IV-TR	DSM-IB-TR anxiety	-	7.9 years (total sample, 7.8 nonanxious and 8.0 anxiety disorder)	UPDRS-III = 18.0 (total sample), 18.5 nonaxious sample, 17.4 (anxiety disorder)	H-Y stages: 1 = 18 1.5 = 2 2 = 64 2.5 = 23 3 = 1 4 4 = 5 5 = 1	Anxiety NOS manifested as: excessive and recurrent situational anxiety related to motor deficits, corresponding to ''wearing off'' of antiparkinsonian medications
Pontone, 2011 [11]	Determine whether anxiety in general or specific anxiety subtypes have independent effect on health status in PD	Outpatient clinic	Cross-sectional	249	16	MMSE <24 excluded	28.3 (MMSE)	SCID-DSM-IV-TR	DSM-IV-TR	8.43% of PD participants had fluctuation-associated anxiety	8.3 years	-	2.2	Fluctuation associated anxiety subgroup: higher proportion female, younger age of onset, longer PD duration, higher daily levodopa dose, greater complications of therapy (UPDRS-IV) scores, poorer quality of life (higher PDQ-8 scores)
Racette, 2002 [28]	Investigate levodopa-related mood fluctuations	Outpatient clinic	Case-control study	70	12		-	DSM-IV	Mood fluctuations	81% had "off" state anxiety	In mood fluctuators group: 12.2 years In sequentially ascertained PD controls group:	-	-	Mood fluctuations (including anxiety) associated with dementia, nonfluctuating clinical depression,

(*continued on next page*)

TABLE 4. (*continued*)

Study	Study Aim	Sample	Study design	Sample size	Quality Score	Cognitive status	Mean MMSE/ MoCA score	Anxiety measures	Anxiety symptom/ type	Prevalence	Disease Duration (years)	MDS UPDRS Total Score	Hoehn & Yahr	Characteristics/ Markers/ Symptomatology
											6.3 years In motor fluctator PD controls group: 9.9. years			psychosis younger age at onset and longer disease duration
Raudino, 2001 [107]	Examine the frequency and characteristics of nonmotor PD symptoms, looking also for possible distinctive features of patients with this type of fluctuations	Outpatient clinic	Cross-sectional	47	12	-	-	Semi-structured interview assessing motor "off" symptoms	Fluctuates with motor symptoms	8.51% with anxiety symptoms related to "off" state	6.9	-	3	-
Richard, 2001 [22]	To better understand mood fluctuations, including their relationship to motor function and level of anxiety	Outpatient clinic	Pilot study	16	13	13 patients without dementia. Mental status not reported in remaining three.	-	SAS	Mood and anxiety fluctuations	43.75% with daily anxiety fluctuations	-	-	-	Association between increased anxiety, decreased mood and reduced motor function
Richard, 2004 [21]	To better understand the phenomenology of mood, anxiety, and motor fluctuations in PD	Outpatient clinic	Cross-sectional	87	13	-	-	SAS	Anxiety fluctuations	30.2% demonstrated evidence of anxiety fluctuations	-	-	Anxiety fluctuations H-Y = 2.7 Nonflucuations = 2.1 H-Y	Not all patients exhibited a temporal relationship between emotional and motor fluctuations. Anxiety fluctuations were associated with higher scores on psychiatric rating scales, history of depression or anxiety, use of psychotropic medications mood fluctuations and motor fluctuations
Rizos, 2014 [19]	Describe the range and patterns of non-motor symptoms that occur during early morning off states across all disease stages of PD	Outpatient clinic	Cross-sectional	320	16	Not measured	-	NMSQuest	Early morning "off" states diagnosed by clinical interview.	49.7% prevalence anxiety during morning "off" state	7	-	2.7	Early morning "off" associated with urgency of urination, anxiety, dribbling of saliva, pain, low mood, limb paresthesia and dizziness.
Siemers, 1993 [20]	Further investigate the relationship between anxiety and response fluctuations in PD	Outpatient clinic	Cross-sectional	19	12	No dementia, all had MMSE scores of 23 or greater	28.0 (MMSE)	STAI	Anxiety correlated with motor fluctuations	73.68%	8.74	60.5	3	Trait anxiety was associated with depression Higher trait anxiety associated with higher UPDRS scores
Starkstein, 2014 [32]	Examine the syndromal pattern of the anxiety spectrum in a large series of patients with PD	Outpatient clinic	Cross-sectional	342	14	MMSE <23 Excluded	Persistent anxiety with depression group: 28.2 (MMSE) Episodic anxiety, no	MINI (DSM-IV)	Episodic anxiety	40% episodic anxiety, no depression 36% persistent and episodic anxiety with	9.8	26.5[a]	2	Anxiety groups were associated with female sex, use of psychotropic medication, personal history of anxiety and depression, and higher UPDRS-I and UPDRS-IV

(*continued on next page*)

TABLE 4. (*continued*)

Study	Study Aim	Sample	Study design	Sample size	Quality Score	Cognitive status	Mean MMSE/ MoCA score	Anxiety measures	Anxiety symptom/ type	Prevalence	Disease Duration (years)	MDS UPDRS Total Score	Hoehn & Yahr	Characteristics/ Markers/ Symptomatology
							depression group: 28.3 Persistent and episodic anxiety with depression group: 28.2			depression 47% persistent anxiety with depression				scores. Persistent anxiety and depression symptoms were associated.
Storch, 2013 [25]	Evaluate frequency, severity, and correlation of non-motor symptoms with motor complications in fluctuating PD	Outpatient clinic	Cross-sectional	100	16	MMSE ≤23 excluded	-	VAS	Nonmotor fluctuations	-	11.3	UPDRS I = 2.9, UPDRS II = 14.5, UPDRS III = 19.1, UPDRS IV = 7.2, H-Y = 2.7	-	Anxiety fluctuations were associated with motor fluctuations, whereby more frequent and severe symptoms were reported in the "off" state Anxiety had a negative impact on HRQoL
Vazquez, 1993 [18]	Detect the presence and frequency of "panic-disorder like states" in patients with complicated PD, and their relation to other clinical, epidemiological, and pharmacological parameters, and most particularly to levodopa use	Outpatient and admitted	Cross-sectional	31	10	-	-	HDS HAS	"Panic attacks" complication of levodopa	90.3% had "panic attacks" associated with "off" state	-	30.6[a]	3	PA related to standing/gait troubles, depression, dyskinesias, younger age of PD onset, starting levodopa therapy sooner than those without PA, higher levodopa doses than those without PA and the motor "off" state
Witjas, 2002 [27]	Assess the frequency and disability caused by nonmotor fluctuations in PD	-	Cross-sectional	50	10	MMSE ≤24 excluded	27.1 (MMSE)	Structured non-motor fluctuations interview with neurologist	Non-motor fluctuations	66% had fluctuating anxiety	12.7	UPDRS II on = 11.3 UPDRS II off = 25.4 UPDRS III on = 18.5 UPDRS III off = 44.4	H-Y on = 2.3 H-Y off = 3.8	Anxiety correlated with greater level of disability Fluctuating anxiety associated with the "off" state

Notes: Dashes indicate no data is available. MMSE: Mini-Mental State Examination; UPDRS: Unified Parkinson's Disease Rating Scale; LEDD: Levodopa equivalent daily dose; PDAMCQ: Parkinson's disease Anxiety-Motor Complications Questionnaire; UPDRS-ADL: Unified Parkinson's Disease Rating Scale Activities of Daily Living; GI: Gait Impairment; PDD: Parkinson's disease dementia; QC: Wearing-off Questionnaire Card [106]; GMS: Geriatric Mental State [108]; HDS: Hamilton Depression Scale [109]; MoCA: Montreal Cognitive Assessment; H-Y: Hoehn and Yahr Scale; HARS: Hamilton Anxiety Scale [110]; FOF: Fear of Falling; VAS: Visual Analogue Scale [111]; BAI: Beck Anxiety Inventory [110]; HADS: Hospital Anxiety and Depression Scale [112]; MINI: Mini-International Neuropsychiatric Interview [102]; PAS: Parkinson Anxiety Scale [80]; SAS: Zung Self-Rating Anxiety Scale [98]; STAI: State-Trait Anxiety Inventory [113]; CAS: Clinical Anxiety Scale [114]; NMSQuest: Non-motor symptom questionnaire [115]; HRQoL: Health-Related Quality of Life; PA: Panic Attacks;

[a] UPDRS III only reported.

TABLE 5. Studies Reporting Fear of Falling in Patients with Parkinson's Disease

Study	Study Aim	Sample	Study Design	Sample size	Quality Score	Cognitive status	Mean MMSE/ MoCA score	Anxiety measures	Prevalence	Disease Duration (years)	MDS UPDRS Total Score	Hoehn & Yahr	Characteristics/Markers/ Symptomatology
Adkin, 2003 [39]	Evaluate the relationship between FOF and postural control in PD	Outpatient Clinic	Cross-sectional	58	10	MMSE <27 excluded	-	ABC	-	6.5	-	-	Individuals with greater degree of posture impairment reported greater FOF.
Bryant, 2014 [38]	Investigate the relationship between FOF, gait characteristics, and balance in PD	Outpatient clinic	Cross-sectional	79	11	Severe cognitive deficits (on the NCSE) excluded	-	ABC	44% of participants had a high FOF.	8.7	UPDRS III: high FOF 21.77 (8.23), low FOF 14.98 (6.78)	2.44	Participants with high FOF had lower speed and stride length for forward walking and backward walking compared to those with a low level of FOF. Participants with high FOF also had longer time to take five steps, time to turn, time to walk sideways, and time to complete the up and go test than those with a low level of FOF. Lastly, participants with high FOF had a greater number of steps to complete the turn and steps to walk sideways than those with a low level FOF.
Bryant, 2015 [47]	Study the associations between falls, FOF, and activity limitations in PD	Outpatient clinic	Cross-sectional	83	12	Severe cognitive deficits (on the NCSE) excluded	-	ABC		Nonfallers: 7.84 +/-5.07, rare fallers: 8.60 +/-5.38, frequent fallers: 7.15 +/-6.13	frequent fallers: 2.74 (0.47), UPDRS III- nonfallers: 16.0 (7.76), rare fallers: 19.43 (10.19), frequent fallers: 22.47 (6.92)	nonfallers: 2.26 (0.48), rare fallers: 2.60 (0.50),	Participants who were frequent fallers or rare fallers had a greater fear of falling than non-fallers.
Franzen, 2016 [37]	Investigate modifiable factors associated with concerns about falling in elderly with mild−to−moderate PD	Outpatients	Retrospective cross-sectional	89	12	MMSE ≤24 excluded	28.0 (MMSE)	FES-I	Low concerns about falling: 12% Moderate concerns: 39% High concerns: 48%	5.8	37[a]	-	Depressive symptoms contributed most to FOF, followed by balance performance and use of mobility devices
Friedman, 2002 [56]	Determine the temporal relationship between falls and FOF	Outpatient clinic	Longitudinal	22	14	MMSE >17	28 (MMSE)	Two clinical questions	-	-	-	-	Falls at baseline were an independent predictor of developing FOF 20 months later and FOF at baseline was a predictor of falling at 20 months. Having PD predicted falls, but not FOF.
Griffin, 2011 [41]	Identify the characteristics of FoF in PD and assess its impact on QoL	Outpatient clinic	Repeated measures design with 2 within subject factors	130	13	Dementia excluded	29.2 (MMSE)	FES	-	-	UPDRS-III off medication 25.6 (7.9) and on medication = 11.2 (9.34);	H&Y stage off medication 2.34 (0.37): 47.4% at stage 2, 36.8% at stage 2.5, and 15.8% at stage 3; on medication = 1.76 (0.63): 31.6% at stage 1, 57.9% at stage 2, and 10.5% at stage 3	Greater FOF was associated with the presence of obstacles compared to open ground
Grimbergen, 2013 [49]	Evaluate the effect of fall frequency, FOF, balance confidence, and balance impairment on HRQoL in PD	Outpatient clinic	Cross-sectional	74	12	MMSE >23	-	TM and ABC	14% indicated they were very fearful of falling; 45% indicated they were somewhat fearful of falling	11.49	40.9	2.59	FOF had the strongest association with reduced HrQOL, compared to balance confidence, and fall frequency.
Hadoush, 2018 [44]	Investigate the therapeutic effects of bilateral anodal tDCS stimulation on balance and fear of falling (FOF) outcomes in patient with PD	-	Cross-sectional	18	10	-	-	FES-I	-	male: 7.4 female: 7.0	-	H-Y male: 2.5 H-Y female: 2.8	-

(*continued on next page*)

TABLE 5. (*continued*)

Study	Study Aim	Sample	Study Design	Sample size	Quality Score	Cognitive status	Mean MMSE/ MoCA score	Anxiety measures	Prevalence	Disease Duration (years)	MDS UPDRS Total Score	Hoehn & Yahr	Characteristics/Markers/ Symptomatology
Jonasson, 2015 [116]	Identify explanatory factors of concerns about falling in people with PD by focusing on personal and environmental factors as well as PD-related disabilities	Outpatient clinic	Cross-sectional	241	15	-	26 (Median, MoCA)	FES-I	46% reported FOF	8	30[a]	3	Walking difficulties, orthostatism, motor symptoms, age, and fatigue were explanatory factors of concerns about falling
Jonasson, 2018 [117]	Describe experiences of FOF in PD	Outpatient Clinic	Cross-sectional	12	14	Exclusion criteria: pronounced cognitive difficulties that made patient unable to give informed consent or take part in the majority of the data collection	23.5 (MoCA)	Questions about intensity of FOF	33% were very much afraid of falling 25% were somewhat afraid of falling 42% were a little afraid of falling	9	-	-	There were three themes that arose from the qualitative interviews: fear of falling as a disturbance in everyday life, fear of falling as a varying experience, and handling fear of falling by adopting different strategies.
Kader, 2016 [48]	Investigate how fall-related activity avoidance relates to FOF in PD	Outpatient clinic	Cross-sectional	251	14	Severe cognitive difficulties (clinician rated) excluded	-	mSAFFE	48% of participants endorsed a FOF.	8	30[a]	3	70% of those with FOF reported avoiding fall-related activities.
Kwon, 2019 [40]	Evaluate the relationship between gait and motor symptoms of PD or the risk of falling in PD	Outpatient clinic	Cross-sectional	24	14	MoCA	25 (MoCA)	FFM	-	1.13	UPDRS III: 17.13 (6.40), UPDRS II: 5.46 (4.11)	HY: 1.88 (0.40)	FFM negatively correlated with backward gait speed but not with forward gait or dual-task gait speed.
Lindholm, 2014 [43]	Investigate potential contributing factors to fear of falling (FOF) among people with idiopathic PD	Outpatient clinic	Retrospective cross-sectional	104	15	-	28.0 (MMSE)	FES(S)	37% of participant reported having FOF	5	13[a]	-	Strongest contributing factor to FOF was walking difficulties. Needing help from others in daily activities, fatigue and functional balance performance were associated with FOF.
Mak, 2009 [45]	Whether FOF could independently predict recurrent falls in people with PD	Outpatients	Cross-sectional	70	12	MMSE <24 excluded	-	ABC	-	7.2-9.4	-	2.8-3.0	Lower ABC (balance confidence) scores associated with recurrent falls. ABC score cut-off of 69 (out of 100) identified.
Mak, 2012 [118]	Evaluate the relationship between gait impairment, postural stability and muscle weakness and the level of fear of falling in people with PD	Outpatient clinic	Cross-sectional	57	12	MMSE ≥24	-	ABC	-	7.6	22.6[a]	2.5	Greater FOF was associated with increased knee muscle weakness, gait instability, and postural difficulty. The UPDRS-PG had the strongest association with ABC score.
Mehdizadeh, 2016 [14]	Study the relationship between FOF and quality of life	Outpatient clinic	Cross-sectional	139	12	MMSE> 23	-	FES-I	-	-	UPDRS-ADL (off phase): 21.09; UPDRS-ADL (on phase): 12.80	stage 1 - 67.14%, stage 2-32.85%	All dimensions of quality of life was significantly affected by a high FOF. In the drug on-state, the strongest association was found between FOF and the mobility dimension of quality of life. In the drug "off" state, the strongest relation was observed between FOF and mobility as well as activities of daily living dimensions.
Mehdizadeh, 2019 [15]	Study the association between functional balance, FOF, and independence in activities of daily living based on medication state	Outpatient clinic	Cross-sectional	140	12	MMSE >21	-	FES-I	-	-	UPDRS-ADL (off phase): 21.09; UPDRS-ADL (on phase): 12.80	stage 1 - 67.14%, stage 2-32.85%	FOF moderately correlated with functional balance in both "on" and "off" states.
Nilsson, 2011 [55]	Prospectively explore whether FOF and fall rate were affected after STN stimulation in people with PD	Post-operative (DBS)	Pre-post intervention	20	15	No clinical signs of dementia or severe cognitive decline	-	FES(S) SAFFE	-	12.7	UPDRS-III: Before surgery: 36 (without PD medication); 20 (with PD medication)	-	-

(*continued on next page*)

TABLE 5. (*continued*)

Study	Study Aim	Sample	Study Design	Sample size	Quality Score	Cognitive status	Mean MMSE/ MoCA score	Anxiety measures	Prevalence	Disease Duration (years)	MDS UPDRS Total Score	Hoehn & Yahr	Characteristics/Markers/ Symptomatology
											After surgery: without PD medication, STN stimulation turned off: 36; turned on: 27 With PD medication, STN turned on: 20		
Nilsson, 2012 [16]	Evaluate the effect of motor, nonmotor, demographic factors and medications on FOF in PD	Postal Survey	Cross-sectional	131	14	Dementia or severe cognitive impairment (clinician-rated) excluded	-	FES	45% indicated they had a fear of falling	6	-	-	Independent predictors of FOF included: walking difficulties, fatigue, turning hesitations, need help from others in daily activities, and fluctuations.
O'Connell, 2016 [42]	Evaluate the relationship between FOF and dual-task performance in PD	Outpatient clinic	Cross-sectional	31	13	MMSE >20	28	ABC	45% of participants had a high fear of falling (ABC<69).	4	-	stage 1 - 8 (25.8), stage 2 - 4 (12.9), stage 3 - 13 (41.9), stage 4 - 5 (19.4)	FOF increased with age, disease severity, and disease duration. Participants with a high FOF took longer to complete the dual task.
Rahman, 2011 [46]	Identify characteristics of FOF in PD and evaluate the impact of FOF on QoL	Outpatient clinic	Cross-sectional	130	12	-	-	FES CoF SAFFE	-	Non-fallers: 8.56 (4.47), fallers: 13.7 (8.47)	-	HY: non-fallers: 2.30 (1.04), fallers: 2.77 (1.16)	Fallers had greater FOF than non-fallers across all measures. For CoF, SE disability rating and BDI were significant predictors of perceived consequences of falling. For FES, only SE disability rating was a significant predictor of perceived self-efficacy. For SAFFE, SE disability rating and BAI were significant predictors of activity avoidance, as was BDI at trend level.
Thomas, 2010 [36]	Investigate the relationship between FOF and fall frequency among patients with idiopathic PD	Outpatient clinic	Cross-sectional	102	14	-	27.3 (MMSE)	FES	-	-	-	2.5	More frequent freezing, using an assistive walking device, more severe parkinsonism (H-Y stage) and greater cognitive impairment (lower MMSE score) exhibited greater FOF as measured by FES score

Notes: Dashes indicate no data is available. MMSE: Mini-Mental State Examination; UPDRS: Unified Parkinson's Disease Rating Scale; FOF: Fear of Falling; FES: Falls Efficacy Scale [119]; FES-I: Falls Efficacy Scale-International [57]; FES(S): Swedish version of the Falls Efficacy Scale [119]; ABC: Activities-specific Balance Confidence [120]; QoL: Quality of Life; tDCS: Transcranial direct current stimulation; HRQoL: Health-Related Quality of Life; H-Y: Hoehn and Yahr Scale; SAFFE: Survey of Activities and Fear of Falling in the Elderly [121]; mSAFFE: Modified Survey of Activities and Fear of Falling in the Elderly [121]; TM: Tinetti's Mobility Index [122]; MoCA: Montreal Cognitive Assessment; MoCA-K: Korean version of the Montreal Cognitive Assessment; FFM: Fear of Falling Measure [123]; CoF: Consequences of Falling [121]; SE: Schwab & England [124]; NCSE: Neurobehavioral Cognitive Status Examination [125]; BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory; UPDRS-ADL: Unified Parkinson's Disease Rating Scale Activities of Daily Living; UPDRS-PG: Unified Parkinson's Disease Rating Scale − Posture and Gait [101];

[a] UPDRS III only reported.

cognitive status of their participants. Fifty-two studies (87%) met the cut-off score of 12 points on the modified QUADAS tool. Scores on the QUADAS tool ranged from 10−16 points, with a mean of 13 points.

Of the 60 studies identified, 14 focused on Anxiety NOS (or equivalent, i.e., anxiety symptoms, atypical anxiety, stress) in PD (Table 3), 31 reported on fluctuating anxiety (Table 4) and 22 reported Fear of Falling (FOF) (Table 5). All studies used a cross-sectional design. A wide range of assessment instruments is used for each of these presentations of anxiety (listed in Tables 3-5).

Anxiety NOS

Of the 14 studies reporting *Anxiety NOS* (or equivalent), anxiety was a primary outcome measure in 12 studies and a secondary outcome measure in two studies. While the majority of studies (N = 10) diagnosed Anxiety NOS (or equivalent) according to the DSM criteria (3 using DSM-III; 7 using DSM-IV), one study used the International Classification of Diseases (ICD-9) criteria, and another used the Present State Examination (PSE) criteria.

Prevalence

A weighted mean of 14.9% (range: 2%−33 %) of the total of 1,452 patients experienced Anxiety NOS (or equivalent).

Symptomatology

Anxiety was assessed in only the "on" motor state in four studies and both "on" and "off" states in one study. Nine studies did not report whether anxiety was assessed in the "on" or "off" state. The symptomatology of Anxiety NOS included psychological distress attributed to the diagnosis of PD,[6,7] stress or worry, insecurity about the future, worry related to motor symptoms and wearing-off medication, fear of losing control of motor and/or bodily functions due to disability,[6] social embarrassment due to motor "off" states, social withdrawal due to motor symptoms or "off" states, frustration or anger relating to cognitive problems, agitation, inner unrest, internal tremor or inability to relax,[7] excessive and recurrent situational anxiety related to motor deficits, panic attack-like episodes, persistent excessive worry not meeting criteria for generalized anxiety disorder.[8]

Clinical correlates

Anxiety NOS was associated with minor depression[8] and depressive symptoms,[9] on-off motor symptoms,[7, 8, 10] muscle cramps,[9] poorer quality of life,[7,8] younger age of PD onset,[9,11, 12] pharmacological treatment for anxiety or depression,[12] uncertainty of symptoms,[6] and gait impairment.[10] Pontone et al.[11] identified characteristics associated with anxiety NOS subtypes defined as anticipatory anxiety, fluctuation associated anxiety and generalized worry. In this study, anticipatory anxiety was associated with a higher levodopa daily dose. Fluctuation associated anxiety was associated with female sex, younger age of PD onset, longer PD duration, higher daily dose of levodopa, more severe motor complications of therapy, and poorer quality of life. Lastly, generalized worry was associated with poorer global cognition.

Fluctuating Anxiety

Of the 31 studies reporting fluctuating anxiety, anxiety was a primary outcome in 19 studies and a secondary outcome in 12 studies. Seven of these studies were also identified as focusing on Anxiety NOS[7, 8, 10, 13] and FOF.[14-16]

Prevalence

A weighted mean of 34.2% (range: 3.8−100) of the total of 2,174 patients experienced fluctuating anxiety.

Symptomatology

Anxiety was assessed in only the "on" motor state in nine studies and both "on" and "off" states in 16 studies. Fluctuating anxiety was identified as anxiety related to the wearing-off phenomenon (nine studies), anxiety associated with motor fluctuations (15 studies), anxiety as a side effect of levodopa (four studies) and episodic anxiety (five studies), of which one also reported avoidance behavior anxiety subtypes.[17] Characterized the most common anxiety symptoms reported during the "off" state: feeling anxious, feeling sad, avoiding situations, palpitations, dizziness, and chills or hot flushes. Vazquez et al.[18] reported that panic attacks were associated with the motor "off" state. Rizos et al.[19] identified that wearing-off

anxiety was associated with urgency of urination, drooling, pain, low mood, limb paresthesia and dizziness.

Clinical correlates

Of the 15 studies reporting on fluctuation-related anxiety, six identified an association between depression symptoms and fluctuation-related anxiety.[18, 20-24] Four studies reported that anxiety was more severe in the off-medication state[23, 25-27] and as such was reduced in the on-mediation state.[10] Similarly, worry, social withdrawal and social embarrassment due to motor "off" states were symptoms associated with PD-anxiety.[7] Moreover, three studies reported FOF was associated with fluctuations,[16] such that FOF fluctuated between "on" and "off" states,[15] and FOF increased in the "off" state.[14] Three studies found that poorer motor function was associated with fluctuation-related anxiety.[20,22,23] In the subgroup of PD patients with fluctuation associated anxiety identified by Pontone et al.,[11] patients were more frequently female, with a younger age of onset, longer PD duration, higher daily levodopa dose, greater complications of therapy (MDS-UPDRS-IV) scores and a poorer quality of life. Richard et al.[21] also found that anxiety fluctuations were associated with higher scores on depression and anxiety rating scales, a history of depression or anxiety, and use of psychotropic medications. Racette et al.[28] found that anxiety fluctuations were associated with dementia, psychosis, younger age of PD onset, and longer disease duration. Storch et al.[25] found that anxiety was associated with worse health related quality of life.

The four studies that evaluated medication related anxiety revealed mixed findings. Two studies found that anxiety increased in the medication off state.[29, 30] Maricle et al.[31] found that anxiety fluctuations were related to levodopa dosing. Vazquez et al.[18] found that panic attacks were associated with starting levodopa therapy sooner, and higher levodopa doses than those without panic attacks.

Of the five studies focusing on episodic anxiety, three identified an association between depression symptoms and episodic anxiety,[32-34] and two found that time of day was associated with episodic anxiety.[31,35] Fernie et al.[35] revealed that cognitive processes and negative metacognitions predicted episodic distress, independent of motor state. Starkstein et al.[32] found that episodic anxiety without depression and persistent anxiety with depression were associated with female sex, use of psychotropic medication, personal history of anxiety and depression, and higher UPDRS-I and UPDRS-IV scores compared to patients without anxiety. Broen et al.[34] found that episodic anxiety was associated with PD-specific disturbances of activities of daily living, complications of therapy, higher depression scores, female sex and a history of anxiety. Brown et al.[33] found that episodic anxiety was predicted by younger age, female gender, younger age of PD onset, higher LEDD and greater disability.

Fear of Falling

FOF was reported in 22 studies. Anxiety was a primary outcome in 17 studies and a secondary outcome in five studies. Anxiety was assessed in only the "on" motor state in 10 studies, the "off" state only in one, and both "on" and "off" states in four studies. Six studies did not report whether anxiety was assessed in the "on" or "off" state, one of which assessed anxiety via a postal survey. One study assessed anxiety in only drug-naïve patients.

Prevalence

A weighted mean of 51.5% (range 14%−100%) of the sample of 1,012 patients experienced FOF.

Symptomatology

An association between FOF and walking and gait difficulties was reported. Specifically, the following walking characteristics were associated with FOF: using an assistive walking device,[36,37] more frequent freezing,[36] turning hesitations,[16] a lower speed and stride length for forward and backward walking, a greater time to take five steps, turn, complete the up and go test, a greater time and number of steps to walk sideways and a greater number of steps to complete a turn.[38] Moreover, the following gait and posture characteristics were associated with FOF: a greater degree of posture impairment,[39] greater UPDRS-derived Postural Instability and Gait Difficulty (UPDRS-PG) scores[15] and lower backward gait speed.[40] Increased FOF was observed in the presence of obstacles, compared to open ground Griffin et al.,[41]

and during motor dual-tasks (i.e., carrying a glass of water).[42]

Five studies demonstrated that balance impairments were associated with FOF [15, 37, 41, 43, 44]: lower balance confidence,[45] functional balance[15, 37, 43] and orthostasis.[44]

Clinical correlates

Characteristics associated with FOF included increased age,[42,44] needing help from others in daily activities,[16,43] a history of falls,[46,47] avoiding fall-related activities[48] and a reduced quality of life.[14,49] In particular, in the "on" drug state, the mobility dimension of quality of life demonstrated the strongest association with FOF; whilst mobility and activities of daily living dimensions of quality of life showed the greatest association with FOF in the "off" state.[14]

Three studies reported an association between FOF and a greater severity of PD symptoms.[36,42,46] Six studies cited cognitive and psychiatric symptoms associated with FOF, including greater global cognitive impairment,[36] fatigue[16,43,44] and depressive symptoms.[37,46]

DISCUSSION

The present systematic review is the first to comprehensively examine atypical anxiety disorders in PD. The 60 included studies were published between 1987 and 2021, with the majority[38] of papers being published over the past 10 years, likely reflecting an increased awareness of and interest in anxiety in PD. Overall, our review suggested that atypical anxiety in PD is a protean syndrome associated with a poor quality of life, and greater functional disability, thus requiring greater attention towards better ways to identify and manage atypical anxiety presentations in routine clinical practice.

Prevalence

Anxiety NOS accounted for a weighted mean prevalence of 14.9% (range 2%−33%) in a total of 1,452 patients that experienced anxiety across 14 studies and was comparable to previously reported average of 13%.[1] On the other hand, the prevalence of both fluctuating anxiety and FOF exceeded the average overall prevalence rates for anxiety reported in literature (31%). Our review suggested the requirement for greater attention towards finding well defined guidelines to describe atypical presentations of anxiety in PD.

Symptomatology

Our review defined a variety of anxiety symptoms associated with motor and non-motor symptoms of PD, complications of PD medications such as specific anxiety symptomatology associated with "on" and "off" fluctuations (or both), and to a lesser extent anxiety associated with cognitive symptoms.[6-8] While the validated Parkinson's Anxiety Scale (PAS) identifies anxiety encompassing three subscales of persistent anxiety, episodic anxiety and avoidance behaviors, there still remains the need to better identify PD-specific atypical anxiety presentations described in our review. Addressing this unmet need, the PD specific Anxiety Inventory (PDSAI) was recently developed to capture symptomatology of atypical anxiety.[7] The PD-SAI content includes disease, motor and non-motor, complications of therapy, fluctuations, cognition and social domains. The validation of the PDSAI is currently underway.

The further characterization of atypical anxiety, via the PDSAI as well as other methods can improve recognition and treatment of this non-motor complication in routine clinical practice in several important ways. First, improved understanding of atypical anxiety will facilitate the effective screening for prominent anxiety symptoms during psychiatry and neurology appointments as it will increase the precision and specificity of the interview probes utilized during routine clinical encounters. Second, it will facilitate the development of personalized treatment plans and more precise clinical outcome assessment once PD patients engage in treatment. Third, an expanded conceptualization of anxiety in PD patients will help to improve communication about anxiety presentation across various sectors of PD community and improve anxiety treatment in non-specialty centers, where there is limited knowledge about PD.[50] Lastly, the expanded definition of PD anxiety may improve clinical trial design and outcome assessment and facilitate the development of a conceptual model of PD anxiety to inform future treatment development and biomarker initiatives.

Classification

Almost 15% of PD patients experience anxiety that cannot be classified into one of the specified DSM categories, and hence is often classified as 'Anxiety NOS' or equivalent terminology. This category does not constitute a specific clinical phenotype of anxiety, but rather a rest category for both atypical presentations of anxiety, as well as PD-specific anxiety presentations, such as 'wearing-off' (or 'off')-related anxiety and FOF. Although the diagnostic inadequacy of the DSM as applied to PD anxiety has been frequently described, few efforts have been undertaken to overcome this problem. In a hypothesis-free approach, Starkstein et al. conducted a principal component analysis that supported three different phenotypes of anxiety: 'episodic anxiety without depression,' 'persistent anxiety with depression,' and 'both persistent and episodic anxiety with depression,' where 'episodic' refers to both panic attacks as well as situational anxiety, and 'persistent' refers to generalized and social anxiety.[32] Such hypothesis-free approaches can lead to new classifications that better represent the clinical phenotypes in PD and may be more useful in clinical practice than strictly adhering to existing DSM classifications. A problem with characterizing, and thus with classifying, fluctuating anxiety symptoms of PD, for example, in the context of motor fluctuations, is the lack of a clear definition of such mood and anxiety fluctuations, as well as of a standardized way to assess such these.[51] Experience sampling techniques (also known as ecological momentary assessment techniques) may provide new insights in the phenomenology of anxiety and help develop a more appropriate classification system.[52] For another PD specific anxiety, 'fear of falling,' several validated assessment instruments are available.[53,54]

Clinical and Neurobiological Correlates

Overall, atypical anxiety was associated with current depression, a history of depression and anxiety, younger onset age, female gender, motor fluctuations and longer duration of the disease. Patients with FOF had a more advanced disease and FOF was associated with specific motor complications of PD, comprehensively outlined in our review. The development of atypical anxiety in PD over time is complex[21, 45, 55-57] such that anxiety in PD can arise at any point in the course of PD. Moreover, the causal and maintaining factors of anxiety in PD are heterogeneous and individualized assessment is needed to guide effective treatment. In some cases, characteristics of atypical anxiety may be representative of underlying mechanism, although the relationship is likely complex. For example, episodes of anxiety that occur with motor fluctuations appear to be associated with alterations in plasma dopamine levels in later-stage disease yet increasing levodopa dosage does not reliably improve anxiety.[30,58-60] Alternatively, given the high comorbidity of anxiety and depression in PD, one might assume shared disruption of limbic circuitry as a cause for atypical anxiety. However, secondary outcome data from antidepressant trials in PD do not reliably show improvement in anxiety as depression remits, and the presence of high anxiety predicted diminished responsiveness for depressive symptoms.[61,62] These trials were not designed to detect changes in anxiety so they should be interpreted with caution but highlight the need for additional study. The relationship of a history of anxiety or depression to atypical anxiety is interesting as both are associated with an almost two-fold increase in risk for later PD, suggesting that some anxiety and depressive disorders may be prodromal or pre-motor symptoms of PD.[63,64] Further, the association between PD and anxiety and depressive disorders is bidirectional, as first-degree relatives of people with PD have an increased risk of anxiety and depressive disorders compared to control probands.[65] A shared neuropathological substrate could explain the increased risk of anxiety with later PD and might also be the reason for the atypical features and association with younger age of PD onset.[13] A recent systematic review of the literature on fMRI and anxiety in PD implicated the amygdala, caudate, and putamen.[66] This review revealed that anxiety, particularly dopamine-related anxiety, was associated with left amygdala volume and alterations in network connectivity.[67-69] In addition, alterations in the caudate and putamen were observed across neuroimaging (functional, resting state, and structural) studies examining anxiety in PD.[70-75] A better understanding of the pathophysiology of atypical anxiety is needed to clarify its association with PD and ultimately to inform controlled trials.

Cognitive impairment

Although there were small studies describing cognitive characteristics of atypical anxiety, there was no

study specifically investigating atypical anxiety in patients with significant cognitive impairment or dementia. Several studies have shown links between anxiety and cognition. A recent meta-analysis showed that people with prior history of anxiety have a higher risk of all-cause dementia than persons without this history.[76] In newly diagnosed PD, anxiety increases the risk of cognitive impairment, namely in the memory domain.[77] Anxiety is also linked to verbal memory impairment in PD.[78] In a study exploring anxiety-related brain modifications in a large sample of PD patients without dementia, those with clinically significant anxiety had deficits in attention and working memory compared with those without anxiety.[79] With the Parkinson Anxiety Scale[80] whose subscales capture some manifestations of atypical anxiety, persistent anxiety tended to increase as cognitive impairment was more severe and avoidance behavior were more frequent in PD patients with cognitive impairment than in PD patients with normal cognition.[81] However, the specific influence of atypical anxiety on cognition is not known and further studies are needed to determine both the links between atypical anxiety and cognition and how atypical anxiety contributes to cognitive progression of PD.

LIMITATIONS

Due to the nature of atypical anxiety, although we kept our search strategy broad, not all presentations of atypical anxiety may have been captured. Another limitation is that assessment across studies vary greatly, with some using diagnostic criteria, such as those of the DSM or ICD, whereas others use cut-off scores on a variety of rating scales. Moreover, the assessment instruments used in the studies may be specifically sensitive to capture one presentation of atypical anxiety, while not being sensitive enough to capture other presentations. In addition, only four studies included patients with dementia in which presentations of atypical anxiety may differ from that in non-demented patients. All these factors make a comparison between studies difficult.

While we comprehensively examined the prevalence and phenomenology of atypical anxiety in PD, the present review did not address treatment. The evidence-base for treatment trials for atypical presentations of anxiety is sparse. To our knowledge there are no treatment trials focused on Anxiety NOS. In preliminary studies, treatment of fluctuating anxiety has been examined with a pharmacological (rotigotine)[82,83] and a non-pharmacological (acceptance and commitment therapy; BEWARE training) intervention,[83] while approaches like Deep Brain Stimulation[55] and transcranial direct current stimulation (tDCS)[44] have been explored for FOF. Further clinical trials are needed to establish efficacious treatments.

Until such evidence exists, we recommend the following treatment guidelines for atypical anxiety recommended in an earlier edition of the American Journal of Geriatric Psychiatry by Pontone GM et al.[84] Given the heterogeneity of anxiety presentations in PD, the importance of tailoring interventions to meet the specific needs and unique symptom profiles of each individual cannot be overstated. In order to facilitate the timely and personalized management for all forms of clinically significant anxiety in PD, routine screening every 6–12 months, combining the use of validated self-report scales, and skilled clinical interview (which directly assesses the atypical manifestations of PD anxiety described herein) as well as collateral information from the caregiver, is encouraged.[85]

CONCLUSION

Atypical anxiety disorders in PD patients are currently characterized as anxiety NOS, anxiety associated with motor fluctuations, and FOF. They substantially influence daily functioning and quality of life of PD patients. Atypical anxiety symptoms increase with disease progression, and it is essential to identify and appropriately treat such symptoms at early stages in order to improve clinical management and long-term outcomes. Therefore, improving assessment and recognition of atypical anxiety, developing a more appropriate classification of PD-related anxiety, elucidating pathophysiological mechanisms and examining the association of cognitive impairment with atypical anxiety in PD are important next steps toward achieving these goals.

AUTHOR CONTRIBUTIONS

Nadeeka N. Dissanayaka, Elana J. Forbes, Kate Perepezko, Albert F.G. Leentjens, Roseanne D.

Dobkin, Kathy Dujardin and Gregory M. Pontone made substantial contributions to the conception/design of the work, data interpretation and drafting and critically revising the work for important intellectual content. Elana J. Forbes and Kate Perepezko contributed to data acquisition and analysis.

DATA STATEMENT

The data has not been previously presented orally or by poster at scientific meetings

DISCLOSURES

Dr. Nadeeka Dissanayaka is supported by the National Health and Medical Research Boosting Dementia Research Leadership Fellowship (APP1137339).

The authors report no conflicts with any product mentioned or concept discussed in this article.

SUPPLEMENTARY MATERIALS

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jagp.2022.02.004.

References

1. Broen MPG, Narayen NE, Kuijf ML, et al: Prevalence of anxiety in Parkinson's disease: a systematic review and meta-analysis. Mov Disord 2016; 31:1125–1133
2. Dissanayaka NNNW, White E, O'Sullivan JD, et al: The clinical spectrum of anxiety in Parkinson's disease. Mov Disord 2014; 29:967–975
3. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders (DSM-5). 5th ed. Washington, DC Arlington, VA: American Psychiatric Association, 2013
4. Moher D, Liberati A, Tetzlaff J, et al: Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Bmj-Brit Med J 2009; 339:b2535
5. Whiting P, Rutjes AW, Reitsma JB, et al: The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. BMC Med Res Methodol 2003; 3:25
6. Thordardottir B, Nilsson M, Iwarsson S, et al: "You plan, but you never know" - participation among people with different levels of severity of Parkinson's disease. Disabil Rehabil 2014; 36:2216–2224
7. Dissanayaka NNW, O'Sullivan JD, Pachana NA, et al: Disease-specific anxiety symptomatology in Parkinson's disease. Int Psychogeriatr 2016; 28:1153–1163
8. Pontone GM, Williams JR, Anderson KE, et al: Prevalence of anxiety disorders and anxiety subtypes in patients with Parkinson's disease. Mov Disord 2009; 24:1333–1338
9. Chen Y-K, Lu J-Y, Chan DML, et al: Anxiety disorders in Chinese patients with Parkinson's disease. Int J Psychiatry Med 2010; 40:97–107
10. Ehgoetz Martens KA, Ellard CG, Almeida QJ: Evaluating the link between dopaminergic treatment, gait impairment, and anxiety in Parkinson's Disease. Movement Disorders Clinical Practice 2016; 3:389–394
11. Pontone GM, Williams JR, Anderson KE, et al: Anxiety and self-perceived health status in Parkinson's disease. Parkinsonism Relat Disord 2011; 17:249–254
12. Dissanayaka NNW, White E, O'Sullivan JD, et al: Characteristics and treatment of anxiety disorders in Parkinson's Disease. Movement Disorders Clinical Practice 2015; 2:155–162
13. Pontone GM, Palanci J, Bienvenu OJ, et al: Familial aggregation of panic disturbances in Parkinson's Disease. J Neuropsychiatry Clin Neurosci 2011; 23:417–424
14. Mehdizadeh M, Lajevardi L, Habibi SAH, et al: The association between fear of falling and quality of life for balance impairments based on hip and ankle strategies in the drug On- and Off-phase of patients with idiopathic Parkinson' disease. Med J Islam Repub Iran 2016; 30:453
15. Mehdizadeh M, Martinez-Martin P, Habibi SA, et al: The association of balance, fear of falling, and daily activities with drug phases and severity of disease in patients with Parkinson. Basic Clin Neurosci 2019; 10:355–362
16. Nilsson MH, Hariz GM, Iwarsson S, et al: Walking ability is a major contributor to fear of falling in people with Parkinson's disease: implications for rehabilitation. Parkinsons Dis 2012; 2012:713236
17. Leentjens AF, Dujardin K, Marsh L, et al: Anxiety and motor fluctuations in Parkinson's disease: a cross-sectional observational study. Parkinsonism Relat Disord 2012; 18:1084–1088
18. Vazquez A, Jimenezjimenez FJ, Garciaruiz P, et al: Panic attacks in Parkinsons-disease - a long-term complication of levodopa therapy. Acta Neurol Scand 1993; 87:14–18
19. Rizos A, Martinez-Martin P, Odin P, et al: Characterizing motor and non-motor aspects of early-morning off periods in Parkinson's disease: an international multicenter study. Parkinsonism Relat Disord 2014; 20:1231–1235
20. Siemers ER, Shekhar A, Quaid K, et al: Anxiety and motor performance in Parkinson's disease. Mov Disord 1993; 8:501–506
21. Richard IH, Frank S, McDermott MP, et al: The ups and downs of parkinson disease: a prospective study of mood and anxiety fluctuations. Cogn Behav Neurol 2004; 17:201–207
22. Richard IH, Justus AW, Kurlan R: Relationship between mood and motor fluctuations in Parkinson's disease. J Neuropsychiatry Clin Neurosci 2001; 13:35–41
23. Nissenbaum H, Quinn NP, Brown RG, et al: Mood swings associated with the 'on-off' phenomenon in Parkinson's disease. Psychol Med 1987; 17:899–904
24. Henderson R, Kurlan R, Kersun JM, et al: Preliminary examination of the comorbidity of anxiety and depression in Parkinson's disease. J Neuropsychiatry Clin Neurosci 1992; 4:257–264
25. Storch A, Schneider CB, Wolz M, et al: Nonmotor fluctuations in Parkinson disease: severity and correlation with motor complications. Neurology 2013; 80:800–809

26. Ossig C, Sippel D, Fauser M, et al: Assessment of nonmotor fluctuations using a diary in advanced Parkinson's disease. J Parkinsons Dis 2016; 6:597–607
27. Witjas T, Kaphan E, Azulay JP, et al: Nonmotor fluctuations in Parkinson's disease - Frequent and disabling. Neurology 2002; 59:408–413
28. Racette BA, Hartlein JM, Hershey T, et al: Clinical features and comorbidity of mood fluctuations in Parkinson's disease. J Neuropsychiatry Clin Neurosci 2002; 14:438–442
29. Menza MA, Sage J, Marshall E, et al: Mood changes and 'on-off' phenomena in Parkinson's disease. Mov Disord 1990; 5:148–151
30. Kulisevsky J, Pascual-Sedano B, Barbanoj M, et al: Acute effects of immediate and controlled-release levodopa on mood in Parkinson's disease: a double-blind study. Mov Disord 2007; 22:62–67
31. Maricle RA, Nutt JG, Valentine RJ, et al: Dose-response relationship of levodopa with mood and anxiety in fluctuating Parkinson's disease: a double-blind, placebo-controlled study. Neurology 1995; 45:1757–1760
32. Starkstein SE, Dragovic M, Dujardin K, et al: Anxiety has specific syndromal profiles in Parkinson disease: a data-driven approach. Am J Geriatr Psychiatry 2014; 22:1410–1417
33. Brown RG, Landau S, Hindle JV, et al: Depression and anxiety related subtypes in Parkinson's disease. J Neurol Neurosurg Psychiatry 2011; 82:803–809
34. Broen MPG, Leentjens AFG, Hinkle JT, et al: Clinical markers of anxiety subtypes in Parkinson disease. J Geriatr Psychiatry Neurol 2018; 31:55–62
35. Fernie BA, Spada MM, Brown RG: Motor Fluctuations and Psychological Distress in Parkinson's Disease. Health Psychol. 2019; 38:518–526
36. Thomas AA, Rogers JM, Amick MM, et al: Falls and the falls efficacy scale in Parkinson's disease. J Neurol 2010; 257:1124–1128
37. Franzen E, Conradsson D, Hagstromer M, et al: Depressive symptoms associated with concerns about falling in Parkinson's disease. Brain Behav 2016; 6:e00524
38. Bryant MS, Rintala DH, Hou J-G, et al: Influence of fear of falling on gait and balance in Parkinson's disease. Disabil Rehabil 2014; 36:744–748
39. Adkin AL, Frank JS: Jog MS. Fear of falling and postural control in Parkinson's disease. Mov Disord 2003; 18:496–502
40. Kwon KY, Park S, Lee HM, et al: Backward gait is associated with motor symptoms and fear of falling in patients with de novo Parkinson's disease. J Clin Neurol 2019; 15:473–479
41. Griffin HJ, Greenlaw R, Limousin P, et al: The effect of real and virtual visual cues on walking in Parkinson's disease. J Neurol 2011; 258:991–1000
42. O'Connell E, Guidon M: Fear of falling and dual-task performance in people with Parkinson's disease. Eur J Physiother 2016; 18:167–172
43. Lindholm B, Hagell P, Hansson O, et al: Factors associated with fear of falling in people with Parkinson's disease. BMC Neurol 2014; 14:19
44. Hadoush H, Al-Jarrah M, Khalil H, et al: Bilateral anodal transcranial direct current stimulation effect on balance and fearing of fall in patient with Parkinson's disease. Neuro Rehabilitation 2018; 42:63–68
45. Mak MKY, Pang MYC: Fear of falling is independently associated with recurrent falls in patients with Parkinson's disease: a 1-year prospective study. J Neurol 2009; 256:1689–1695
46. Rahman S, Griffin HJ, Quinn NP, et al: On the nature of fear of falling in Parkinson's disease. Behav Neurol 2011; 24:219–228
47. Bryant MS, Rintala DH, Hou JG, et al: Relationship of falls and fear of falling to activity limitations and physical inactivity in Parkinson's disease. J Aging Phys Act 2015; 23:187–193
48. Kader M, Iwarsson S, Odin P, et al: Fall-related activity avoidance in relation to a history of falls or near falls, fear of falling and disease severity in people with Parkinson's disease. BMC Neurol 2016; 16:84
49. Grimbergen YA, Schrag A, Mazibrada G, et al: Impact of falls and fear of falling on health-related quality of life in patients with Parkinson's disease. J Parkinsons Dis 2013; 3:409–413
50. Dobkin RD, Rubino JT, Friedman J, et al: Barriers to mental health care utilization in Parkinson's disease. J Geriatr Psychiatry Neurol 2013; 26:105–116
51. van der Velden RMJ, Broen MPG, Kuijf ML, et al: Frequency of mood and anxiety fluctuations in Parkinson's disease patients with motor fluctuations: a systematic review. Mov Disord 2018; 33:1521–1527
52. Mulders AEP, van der Velden RMJ, Drukker M, et al: Usability of the experience sampling method in Parkinson's disease on a group and individual level. Mov Disord 2020; 35:1145–1152
53. Terroba-Chambi C, Bruno V, Millar-Vernetti P, et al: Design and validation of a new instrument to assess fear of falling in Parkinson's disease. Mov Disord 2019; 34:1496–1504
54. Mehdizadeh M, Martinez-Martin P, Habibi SA, et al: Reliability and Validity of Fall Efficacy Scale-International in People with Parkinson's Disease during On- and Off-Drug Phases. Parkinsons Dis 2019; 2019:6505232
55. Nilsson MH, Rehncrona S, Jarnlo GB: Fear of falling and falls in people with Parkinson's disease treated with deep brain stimulation in the subthalamic nuclei. Acta Neurol Scand 2011; 123:424–429
56. Friedman SM, Munoz B, West SK, et al: Falls and fear of falling: which comes first? A longitudinal prediction model suggests strategies for primary and secondary prevention. J Am Geriatr Soc 2002; 50:1329–1335
57. Yardley L, Beyer N, Hauer K, et al: Development and initial validation of the Falls Efficacy Scale-International (FES-I). Age Ageing 2005; 34:614–619
58. Maricle RA, Nutt JG, Carter JH: Mood and anxiety fluctuation in Parkinsons-disease associated with levodopa infusion - preliminary findings. Mov Disord 1995; 10:329–332
59. Pontone GM, Dissanayaka N, Apostolova L, et al: Report from a multidisciplinary meeting on anxiety as a non-motor manifestation of Parkinson's disease (vol 5, 30, 2019). Npj Parkinsons Dis 2020; 5:30
60. Joling M, van den Heuvel OA, Berendse HW, et al: Serotonin transporter binding and anxiety symptoms in Parkinson's disease. J Neurol Neurosurg Psychiatry 2018; 89:89–94
61. Richard IH, McDermott MP, Kurlan R, et al: A randomized, double-blind, placebo-controlled trial of antidepressants in Parkinson disease. Neurology 2012; 78:1229–1236
62. 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
63. Shiba M, Bower JH, Maraganore DM, et al: Anxiety disorders and depressive disorders preceding Parkinson's disease: a case-control study. Mov Disord 2000; 15:669–677
64. Weisskopf MG, Chen HL, Schwarzschild MA, et al: Prospective study of phobic anxiety and risk of Parkinson's disease. Mov Disord 2003; 18:646–651

65. Arabia G, Grossardt BR, Geda YE, et al: Increased risk of depressive and anxiety disorders in relatives of patients with Parkinson's disease. Parkinsonism Relat Disord 2007; 13:S52., -S
66. Perepezko K, Naaz F, Wagandt C, et al: Anxiety in Parkinson's disease: a systematic review of neuroimaging studies. J Neuropsychiatry Clin Neurosci 2021; 33:280–294
67. Zhang HB, Qiu YH, Luo YJ, et al: The relationship of anxious and depressive symptoms in Parkinson's disease with voxel-based neuroanatomical and functional connectivity measures. J Affect Disorders 2019; 245:580–588
68. Tessitore A, Hariri AR, Fera F, et al: Dopamine modulates the response of the human amygdala: a study in Parkinson's disease (vol 22, pg 9099, 2002). J Neurosci 2002; 22, Cp5-Cp
69. Vriend C, Boedhoe PSW, Rutten S, et al: A smaller amygdala is associated with anxiety in Parkinson's disease: a combined FreeSurfer-VBM study. J Neurol Neurosurg Psychiatry 2016; 87:493–500
70. Wabnegger A, Ille R, Schwingenschuh P, et al: Facial Emotion Recognition in Parkinson's Disease: An fMRI Investigation. Plos One 2015; 10:e0136110
71. Heller J, Mirzazade S, Romanzetti S, et al: Impact of gender and genetics on emotion processing in Parkinson's disease - a multimodal study. Neuroimage Clin 2018; 18:305–314
72. Moonen AJH, Weiss PH, Wiesing M, et al: An fMRI study into emotional processing in Parkinson's disease: does increased medial prefrontal activation compensate for striatal dysfunction? Plos One 2017; 12:e0177085
73. Wang XX, Li JY, Wang M, et al: Alterations of the amplitude of low-frequency fluctuations in anxiety in Parkinson's disease. Neurosci Lett 2018; 668:19–23
74. Oosterwijk CS, Vriend C, Berendse HW, et al: Anxiety in Parkinson's disease is associated with reduced structural covariance of the striatum. J Affect Disorders 2018; 240:113–120
75. Carey G, Gormezoglu M, de Jong JJA, et al: Neuroimaging of anxiety in Parkinson's Disease: a systematic review. Mov Disord 2021; 36:327–339
76. Kuring JK, Mathias JL, Ward L: Risk of Dementia in persons who have previously experienced clinically-significant Depression, Anxiety, or PTSD: a systematic review and meta-analysis. J Affect Disorders 2020; 274:247–261
77. Dissanayaka NNW, Lawson RA, Yarnall AJ, et al: Anxiety is associated with cognitive impairment in newly-diagnosed Parkinson's disease. Parkinsonism Relat Disord 2017; 36:63–68
78. Forbes EJ, Byrne GJ, O'Sullivan JD, et al: Defining atypical anxiety in Parkinson's disease. Movement Disorders Clinical Practice 2021; 8:571–581
79. Carey G, Lopes R, Viard R, et al: Anxiety in Parkinson's disease is associated with changes in the brain fear circuit. Parkinsonism Relat Disord 2020; 80:89–97
80. Leentjens AFG, Dujardin K, Pontone GM, et al: The Parkinson Anxiety Scale (PAS): development and validation of a new anxiety scale. Mov Disord 2014; 29:1035–1043
81. Dujardin K, Moonen AJH, Behal H, et al: Cognitive disorders in Parkinson's disease: confirmation of a spectrum of severity. Parkinsonism Relat Disord 2015; 21:1299–1305
82. Fanciulli A, Assogna F, Caltagirone C, et al: Rotigotine for anxiety during wearing-off in Parkinson's disease with dementia. Aging Clin Exp Res 2013; 25:601–603
83. Ghielen I, van Wegen EEH, Rutten S, et al: Body awareness training in the treatment of wearing-off related anxiety in patients with Parkinson's disease: Results from a pilot randomized controlled trial. J Psychosom Res 2017; 103:1–8
84. Pontone GM, Mills KA: Optimal Treatment of Depression and Anxiety in Parkinson's Disease. Am J Geriatr Psychiatry 2021; 29:530–540
85. Weintraub D, Aarsland D, Chaudhuri KR, et al: The neuropsychiatry of Parkinson's disease: advances and challenges. Lancet Neurol 2022; 21:89–102
86. Fleminger S: Left-sided Parkinson's disease is associated with greater anxiety and depression. Psychol Med 1991; 21:629–638
87. Lauterbach EC, Freeman A, Vogel RL: Differential DSM-111 psychiatric disorder prevalence profiles in dystonia and Parkinson's disease. J Neuropsychiatry Clin Neurosci 2004; 16:29–36
88. Leentjens AFG, Dujardin K, Marsh L, et al: Anxiety rating scales in parkinson's disease: a validation study of the hamilton anxiety rating scale, the beck anxiety inventory, and the hospital anxiety and depression scale. Mov Disord 2011; 26:407–415
89. Menza MA, Robertson-Hoffman DE, Bonapace AS: Parkinson's disease and anxiety: comorbidity with depression. Biol Psychiatry 1993; 34:465–470
90. Qureshi SU, Amspoker AB, Calleo JS, et al: Anxiety disorders, physical illnesses, and health care utilization in older male veterans with Parkinson disease and comorbid depression. J Geriatr Psychiatry Neurol 2012; 25:233–239
91. Stein MB, Heuser IJ, Juncos JL, et al: Anxiety disorders in patients with Parkinson's disease. Am J Psychiatry 1990; 147:217–220
92. Tudorica V, Zaharia C, Pirscoveanu D, et al: Study on anxiety in patients with Parkinson's disease. Rom J Neurol 2009; 7:46–49
93. American Psychiatric Association: Diagnostic and Statisticial Manual of Mental Disorders. 4th ed. (DSM-IV) Washington, D.C: American Psychiatric Association, 1994
94. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders. 3rd rev. ed. (DSM-III-R) Washington, D.C: American Psychiatric Association, 1987
95. American Medical Association: International Classification of Diseases. 9th revision Chicago, Ill: American Medical Association, 1999 Clinical modification: ICD-9-CM
96. Wing JK, Cooper JE, Sartorius N: Measurement and classification of psychiatric symptoms; An instruction manual for the PSE and Catego program. London: Cambridge University Press, 1974
97. Sheehan DV, Lecrubier Y, Sheehan KH, et al: The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998; 59(Suppl 20):22–33, quiz 4-57
98. Zung WW: A rating instrument for anxiety disorders. Psychosomatics 1971; 12:371–379
99. Robins LN, Helzer JE, Croughan J, et al: "National-institute-of-mental-health diagnostic interview schedule - its history, characteristics, and validity. Arch Gen Psychiat 1981; 38:381–389
100. Mannuzza S, Fyer AJ, Klein DF, et al: Schedule for affective-disorders and schizophrenia - lifetime version modified for the study of anxiety disorders (Sads-La) - rationale and conceptual development. J Psychiatr Res 1986; 20:317–325
101. Goetz CG, Tilley BC, Shaftman SR, et al: Movement disorder society-sponsored revision of the unified parkinson's disease rating scale (MDS-UPDRS): scale presentation and clinimetric testing results. Mov Disord 2008; 23:2129–2170
102. Folstein MF, Robins LN, Helzer JE: The mini-mental state examination. Arch Gen Psychiat 1983; 40:812
103. Mayeux R, Stern Y, Rosen J, et al: Depression, intellectual impairment, and Parkinson disease. Neurology 1981; 31:645–650

104. Jenkinson C, Fitzpatrick R, Peto V, et al: The PDQ-8: development and validation of a short-form Parkinson's disease questionnaire. Psychol Health 1997; 12:805–814
105. Teng EL, Chui HC: The modified mini-mental state (3ms) examination. J Clin Psychiatry 1987; 48:314–318
106. Melo LM, Chien HF, Barbosa ER: Identification of wearing-off manifestations (reduction of levodopa effect) in Parkinson's disease using specific questionnaire and comparison of the results with routine ambulatory evaluations. Arq Neuro-Psiquiat 2010; 68:506–510
107. Raudino F: Non motor off in Parkinson's disease. Acta Neurol Scand 2001; 104:312–315
108. Copeland JR, Kelleher MJ, Kellett JM, et al: A semi-structured clinical interview for the assessment of diagnosis and mental state in the elderly: the Geriatric Mental State Schedule. I. Development and reliability. Psychol Med 1976; 6:439–449
109. Bech P, A C: The Hamilton scales. 1st ed. Berlin, Heidelberg: Springer, 1990
110. Beck AT, Steer RA: Beck Anxiety Inventory Manual. San Antonio, TX: Psychological Corporation, 1993
111. Mccormack HM, Horne DJD, Sheather S: Clinical-applications of visual analog scales - a critical-review. Psychol Med 1988; 18:1007–1019
112. Zigmond AS, Snaith RP: The hospital anxiety and depression scale. Acta Psychiat Scand 1983; 67:361–370
113. Spielberger CD, Gorsuch RL, Lushene R, et al: Manual for the State-Trait Anxiety Inventory. Palo Alto, CA: Consulting Psychologists Press, 1983
114. Snaith RP, Baugh SJ, Clayden AD, et al: The Clinical Anxiety Scale - an Instrument Derived from the Hamilton Anxiety Scale. Br J Psychiatry 1982; 141:518–523
115. Chaudhuri KR, Healy DG, Schapira AH, et al: Non-motor symptoms of Parkinson's disease: diagnosis and management. Lancet Neurol 2006; 5:235–245
116. Jonasson SB, Ullen S, Iwarsson S, et al: Concerns about falling in Parkinson's disease: associations with disabilities and personal and environmental factors. J Parkinson Dis 2015; 5:341–349
117. Jonasson SB, Nilsson MH, Lexell J, et al: Experiences of fear of falling in persons with Parkinson's disease - a qualitative study. Bmc Geriatr 2018; 18:44
118. Mak MKY, Pang MYC, Mok V: Gait difficulty, postural instability, and muscle weakness are associated with fear of falling in people with parkinson's disease. Parkinsons Dis 2012; 2012:901721
119. Tinetti ME, Richman D, Powell L: Falls efficacy as a measure of fear of falling. J Gerontol 1990; 45:P239–PP43
120. Powell LE, Myers AM: The activities-specific balance confidence (Abc) scale. J Gerontol A Biol Sci Med Sci 1995; 50:M28–M34
121. Yardley L, Smith H: A prospective study of the relationship between feared consequences of falling and avoidance of activity in community-living older people. Gerontologist 2002; 42:17–23
122. Tinetti ME: Performance-oriented assessment of mobility problems in elderly patients. J Am Geriatr Soc 1986; 34:119–126
123. Velozo CA, Peterson EW: Developing meaningful fear of falling measures for community dwelling elderly. Am J Phys Med Rehab 2001; 80:662–673
124. McRae C, Diem G, Vo A, et al: Reliability of measurements of patient health status: a comparison of physician, patient, and caregiver ratings. Parkinsonism Relat Disord 2002; 8:187–192
125. Oehlert ME, Hass SD, Freeman MR, et al: The neurobehavioral cognitive status examination: accuracy of the "screen-metric" approach in a clinical sample. J Clin Psychol 1997; 53:733–737