Chapter 3

The assessment of depression in Parkinson's disease

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3.1 Abstract

Motor symptoms form the hallmark of Parkinson's Disease (PD), although features like depression are often present. Depression rating scales (e.g. MADRS) used in PD measure affective, cognitive and somatic symptoms. An important clinical question is which items of the MADRS are likely to be influenced by PD symptoms.

Depression was assessed in 43 PD patients who scored below the cut-off of the MADRS and who differed widely in motor severity.

PD patients scored relatively highest on Concentration difficulties, Reduced sleep and Inner tension. Reduced Sleep, Lassitude and Suicidal thoughts were associated with motor severity and specifically with Bradykinesia, Rigidity and Axial impairment, however not with Tremor.

To avoid a possible influence on our results of coincidentally included PD patients with a depression, all associations between somatic MADRS items and motor severity were corrected for the influence of affective symptoms of depression. All associations remained significant.

In conclusion, the items Reduced sleep and Lassitude of the MADRS are likely to be influenced by motor symptoms. The high score on Concentration difficulties is suggested to be a reflection of cognitive dysfunction in PD. Thus, when assessing depression in PD, using a depression rating scale like the MADRS, adjusted cut-off scores are required.

3.2 Introduction

The reported prevalence of depression in Parkinson's Disease (PD) is approximately 40 % (Cummings & Masterman, 1999). However, this prevalence varies due to inconsistent methodology, such as different research instruments used to measure the depressive symptoms and the different definitions of depression applied (Murray, 1996).

Several attempts were made to find a consistent profile of depression symptoms in PD. Up to now, no specific symptomatology has been identified that is able to distinguish between depression in PD and depression in other neurological diseases or in physically healthy subjects (Leentjens, 2004). However, *somatic* symptoms and symptoms related to *mood* are common features of depression in PD, whereas *feelings of guilt* and *self-blame tendencies* are less common (Huber et al., 1990).

The Montgomery-Åsberg Depression Rating Scale (MADRS; Montgomery & Asberg, 1979) is one of the main instruments used in clinical neurological and neuropsychological practice and in depression research. This scale contains items that measure affective symptoms (e.g. Reported sadness and Pessimistic thoughts) as well as items that measure somatic symptoms (e.g. Reduced sleep and Lassitude) and cognitive symptoms (e.g. Concentration difficulties) of depression. Leentjens et al. (2003a) found that the affective symptoms of depression (e.g. depressed mood and loss of interest and pleasure in activities) are important symptoms for establishing the diagnosis of depression in PD. However, also somatic symptoms (i.e. reduced appetite and early morning wakening) contribute significantly to this diagnosis. This documents the overlap between depression and PD symptoms, which is confirmed by Starkstein et al. (2001) who showed parkinsonism in a subgroup of depressed patients without PD. Examples of these overlapping symptoms are cognitive dysfunction, psychomotor retardation, flat affect, masked face, anergia, anxiety and sleep disorders (Edwards et al., 2002).

Although adjusted cut-off scores have been determined for the MADRS (Leentjens et al., 2000), it is an important clinical question to what extent PD symptoms influence the assessment of depression in PD and specifically which items of the MADRS are likely to measure PD symptoms. The aim of this study was therefore to address the implications of overlapping of symptoms of depression and motor symptoms of PD for the assessment of depression in PD. In other words, which items of the MADRS are likely to be influenced by motor symptoms of PD? Symptoms of depression were measured in a sample of PD patients who scored below the cut-off score of the MADRS (<15) and who differed widely in motor severity (as is reflected by the Unified Parkinson's Disease Rating Scale (UPDRS) part III score). This sample enabled us to investigate the associations between symptoms of

depression and PD symptoms in detail and assured us that a possible influence of depression on the motor severity was minimized. The possibility, however, still existed that PD patients with a partially or fully symptomatic depression were coincidentally included. These patients should, according to the DSM-IV, have at least a depressed mood and/or anhedonia. Therefore, to control for the possibility of included depressed PD patients, associations between somatic items and motor symptoms which may be found in this study will be corrected for the influence of affective symptoms of depression as measured with the MADRS items Reported sadness and Inability to feel. In addition, to gain more qualitative insight in the assessment of depression in PD the scoring pattern of PD patients on the MADRS will be analyzed, i.e. on which MADRS items do PD patients score relatively high?

3.3 Methods

Subjects

43 PD patients participated in this study. The group consisted of 30 men (69.8%) and 13 (30.2%) women (Table 3.1 describes demographic and illness characteristics). All patients were diagnosed with idiopathic PD according to the criteria of the UK Parkinson's Disease Society Brain Bank. The motor severity of patients differed widely (M=34.4, SD=16.3, range 8–74). Exclusion criteria were a MADRS total score > 14 (Leentjens et al., 2000) and other neurological and psychiatric disorders. This study was approved by the Medical Ethical Committee of the University Medical Center Groningen. All participants signed an informed consent prior to study inclusion according to the declaration of Helsinki.

Table 3.1 Demographic and illness characteristics of PD patients (n=43)

	Mean (SD)	Range
Age	62.0. (9.2)	41-77
Disease duration (years)	8.9 (5.3)	1-20
UPDRS part III total	34.4 (16.3)	8-74
UPDRS Tremor	4.6 (4.1)	0-15
UPDRS Bradykinesia	16.0 (7.9)	2-33
UPDRS Rigidity	6.8 (3.8)	0-17
UPDRS Axial impairment	5.5 (4.5)	0-15

Tremor: UPDRS items 20, 21 (scoring range (sr): 0-35), Bradykinesia: UPDRS items 23, 24, 25, 26, 31 (sr: 0-36), Rigidity: UPDRS item 22 (sr: 0-20), Axial involvement: UPDRS items 27, 28, 29, 30 (sr: 0-16)

Statistical analyses

Preceding the statistical analyses, scores on UPDRS items were converted to z-scores. Composite variables were formed for Tremor (UPDRS items 20, 21), Bradykinesia (UPDRS items 23, 24, 25, 26, 31) and Axial impairment (UPDRS items 27, 28, 29, 30). Since, rigidity was measured by one specific UPDRS item (item 22), a composite variable was not formed for this motor symptom.

Normality of data was analyzed. All variables were normally distributed except some of the MADRS items and UPDRS composite variables.

Before calculating associations between MADRS and motor symptoms, the scoring pattern of PD patients on the MADRS was analyzed, i.e. on which items of the MADRS do PD patients score relatively high? For this purpose a repeated measures ANOVA with Bonferroni post-hoc analysis, which is robust against deviations from normality (Stevens, 2002), was performed.

Hereafter one-tailed correlations, which were predictably based on previous literature (Gupta & Bhatia, 2000; Papapetropoulos et al., 2006; Rojo et al., 2003; Tandberg et al., 1997; Wichowicz et al., 2006), were determined between the scores on the depression scale and the motor symptoms of PD. A Pearson correlation was calculated between the MADRS total and UPDRS part III total and Spearman correlations were determined between the individual MADRS items and UPDRS part III total. Spearman correlations were also determined between MADRS items that showed a significant association with the UPDRS part III total and composite variables of the UPDRS part III: Tremor, Bradykinesia, Axial impairment and Rigidity. Bonferroni k-1 corrections (Holm, 1979) were used to correct for 10 (10 MADRS items x UPDRS part III total) and 8 (2 MADRS items x 4 UPDRS composite variables) comparisons.

3.4 Results

The mean score of PD patients on the MADRS total was 8.2 (SD=3.6). The repeated measures ANOVA showed that the MADRS items differed significantly (F=9.81, p=0.00). The Bonferroni post hoc analysis showed that PD patients obtained relatively the highest scores on Concentration difficulties, Reduced sleep and Inner tension (see table 3.2 for an ordering of MADRS items according to mean scores and the results of the Bonferroni post hoc analysis).

No association was found between the MADRS total score and motor severity (UPDRS part III total), r=0.18, p=0.13. However the individual MADRS items Reduced sleep and

Suicidal thoughts were, after Bonferroni k-1 correction, associated with motor severity (UPDRS part III total; see table 3.3). The MADRS item Lassitude was also associated with motor severity, however, this relation just did not pass the conservative Bonferroni correction.

Table 3.2 Mean, standard deviation and range of scores on MADRS items (n=43)

	M (SD)	Range
6 – Concentration difficulties*	1.72 (1.24)	0 – 4
4 – Reduced sleep**	1.30 (1.39)	0 – 5
3 – Inner tension***	1.19 (1.12)	0 – 4
2 – Reported sadness****	0.84 (1.05)	0 – 4
7 – Lassitude	0.84 (0.92)	0 – 3
1 – Apparent sadness	0.77 (1.13)	0 – 4
8 – Inability to feel	0.47 (0.74)	0 – 3
9 – Pessimistic thoughts	0.40 (0.58)	0 – 2
5 – Reduced appetite	0.37 (0.87)	0 – 4
10 – Suicidal thoughts	0.33 (0.52)	0 – 2

* The score on Concentration difficulties was significantly higher than the scores on Reported sadness (p=0.01), Lassitude (p=0.01), Apparent sadness (p=0.03), Inability to feel (p=0.00), Pessimistic thoughts (p=0.00), Reduced appetite (p=0.00) and Suicidal thoughts (p=0.00).

** The score on Reduced sleep was significantly higher than the scores on Inability to feel (p=0.02), Pessimistic thoughts (p=0.01), Reduced appetite (p=0.01) and Suicidal thoughts (p=0.00).

*** The score on Inner tension was significantly higher than the scores on Inability to feel (p=0.04), Pessimistic thoughts (p=0.00), Reduced appetite (p=0.03) and Suicidal thoughts (p=0.00).

**** The score on Reported sadness was significantly higher than the score on Suicidal thoughts (p=0.03).

Table 3.3 Correlations between UPDRS III and MADRS items (n=43)

	UPDRS III	
	r	p
1 – Apparent sadness	-0.30	0.027
2 – Reported sadness	0.26	0.049
3 – Inner tension	0.04	0.399
4 – Reduced sleep	0.39*	0.005
5 – Reduced appetite	-0.21	0.087
6 – Concentration difficulties	-0.23	0.072
7 – Lassitude	0.37	0.007
8 – Inability to feel	-0.05	0.369
9 – Pessimistic thoughts	0.21	0.087
10 – Suicidal thoughts	0.38*	0.006

* Correlation remained significant after Bonferroni k-1 correction

To avoid a possible influence of coincidentally included PD patients with a partially or fully symptomatic depression on the associations between Reduced sleep, Lassitude and the motor symptoms partial correlations were determined between Reduced sleep, Lassitude and motor severity, controlling for the affective symptoms of depression (MADRS Reported sadness and Inability to feel). All previously found associations remained significant.

In addition, it was found that Reduced sleep was related to Axial involvement and Suicidal thoughts was associated with Bradykinesia and Axial involvement, both after Bonferroni k-1 correction. However, without the Bonferroni k-1 correction Reduced sleep was also significantly associated with Bradykinesia and Rigidity and Suicidal thoughts with Rigidity. Interestingly, tremor was not associated with any of these symptoms of depression (see table 3.4).

Table 3.4 Correlations between the MADRS items Reduced sleep, Suicidal thoughts and Tremor, Bradykinesia, Rigidity and Axial involvement (n=43)

	Reduced sleep		Suicidal thoughts	
	r	p	r	p
Tremor	0.18	0.127	0.17	0.146
Bradykinesia	0.31	0.023	0.40*	0.004
Rigidity	0.32	0.020	0.33	0.018
Axial involvement	0.38*	0.008	0.41*	0.004

* Correlation remained significant after Bonferroni k-1 correction
Tremor: UPDRS items 20, 21
Bradykinesia: UPDRS items 23, 24, 25, 26, 31
Rigidity: UPDRS item 22
Axial involvement: UPDRS items 27, 28, 29, 30

3.5 Discussion

The aim of this study was to address the implications of the overlap of symptoms of depression and motor symptoms of PD for the assessment of depression in PD. In other words, which items of the MADRS are likely to be influenced by motor symptoms of PD? This information is especially relevant for the neurological and neuropsychological practice in which depression rating scales, such as the MADRS, are often used. Symptoms of depression were measured in a sample of PD patients who scored below the cut-off score of the MADRS (<15) and who differed widely in motor severity. This sample enabled to investigate the associations between symptoms of depression and PD symptoms in detail,

and assured us that a possible influence of depression on the motor severity was minimized. In addition, to gain more qualitative insight in the assessment of depression in PD the scoring pattern of PD patients on the MADRS was analyzed, i.e. on which MADRS items do PD patients score relatively high?

Of all items of the MADRS PD patients scored relatively highest on *Concentration difficulties*. This cognitive item represents a difficulty in collecting one's thoughts mounting to an incapacitating lack of concentration (Montgomery & Asberg, 1979). Cognitive dysfunctions are often present in PD patients and consist of executive, memory and visuospatial dysfunction (Dubois & Pillon, 1997). The scores on Concentration difficulties might thus have been (partially) determined by the cognitive dysfunctions of PD patients, suggesting that Concentration difficulties is not a core symptom of depression in PD. This is confirmed by a previous study of our research group in which we found that cognitive symptoms measured with a depression scale might be based on the striatal dopaminergic dysfunction, typical for PD (Koerts et al., 2007), and by Ehrt et al. (2006) who reported that compared to depressed patients without PD, PD patients scored only higher on Concentration difficulties of the MADRS. It would thus be interesting to determine in future research to what extent the assessment of depression in PD is influenced by cognitive dysfunction.

Inner tension is an other item of the MADRS on which PD patients scored relatively high. It represents feelings of ill-defined discomfort, edginess, inner turmoil, mental tension mounting to either panic, dread or anguish (Montgomery & Asberg, 1979). This result is consistent with previous studies in which it was found that approximately 40% of PD patients are anxious (Richard, 2005) and are often stressed (Macht et al., 2005). Higher scores on Inner tension may be a reflection of a psychological reaction to having PD, i.e. patients may be worried about their health or they may be afraid of being negatively evaluated in public. On the other hand the relatively high scores can also be a consequence of the neurochemical changes of the disease itself, since anxiety and depression both have a higher prevalence in PD compared to matched medical controls (Menza et al., 1993b). It thus remain unclear what causes the relatively high score on Inner tension.

Reduced sleep is the item of the MADRS on which PD patients also obtained one of the highest score. This item represents the experience of reduced duration or depth of sleep compared to the subject's own normal pattern when well (Montgomery & Asberg, 1979). Nocturnal problems are frequent in PD and studies suggest that approximately two-thirds of

PD patients reported night time sleeping problems (Gjerstad et al., 2007; Tandberg et al., 1997). Reduced sleep also showed a positive association with motor severity (this association remained significant after the correction for possible influence of coincidentally included depressed PD patients, as described above) and was specifically related to Axial involvement (and without the Bonferroni k-1 correction also to Bradykinesia and Rigidity). These results are consistent with previous research in which is was found that night time sleeping problems may be caused by increased muscle activity at night (Stocchi et al., 1998; Van Hilten et al., 1993). Inability to turn or get out of bed are other frequent problems experienced by PD patients during the night (Lees et al., 1988), both increasing in frequency as PD develops (Gjerstad et al., 2007). Higher scores on the Reduced sleep item of the MADRS may thus be a consequence or related to the motor symptoms of PD and suggests that this symptom is non-specific for depression in PD as was previously reported by Starkstein et al. (1990b).

PD patients scored lowest on the MADRS item *Suicidal thoughts,* which was positively associated with motor severity. This item represents the feeling that life is not worth living, that a natural death would be welcome and includes also suicidal thoughts and preparations for suicide (Montgomery & Asberg, 1979). However, 98 % of our population scored less than two on this item, which signifies patients are weary of life but have only *fleeting* suicidal thoughts and may not reflect *genuine* suicidal thoughts and preparations for suicide (Montgomery & Asberg, 1979). This relationship may therefore reflect a psychological reaction to having PD, but *not* suicidal thoughts, as suggested by the name of the item. However, a serotonergic mechanism could also be involved since it has been associated with the disease stage of PD (Kerenyi et al., 2003) as well as with suicidal behavior (Kamali et al., 2001).

Finally, the MADRS item *Lassitude* was also positively associated with the motor severity of PD patients (also after correction for a possible influence of coincidentally included depressed PD patients, as described above) and specifically with Bradykinesia, Rigidity and Axial involvement (data not shown). Although this association just did not pass the conservative Bonferroni k-1 correction, it is worth discussing. Lassitude represents difficulty getting started or slowness initiating and performing everyday activities, according to the MADRS (Montgomery & Asberg, 1979) and is closely related to fatigue, which can be defined as an overwhelming sense of tiredness, lack of energy or feeling of exhaustion (Krupp & Pollina, 1996). According to Karlsen et al. (1999) fatigue has a prevalence of approximately 44 % in PD and is associated with the motor severity of PD.

Furthermore, Garber & Friedman (2003) showed that fatigue in PD was related to physical activity and physical function. Therefore, this association between Lassitude and motor severity suggests that the motor symptoms of PD might cause lassitude during the day.

One other interesting finding is that only Bradykinesia, Rigidity and Axial impairment were associated with the items of the MADRS (with or without the Bonferroni k-1 correction) and Tremor was not. Papapetropoulos et al. (2006) previously showed that depressed PD patients scored higher on the Bradykinesia and Axial impairment items of the UPDRS. Moreover, these associations are consistent with the finding that patients with the akinetic-rigid form of PD are more often depressed than PD patients with a tremor-dominant form (Starkstein et al., 1998) and the suggestion that the pathology of tremor-dominant PD differs from the pathology of the akinetic-rigid form of PD (Bergman & Deuschl, 2002).

This study addresses the specificity of depressive symptoms in PD patients. When investigating the clinimetric properties of the MADRS this often is studied using different groups of patients, e.g. PD patients without depression, PD patients with depression, depressed patients without PD and healthy controls. We specifically sought to determine the influence of motor symptoms of PD on symptoms measured with the MADRS in PD patients. These associations can not be determined in patients with depression without PD, nor in healthy controls. Also, in our opinion it is difficult to determine these associations in PD patients who are depressed. In the latter group the MADRS probably measures symptoms of both depression and PD, and also the assessment of motor symptoms with the UPDRS can be influenced by symptoms of depression, e.g. psychomotor retardation. In this study associations between symptoms of depression and motor symptoms of PD were therefore determined in PD patients who scored below the cut-off of the MADRS. In future research, however, it would be interesting to compare the associations between symptoms of depression and motor symptoms of PD in non-depressed PD patients to the associations between symptoms of depression and motor symptoms in depressed PD patients.

In conclusion, depression rating scales measure more than just depression in PD. Especially the somatic items Reduced sleep and Lassitude are likely to reflect motor symptoms of PD. Moreover with the cognitive item Concentration difficulties cognitive dysfunction of PD patients is suggested to be measured, however future research should clarify this.

More generally these results suggest that depression and PD cannot be considered as two separate syndromes due to the symptomatic overlap. This is confirmed by neuroimaging

studies which suggest that PD and depression also have a neurochemical overlap (Martinot et al., 2001; Meyer et al., 2001; Remy et al., 2005).

It is however still important to recognize a depression in PD patients. When using depression rating scale for this purpose one should be aware of a confounding influence of motor and cognitive symptoms. In this matter it is important to qualitatively describe the answers of PD patients on the items of depression rating scale, since the quantitative scores are not sufficient. In addition, cut-off scores, adjusted for somatic (and cognitive) co morbidity (e.g. Leentjens et al. (2000)) are required.