Depression and Anxiety in Parkinson's Disease

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Definition and Diagnosis

Anxiety and depressive disorders are common neuropsychiatric complications of Parkinson's disease (PD). Whilst they may have particular characteristics (1), and their assessment is complicated by the overlap of symptoms with other manifestations of PD, there is no clearly defined difference to depressive or anxiety disorders in non-PD patients. Therefore, diagnosis of anxiety and depressive disorders is based on standard criteria, including ICD-10 diagnostic criteria and the definitions of anxiety and depressive disorders in the DSM Diagnostic and Statistical Manual of Mental Disorders (DSM) 5 criteria by the American Psychiatric Association (see box 1):

Box 1: Major Depressive Disorder

A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, hopeless) or observation made by others (e.g., appears tearful). (*Note:* In children and adolescents, can be irritable mood.)

2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation.)

3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. (*Note:* In children, consider failure to make expected weight gain.)

4. Insomnia or hypersomnia nearly every day.

5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).

6. Fatigue or loss of energy nearly every day.

7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).

8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).

9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

C. The episode is not attributable to the physiological effects of a substance or to another medical condition.

Note: Criteria A-C represent a major depressive episode.

D. The occurrence of the major depressive episode is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified and unspecified schizophrenia spectrum and other psychotic disorders.

E. There has never been a manic episode or a hypomanic episode.

Note: This exclusion does not apply if all of the manic-like or hypomanic-like episodes are substance induced or are attributable to the physiological effects of another medical condition.

Adapted from: Diagnostic and Statistical Manual of Mental Disorders (DSM) 5 criteria, *The American Psychiatric Association, 2013.*

Box 2: Generalised Anxiety Disorder

A. Excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least 6 months, about a number of events or activities (such as work or school performance).

B. The individual finds it difficult to control the worry.

C. The anxiety and worry are associated with three (or more) of the following six symptoms (with at least some symptoms having been present for more days than not for the past 6 months):

Note: Only one item required in children.

1. Restlessness, feeling keyed up or on edge.
2. Being easily fatigued.
3. Difficulty concentrating or mind going blank.
4. Irritability.
5. Muscle tension.
6. Sleep disturbance (difficulty falling or staying asleep, or restless, unsatisfying sleep).

D. The anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

E. The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition (e.g., hyperthyroidism).

F. The disturbance is not better explained by another medical disorder (e.g., anxiety or worry about having panic attacks in panic disorder, negative evaluation in social anxiety disorder [social phobia], contamination or other obsessions in obsessive-compulsive disorder, separation from attachment figures in separation anxiety disorder, reminders of traumatic events in posttraumatic stress disorder, gaining weight in anorexia nervosa, physical

complaints in somatic symptom disorder, perceived appearance flaws in body dysmorphic disorder, having a serious illness in illness anxiety disorder, or the content of delusional beliefs in schizophrenia or delusional disorder).

Adapted from: Diagnostic and Statistical Manual of Mental Disorders (DSM) 5 criteria, *The American Psychiatric Association, 2013.*

The types of depressive disorders seen in PD include major depression, minor depression and dysthymia. Patients with minor depressive disorder patients do not formally DSM V satisfy criteria but suffer from significant depressive symptoms interfering in their lives (2). Dysthymia, now called persistent depressive disorder in DSM V, is major depressive disorder lasting for at least 2 years (3). However, subsyndromal depression not fulfilling full diagnostic criteria for depression is common and should be included in the assessment of depressive symptoms of PD (4). Anxiety can present with panic attacks, phobias or generalized anxiety disorder (5). Both disorders in PD can be episodic or non-episodic, and may be associated with off-periods, with or without motor features (6).

Subtypes of depression and anxiety in PD

Within the definitions of anxiety and depressive disorders, the symptoms of depression and anxiety in patients with PD vary. The PROMS-PD study sub-classified PD patients according to their neuropsychiatric phenotype (7, 8) into four clinical phenotypes: anxious-depressed, predominantly depressed, predominantly anxious and healthy subgroup. The investigators reported that the depression phenotype was related to more axial motor symptoms, whereas anxiety was more commonly found among patients with motor fluctuations as well as younger age of onset (below the age of 55 years). Patients with the postural instability and gait disorder (PIGD) or non-tremor dominant motor subtypes were more likely to be represented in any of the mood subgroups when compared with non-PIGD and tremor-dominant patients. Furthermore, cognition was found to be a predictor of depression but not anxiety scores.

Epidemiology

Assessment of prevalence of depression and anxiety in PD is often complicated by overlap of somatic features of depression with other features of PD, coexisting cognitive problems and side-effects of dopaminergic medication (9). However, depressive symptoms in PD are reported to be present in approximately 20-30% of patients with PD (10), with wide variation between studies, ranging from 2.7% to up to 90% in the literature (11). In a review by Reijenders et al (11), the weighted prevalence of major depressive disorder was 17%, that of minor depressive symptoms 22% and dysthymia 13%. The authors concluded an increased prevalence of depression in PD, but lower than generally assumed. Whilst depressive symptoms are also common in the general population, they have clearly been shown to be more frequent in PD patients than age-matched populations, and they are also more common in this neurological condition than in other health problems such as diabetes or osteoarthritis (12). In table 1, a summary of the reported prevalence rates of the different degrees of depressive symptomatology are shown.

Although anxiety is often assessed together with depression and is often comorbid with depression (13) (14), it can occurr independently and has been reported to exert a higher impact on quality of

life among PD patients than depression itself (15, 16). Studies on the prevalence of anxiety are scarce and complicated by symptom overlap and comorbid disorders. Report prevalence rates range from 25% to 52% (17-20). Table 2 summarizes the prevalence of anxiety in PD among different studies.

Overall, depression and anxiety are both inadequately recognized as complications of PD in daily clinical practice, and are not diagnosed in up to 50% of PD patients, although they are more frequently recognised than some other non-motor features, such as those possibly considered more embarrassing (21-23).

In the prediagnostic phase of PD, depression and initiation of an antidepressant treatment are associated with an increase of PD risk of PD with an OR of 1.8 to 2.4 (24-27). Studies have also shown a link between existence of anxiety and the development of PD with a relative risk of 1.5 to 1.6 (24, 28, 29). A premorbid Parkinsonian personality with anxious traits has also been suggested, with lower novelty seeking behaviour and higher harm avoidance (13, 30) (31).

Risk factors for the development of depression in PD patients have been examined in large scale studies, reporting an increased risk among women, in the advanced stages of PD and in patients with cognitive impairment (32).

Genetic risk factors for the development of depression or anxiety in PD have so far shown inconsistent results (33-36), although one study has suggested that depression is more common among carriers of the Gly2019Ser mutation in the LRRK2 gen, when compared with non-carriers (37). A longitudinally followed GBA mutation positive cohort was found to have higher scores of depression (38). The relationship between PARK2, PINK1, PARK7 and DJ1mutations and depression/anxiety has also been studied, but no clear correlation could be found between the mutation carriers and the non-carriers for these genes has been found (39-45).

Risk factors associated with anxiety were examined in a longitudinal study by Zhu et al, who reported that depressive symptoms, insomnia, dysautonomia and cognitive impairment were risk factors associated with higher HADS-A scores (29).

Impact on Quality of life

Anxiety and depression have also been shown to be determinants of poorer quality of life in PD patients (23, 46-55). They result in a reduced health-related quality of life, worse functional status and worse cognitive function (56), and have been linked with an increased mortality (57). Whilst greater evidence exists for the impact of depressive disorders on quality of life, some studies found anxiety to be the main related neuropsychiatric disorder contributing to impaired quality of life (55, 58, 59) (60). One study reported two distinct patterns, distinguishing the impact of depression mainly on the ‘mental component’ from the impact on anxiety mainly based on the ‘physical component’ of quality of life measured by the SF-36 scale (61). In table 3, the effect of neuropsychiatric comorbidity on quality of life among PD patients in different studies is shown.

Scales for depression and anxiety

As depression and anxiety cause considerable burden on patients’ and carers’ quality of life and effective treatment has the potential to improve these symptoms and thereby outcome and prognosis of PD patients, early detection and diagnosis are important. Although common and

relevant to quality of life, they remain undetected in up to 50% of PD patients (9, 22, 62), and screening tools such as scales and questionnaires have an important role in clinical practice and research.

Depression

Several reviews for screening and rating scales for depression have been published. An evaluation of screening methods for depression by the American Academy of Neurology (AAN) in 2006 concluded that the Beck Depression Inventory (BDI), Hamilton Depression Rating Scale (HAMD 17) and Montgomery Asberg Depression Rating (MADRS) Scale had the highest diagnostic accuracy and were adequate to screen PD patients (evidence level B) and highlighted the need for specific validation (63). Similarly, in 2007 a review by the MDS Task Force on Depression rating scales was published, concluding that the Ham-D, BDI, HADS, MADRS and GDS are appropriate as screening scales for depression in PD with the CES-D and CSDD as alternative requiring further validation (64). Williams et al (65) compared 9 scales for the assessment of depression in PD of which the GDS-30 was judged the most efficient screening tool for depression in PD. A more recent review by Torbey et al (66) concluded that the HAM-D and the self-report GDS scales are recommended for screening and measuring severity of depression in PD, with the HADS-D, HDI, and the BDI, and MADRS being valid in PD and the CSDD for screening for PD in patients with and without dementia. Table 4 shows the cut-off scores for the different validated scales for depression in PD (62).

Anxiety

The use of validated scales for assessment of anxiety in PD was also reviewed by a MDS Task Force in 2008 (67), assessing the following scales: Beck Anxiety Inventory (BAI), Hospital Anxiety And Depression Scale-Anxiety (HADS-A), Zung's Self-Rating Anxiety Scale (Zung's SAS), Anxiety Sensitivity Index (ASI), State-Trait Anxiety Inventory (STAI), Hamilton Anxiety Rating Scale (HARS) and section 5 of Neuropsychiatric Inventory (NPI). Since there were no scales fulfilling criteria for a recommended scale for the assessment of anxiety in PD at that point of time, further validation studies were recommended. Since then, the three most commonly applied scales, BAI, HADS and HARS, have been validated for use in PD. Due to limitations of all existing scales for assessment of anxiety in PD, the Parkinson Anxiety Scale (PAS), a PD specific anxiety scale, was developed and reported to have higher specificity and sensitivity for its use as a screening tool than other scales (68). Another anxiety scale for PD patients, the Geriatric Anxiety Inventory (GAI), was developed and validated (69), but further large scale studies to validate these scales in other populations are required.

Biomarkers in depression and anxiety in PD

It has been suggested that in depression there is dysfunction of both dopamine and serotonin systems and their interaction in the brain, contributing to the development of depressive disorders. To date, only a few studies have assessed this interconnection, with important results coming from PET imaging models (70). In rat models, Lee et al found a correlation between a decrement of 5HT-1A receptor binding sites and depression severity. In studies on depression in humans, Drevets et al (71) found reduced 5-HT1A receptor binding sites and reduced serotonin mRNA expression in post-mortem analysis of the brainstem of suicide victims. A recent review on PET imaging and depression by Savitz et al (72) however highlighted mixed results in the literature, some groups reporting a decrease in 5HT-1A receptor binding sites and others hypothesizing an elevation in pre- and postsynaptic binding sites (73). They further hypothesized reduced 5-HT 2A, 5-HT 1B, Dopamine D1, MAO-A and muscarinic M2 receptor binding in patients with mood disorders and concluded that the

role of D2/D3 receptor binding sites is currently unclear, suggesting the current need for further studies.

In PD, there is evidence from imaging studies for both serotonergic (74) and dopaminergic dysfunction. Structural imaging suggests increased frontal atrophy in depressed patients with PD as the most strongly associated neural correlate of neuropsychiatric symptomatology in PD (75). In addition, hyperperfusion in occipital areas and hypoperfusion in fronto-temporo-limbic areas was reported as a potential biomarker for depression in PD (76), and a significant increase in amygdala metabolism in depressed PD patients and decreased caudate metabolism in anxious PD patients (77). In another neuroimaging study of depression, anxiety and apathy in PD increased neural activity in prefrontal regions and decreased functional connectivity between prefrontal and limbic structures was found in depressed PD patients with an inverse correlation between dopaminergic density in the caudate and putamen and the severity of anxiety in PD patients (78). However, further studies to assess potentially involved pathways of neuropsychiatric symptoms in PD are needed.

Blood based biomarkers are of increasing interest in PD with one study reporting that lower plasma levels of peripheral levels of 5-HT and its metabolite 5-HIAA in PD patients correlate with more severe depression and with pain (79). The same group also studied correlations between plasma levels of amino acids and non-motor symptoms and found a correlation between lower levels of ASP and Glutamate and depression as well as sleep disturbances (80). Some other recent studies found a relation between anxiety/depression and lower uric acid levels in serum (81, 82). Studies on inflammatory markers in the cerebrospinal fluid of PD patients, have indicated higher levels of inflammatory parameters such as Interleukin-1 beta, Interleukin-6 and Tumor necrosis factor Alpha in PD patients (83, 84) and have more recently also been linked with non-motor symptoms in PD (85). A recent study on inflammatory biomarkers in depression in PD by Lindqvist et al (86) specifically correlated HADS depression score with higher CRP levels and HADS anxiety score with IP-10 positivity.

Management

Depression

Pharmacological treatment

Although the prevalence of depression and anxiety among PD patients is high and both neuropsychiatric features have a significant impact on quality of life, evidence to guide their treatment is insufficient. Efficacy has been reported for the tricyclic antidepressants (TCA) Desipramine and Nortriptyline, the Serotonin-Noradrenaline reuptake inhibitors (SNRI) Venlafaxine, and the selective Serotonin reuptake inhibitors (SSRI) Citalopram, Sertraline and Paroxetine and in randomized, double-blind, placebo-controlled clinical trials (87-89). However, sample sizes of these studies were small and there is currently still inconclusive evidence on the effectiveness of individual antidepressants compared to each other and even against placebo. Nonetheless, in a recent systematic review on systematic treatments for depression in PD comparing 13 interventional trials, only SSRIs showed a statistically significant improvement of depression (90, 91). In contrast, other studies concluded tricyclic antidepressants to be at a similar level of efficacy as SSRIs (92-94). There is also evidence that dopamine agonists improve depression when compared with placebo, with most evidence available for Pramipexole (95) and transdermal Rotigotine (96). An MDS Evidence-based Review concludes that Pramipexole is efficacious for the treatment of depression in PD (97). The importance of dopaminergic agents in the occurrence of mood disorders of PD is also reflected

in the development of depression in the context of dopamine withdrawal syndrome (DAWS) and increased rates of apathy and depression following rapid medication reduction after Deep Brain Stimulation surgery (98).

The results of pharmacological trials for depression in PD is summarised in table 2.

Current guideline by the AAN state that the TCA Amitriptyline (level C) may be considered for treatment of depression in PD, with currently insufficient evidence to make recommendations on other pharmacological treatments. A more recent meta-analysis with slightly different methodology by Liu et al comparing the efficacy and acceptability of different medications for depression in PD, concluded that TCAs might be the best choice when starting antidepressant treatment in PD due to its favourable balance between benefit and acceptability, followed by Pramipexole, SNRIs and SSRIs (99). Other meta-analyses however concluded that whilst both SSRI and TCA are effective, SSRIs have been tolerability in PD (100) or that the antidepressant effect is only significant for SSRIs and not TCA.

Non-pharmacological treatment

A multidisciplinary approach improves depression scores in PD (101), and can include education about the mood disturbances and its relation to PD, use of skills to cope with these symptoms and emotional support (102), as well as more specific pharmacological and non-pharmacological approaches. Increasingly evidence is emerging on the role of more specific non-pharmacological options. The best evidence exists for cognitive behavioural therapy (CBT), and with evidence for other non-pharmacological interventional strategies (103), including transcranial magnetic stimulation and deep brain stimulation that need further evaluation.

In addition to several smaller publications (103-105), a large controlled trial of cognitive behavioural therapy (CBT) for depression and anxiety in PD patients (106) showed significant improvement of HAM-D scores when comparing 10 sessions of CBT plus clinical monitoring with clinical monitoring only in a cohort of 80 patients, including longer-term effects. A systematic review of CBT therapy for depression in PD by Egan et al, found two randomized controlled trials where significant reductions in depression scores could be seen, with a maintenance of the effect over the follow-up periods of 1- and 6-months. Although the authors concluded that CBT shows promising evidence of efficacy in the treatment of depression and anxiety in PD, they recommend further large-scale studies with longer follow-up periods (107).

Transcranial magnetic stimulation (TMS) for the treatment of mood symptoms in PD has also been assessed in a number of small studies with some encouraging results in some. Whilst there was no clear evidence of an improvement of mood symptoms when compared to sham-TMS (108, 109), others concluded some beneficial effect of TMS on depression (110). Further large-scale studies are needed.

Deep brain stimulation (DBS) has been associated with worsening mood as well as apathy scores (111). However, a review of the effect of DBS on depression in (112) concluded that the results on depression were inconsistent, likely due to the variation in anatomical targets (113-115). However, there a comparison of differential outcomes depending on target selection did not identify any significant differences (116). However, the risk of suicide following DBS surgery has been reported to be significantly increased and needs particular attention (117).

Anxiety

Anxiety has been given less attention than depression, although its prevalence is similar to that of depression in PD and overlap between both is commonly observed. Treatment of anxiety in PD has not been assessed systematically and in large-scale studies. There are currently no randomized, controlled trials for treatment guidelines on anxiety in PD. The MDS Evidence-based medicine review on the treatment of anxiety in PD insufficient evidence as to make recommendations (97).

Conclusions

Understanding of the features, pathophysiology and management of depression and anxiety in PD is increasing, but appropriate management of these neuropsychiatric features still poses an important unmet need in PD patients. Their high prevalence and impact on quality of life highlight the importance of an early detection and detection of biomarkers and risk factors, and better evidence on treatment approaches. Early detection, thorough assessment and adequate treatment can provide substantial improvement in the overall management of patients with PD. Validation of clinical scales, especially for anxiety, and development of biomarkers, and large scale trials to guide management of depression with pharmacological and non-pharmacological options are urgently needed.

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Tables

Table 1: Prevalences (%) of depression in PD among various studies. Taken from *A systematic review of prevalence studies of depression in Parkinson's disease.* Reijnders JS et al. Movement disorders: Official journal of the Movement Disorder Society, 2008.

Study	Sample	Sample size	Quality score	Major depressive disorder	Minor depression	Dysthymia	Clinically relevant depressive symptoms
Structured clinical interview							
Starkstein et al. (1990)	Outpatient clinic	105	5	21	20		41
Starkstein et al. (1992)	Outpatient clinic	92	5	20	21		41
Hantz et al. (1994)	Population	73	7	2.7			2.7
Starkstein et al. (1996)	Outpatient clinic/dementia	33	6	30		27	57
Liu et al. (1997)	Outpatient clinic	109	5	16.5		25.7	42.2
De Rijk and Bijl (1998)	Population	384	5	2.3		4.7	7
Starkstein et al. (1998)	Outpatient clinic	112	6	22		31.3	53.3
Leentjens et al. (2000)	Outpatient clinic	63	6	25			25
Leentjens et al. (2000)	Outpatient clinic	53	6	23			23
Anguenot et al. (2002)	Outpatient clinic	135	6	55.6		2.2	57.8
Naarding et al. (2002)	Outpatient clinic	85	6	23.5			23.5
Weintraub et al. (2003)	Outpatient clinic	77	6	20.8	13		33.8
Lauterbach et al. (2004)	Outpatient clinic	28	5	14.3		3.6	17.9
Nuti et al. (2004)	Outpatient clinic	90	6	21.1		18.8	39.9
Ertan et al. (2005)	Outpatient clinic	109	6	22.9	28.4		51.4
Papapetropoulos et al. (2005)	Brain bank data	67	7				43.3
Costa et al. (2006)	Inpatient clinic	58	5	20.7	34.5		55.2
Costa et al. (2006)	Inpatient clinic	83	6	21.7	25.3		47
Visser et al. (2006)	Outpatient clinic	92	6	19			19
Wichowicz et al. (2006)	Population	100	6	35			35
Clinical interview							
Santamaria et al. (1986)	Outpatient clinic/recent onset	34	4	2.9		29.4	32.3
Mayeux et al. (1988)	Outpatient and inpatient clinic	339	4				47
Brown and MacCarthy (1990)	Outpatient clinic	40	6				25
Aarsland et al. (1996)	Population	235	6	7.7			7.7
Tandberg et al. (1996)	Population	245	6	7.7			7.7
Tandberg et al. (1997)	Population	245	6	7.7			7.7
Tandberg et al. (1998)	Population	239	6	7.8			7.8
Aarsland et al. (1999)	Population	235	5	7.2			7.2
Karlsen et al. (1999)	Population	233	6	7.7			7.7
Cubo et al. (2000)	Outpatient clinic	88	5	7.3			7.3
Giladi et al. (2000)	Outpatient clinic	172	5				33
Larsen et al. (2000)	Population	240	6	7.6			7.6
Krishnan et al. (2003)	Outpatient clinic	126	5				12.7
Rating scale							
Mindham (1970)	Inpatient psychiatric hospital	89	3				89
Tison et al. (1995)	Outpatient clinic and nursing home	60	6				32.7
Meara et al. (1999)	General Practice	132	5				64
Schrag et al. (2000)	General Practice	92	5				19.6
Happe et al. (2001)	Outpatient clinic	56	4				76.4
Schrag et al. (2001)	General Practice	97	5				19.6
Shulman et al. (2001)	Outpatient clinic	99	3				36
Happe et al. (2002)	Outpatient clinic	116	4				37.1
Marinus et al. (2002)	Outpatient clinic	177	4				38.4
Schrag et al. (2002)	General Practice	128	5				20
Shulman et al. (2002)	Outpatient clinic	101	3				44
Rojo et al. (2003)	Outpatient clinic	353	4				56.9
Hely et al. (2005)	Outpatient clinic	52	4				53.6
Holroyd et al. (2005)	Outpatient clinic	100	4				15
Kang et al. (2005)	Population	193	5				13
Prado and Barbosa (2005)	Outpatient clinic	60	4				38.3
Kirsch-Darrow et al. (2006)	Outpatient clinic	80	3				26.3
Weintraub et al. (2006)	Outpatient clinic	130	4				36.2
Weighted mean			5.1	17	22	13	35

Reference (11)

Table 2: Overview of studies reporting clinically relevant anxiety symptoms in PD according to validated rating scales. Taken from *Prevalence of anxiety in Parkinson's disease: A systematic review and meta-analysis.* Broen MP et al. Movement disorders: official journal of the Movement Disorder Society, 2016.

Study	Sample	Sample size	Quality score	Scale used	Cut-off score used	Clinically relevant anxiety symptoms, %
Marinu et al (2002)	Outpatient clinic	177	16	HADS	≥11	19.8
Carod-Artal et al (2007)	Outpatient clinic	144	14	HADS	≥11	23.6
Mondolo et al (2007)	Outpatient clinic	46	14	HADS	≥8	10.8
Carod-Artal et al (2008)	Outpatient clinic	115	14	HADS	≥11	30.4
McKinley et al (2008)	Outpatient clinic	42	15	HADS	≥8	16
Havlikova et al (2008)	Outpatient clinic	150	14	HADS	≥11	30.6
Kulisevsky et al (2008)	Outpatient clinic	1351	19	HADS	≥11	20.8
Rodriquez-Blastez et al (2009)	Outpatient clinic	387	14	HADS	≥11	22
Negres-Pages et al (2010)	Population	422	17	HADS	≥11 (≥8)	27 (51)
Hu et al (2011)	Population	197	14	HADS	≥11	32
Brown et al (2011)	Outpatient clinic	513	16	HADS	≥11	22
Ozdilek et al. (2012)	Outpatient clinic	50	14	HADS	≥10	18
Quelhas et al (2014)	Outpatient clinic	33	14	HADS	≥11 (≥8)	18.2 (54.5)
Fereshtehnejad et al (2015)	Outpatient clinic	140	14	HADS	≥8	38.9
Borek et al. (2006)	Outpatient clinic	120	16	HARS	≥14	23.2
Stefanova et al (2013)	Outpatient clinic	360	19	HARS	≥11	37.8
Jiang et al (2015)	Outpatient clinic	99	14	HARS	>11	25.3
Wu et al (2015)	Outpatient clinic	301	15	HARS	>14	10.6
Schulman et al (2001)	Outpatient clinic	101	16	BAI	≥10	39
Rutten et al (2015)	Outpatient clinic	294	16	BAI	>12	45
Yamanashi et al (2013)	Outpatient clinic	117	15	STAI	41 (men) 42 (women)	55
Weintraub et al (2015)[1]	Outpatient clinic	423	15	STAI	>39	24.6
Siri et al (2010)	Population	486	15	SCL-90	>1	46
Bugalho et al (2012)	Outpatient clinic	36	15	SCL-90-R	>1	28
Henderson et al (1992)	Outpatient clinic	164	16	Zung	>49	15
Baig et al (2015)	Outpatient clinic	769	17	Leeds anxiety score	>7	17.3
Aarsland et al (2009) a	Population	175	16	NPI	≥4	6.9

a: Drug naïve.

Reference (20)

Glossary: BAI, Beck Anxiety Inventory; HADS, Hospital Anxiety and Depression Scale; HARS, Hamilton Anxiety Rating Scale; NPI, Neuropsychiatric Inventory; SCL-90, Symptom Checklist-90; STAI, State-Trait Anxiety Inventory.

Table 3: Determinants of health-related quality of life in PD. Taken from *Neuropsychiatric symptoms, behavioural disorders, and quality of life in Parkinson's disease.* Balestrino R et al, Journal of the neurological sciences, 2017.

References	N.	Specific for NPS	NPS considered in the regression analysis	NPS determinants of HRQoL
1. Cross-sectional studies				
Greene et al.	51	Yes	Depression	Depression
Carod-Artal et al.	115	No	Depression, anxiety	Depression, anxiety
Klepac et al.	124	Yes	Depression	Depression
McKinlay et al.	49	No	Depression, apathy, anxiety, hallucinations	Anxiety, depression, hallucinations
Muslimovic	190	No	Depression, anxiety	Depression, anxiety
Rahman	130	No	Depression, anxiety	Depression, anxiety
Qin	391	No	Depression	Depression
Quelhas et al.	46	No	Depression, anxiety	Anxiety
Žiropađa et al.	102	No	Depression	Depression
Gallagher	89	No	Apathy, psychosis, depression, anxiety, mood/apathy,	Depression
			perception problem/hallucinations	
Naismith et al.	35	No	Depression	Depression
Winter et al.	81	No	Depression	Depression
Benito-León et al.	557	Yes	Apathy	Apathy
Gómez-Esteban et al.	99	Yes	NPS	NPS
Martinez-Martin	411	No	Mood/apathy, perception problem/hallucinations	Mood/apathy
Leroi et al.	99	No	Depression, anxiety, impulsiveness	Depression, impulsiveness
Winter et al.	70	No	Depression	Depression
Bach et al.	1449	No	Depression, psychosis/hallucinations	Depression, psychosis
Hanna et al.	38	Yes	Anxiety, depression	Anxiety, depression
Dubayova et al.	153	No	Depression, anxiety	Depression, anxiety
Rodrìguez-Violante et al.	177	No	Mood/apathy, perception problem/hallucinations	Mood/apathy
Santos-García et al.	150	No	Depression	Depression
Duncan	158	No	Mood/apathy, perception problem/hallucinations,	Depression, anxiety
			depression	
Lawson et al.	219	Yes	Depression, NPS	Depression, NPS
Phu	100	Yes	ICDs and related behaviours, depression	Depression, ICDs and related behaviours
Alvarado Bolaños et al.	492	Yes	Psychotic symptoms, mood/apathy, ICDs	Mood/apathy, ICDs
Fereshtehnejad et al.	157	No	Depression, anxiety, psychosis, apathy	Anxiety, depression
Jones et al.	107	Yes	Depression, anxiety, apathy	Anxiety
Kadastik-Eerme et al.	268	No	Depression	Depression
Skorvanek et al.	291	No	Depression, anxiety, psychosis, DDS	DDS
Diaz et al.	59	No	Depression, anxiety	Anxiety, depression
Fan et al.	134	No	Depression, anxiety	Depression, anxiety
Rieu	136	Yes	Depressive mood, hypomanic mood, anxiety,	Hyperemotionality
			irritability and aggressiveness, hyperemotionality,	
			psychotic symptoms, nocturnal hyperactivity, eating behavior,	
			creativity, hobbyism, punding, risk-taking behavior,	
			compulsive shopping, pathological gambling, hypersexuality,	
			dopaminergic addiction, excess in motivation	
Vela et al.	87	Yes	Depression, ICDs	Depression
2. Longitudinal studies				
Forsaa et al.	82	No	Depression, psychosis	Depression
Marras et al.	362	No	Depression	Depression
Müller	166	No	Depression, apathy	Depression
Prakash et al.	227	No	Apathy, attention, memory, hallucinations, delusions,	Mood/apathy
			depression, anxiety, anhedonia	

Reference: (46)

Glossary: ICDs, impulse control disorders; DDS, dopamine dysregulation syndrome; NPS, neuropsychiatric symptoms.

Table 4: Recommended cut-off scores and performance of screening instruments for depression in PD. Taken from *Accuracy of screening instruments for detection of neuropsychiatric syndromes in Parkinson's disease*. Martinez-Martin P et al. Movement disorders : official journal of the Movement Disorder Society, 2016.

	Cut-off score	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Reference
BDI-I	8/9	92	59	39	96	Leentjens AF et al, 2000
BDI-II	6/7	95	60	62	94	Williams JR et al, 2012
CESD-R	11/12	72	70	62	79	Williams JR et al, 2012
CSDD	5/6	83	73	54	92	Williams JR et al, 2009
GDS-15	4/5	88	85	61	96	Weintraub D et al, 2006
	5/6	84	89	59	97	Baillon S et al, 2014
	7/8	78	88	67	93	Chagas MH et al, 2010
	6/7	79	88	66	93	Chagas MH et al, 2013
GDS-20	10/11	100	76	33	100	Mondolo F et al, 2006
GDS-30	9/10	81	84	58	94	McDonald Wmet al, 2006
	9/10	89	62	71	84	Ertan FS et al, 2005
HADS						
Total score	10/11	92	51	34	96	Leentjens AFG et al, 2001
HADS-D	10/11	100	95	71	100	Mondolo F et al, 2006
HAMD-17	13/14	88	89	74	96	Leentjens AF et al, 2000
IDS-C	11/12	81	79	73	86	Williams JR et al, 2012
IDS-SR	13/14	90	60	61	90	Williams JR et al, 2012
MADRS	14/15	88	89	74	96	Leentjens AF et al, 2000
	7/8	72	82	72	82	Silberman CD et al, 2006
NICE screening questions		100	84	54	100	Baillon S et al, 2014
PHQ-9	5/6	66	80	69	77	Williams JR et al, 2012
	8/9	100	83	63	100	Chagas MH et al, 2013
PHQ-2	2/3	75	89	70	91	Chagas MH et al, 2011
UPDRS-D	1/2	66	81	81	66	Starkstein SE et al, 2007
WHO-5	12/13	88	74	37	97	Schneider CB et al, 2015
Zung's SDS	54/55	89	83	61	96	Chagas MH et al, 2010
	54/55	90	82	59	96	Chagas MH et al, 2013

Reference (62)

Glossary: PPV, Predictive Positive Value; PNV, Predictive Negative Value; BDI, Beck Depression Inventory; CESD-R, Center for Epidemiologic Studies Depression Rating Scale–Revised; CSDD, Cornell Scale for Depression in Dementia; GDS, Geriatric Depression Scale; HADS, Hospital Anxiety and Depression Scale; HADS-D, Depression subscale; HAMD-17, Hamilton Depression Rating Scale; IDS-C, Inventory of Depressive Symptoms–Clinician; IDS-SR, Inventory of Depressive Symptoms–Patient; MADRS, Montgomery-Asberg Depression Rating Scale; NICE, UK National Institute for Health and Clinical Excellence; PHQ, Patient Health Questionnaire; UPDRS-D, Unified Parkinson's Disease Rating Scale–Depression; WHO-5, WHO-Five Well-being Index; Zung's SDS, Zung's Self-rating Depression Scale.