Depression in Parkinson’s Disease: Conceptual Issues and Clinical Challenges

Albert F. G. Leentjens, MD, PhD

ABSTRACT

Background: Depression frequently accompanies Parkinson’s disease (PD) and may have a negative impact on activities of daily living, cognitive performance, and quality of life. Because of the symptom overlap between the 2 disorders, it may be difficult to recognize depression in PD. Moreover, the partially shared pathophysiology may make it difficult to treat depressive symptoms without influencing motor or cognitive function. Objective: To review the current knowledge of the epidemiology, etiology, pathophysiology, and treatment of depression in patients with Parkinson’s disease. Method: Discussion of recent studies and relevant literature. Conclusion: Not only conceptually but also in terms of etiology, pathophysiology, and treatment, the relationship between PD and depression remains a challenge. There are still many questions to be answered. In the therapeutic domain, large, placebo-controlled trials are necessary to evaluate the efficacy of antidepressant treatment and allow the development of evidence-based guidelines. (J Geriatr Psychiatry Neurol 2004; 17:120-126)

Keywords: Parkinson’s disease; depression

Parkinson’s disease (PD) is a true neuropsychiatric disease. Apart from the required motor symptoms, psychopathological symptoms are common and include mood disorders, anxiety disorders, hallucinations, psychosis, cognitive deterioration, and dementia. The obvious explanation for this diverse symptomatology is the fact that the underlying pathophysiological process in PD is not confined to the nigrostriatal dopaminergic system but is widespread. Other parts of the dopaminergic system are involved as well, as are other neurotransmitter systems, such as the serotonergic, noradrenergic, and cholinergic systems. This review discusses the current views on depression in PD.

CONCEPTUAL ISSUES

The co-occurrence of depression and PD often leads to the conceptual discussion whether depressive symptoms should be seen as an intrinsic part of this disease or as a separate disease identity. This discussion is in part due to semantic confusion, but it also touches some basic conceptual issues of psychiatry as a whole. In its classification of psychopathology, the Diagnostic and Statistical Manual of Mental Disorders (DSM IV) of the American Psychiatric Association (APA) uses the term disorder without further specification. Disorders may be diseases, with a specified etiology, course, and prognosis, or syndromes, with a specific constellation of symptoms, but no reference to etiology. As a syndrome, depression can be recognized as a separate entity in PD, but at the same time it is intrinsic to this disease, because the 2 conditions share aspects of their pathophysiology.

Another point of discussion is the question whether depression in PD is “organic” or “reactive.” Although intuitively plausible, there is no evidence for this distinction, which may create the false impression that depressions of presumed reactive origin are not accompanied by physiological changes in the brain, or, vice versa, that psychological factors are not important in depressions with a presumed organic origin. Similarly, it creates the false suggestion that psychotherapy is the preferred treatment in “reactive” depressions as opposed to pharmacotherapy in “organic” depressions. Again there is no evidence to support this position. A distinction between presumed “organic” and “psychological” etiologies does not contribute to our understanding of the syndrome, nor does it help us with diagnostic or therapeutic decisions, and should therefore be abandoned. In the past decade, a more integrated, neuropsychiatric approach to body and mind has been

From the Department of Psychiatry, Maastricht University Hospital, the Netherlands.

Address correspondence to: Albert F. G. Leentjens, MD, PhD, Consultant Psychiatrist, Department of Psychiatry, Maastricht University Hospital, P.O. Box 5800, 6202 AZ Maastricht, the Netherlands; e-mail: a.leentjens@np.unimaas.nl.

DOI: 10.1177/0891988704267456

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promoted, in which biological and psychological processes are considered to be thoroughly intertwined.6-8 In PD, such an integrated neuropsychiatric approach should be encouraged.

**DIAGNOSIS AND ASSESSMENT**

Major depression, as defined by the criteria of the DSM IV, and PD have a number of symptoms in common.4 Tiredness and reduced energy, psychomotor retardation and lack of facial expression, mental slowing, difficulties concentrating, reduced appetite, and insomnia may occur in both depression and PD. This overlap of symptoms may make it difficult to recognize depression in PD patients.

Many studies have addressed the question whether depression in PD is characterized by a specific symptomatology that distinguishes it from depression in physically healthy people or people with other neurological diseases. So far, no consistent profile of depressive symptoms has been identified for depression in PD, although anxiety symptoms may be more prominently present, as well as dysphoria and irritability, whereas self-blame tendencies, feelings of guilt, and suicidality are less prevalent.9-14

From a clinical point of view, studies into the sensitivity, rather than the specificity, of depressive symptoms are more relevant, because in the clinical situation, the question is how to recognize depression in a patient with known PD. The only study that specifically addressed this issue found that core symptoms of depression, lowered mood, anhedonia, and lack of interest also constitute the most sensitive symptoms for depression in PD. Somatic symptoms of depression had less power to discriminate between depressed and nondepressed patients, with the exception of some symptoms, such as reduced appetite and early morning waking, which did have high discriminative properties.15

There is no general agreement on how to deal with these somatic symptoms in the assessment of depression in PD. The DSM IV advises to count all somatic symptoms toward a major depressive episode except when they are clearly and fully accounted for by a general medical condition.15 In clinical practice, it is hardly ever possible to make such an attribution. From a pragmatic point of view, it is advisable to make the syndromal diagnosis of “major depressive disorder” purely on the basis of reported complaints and observed symptomatology. Ignoring vital or physical symptoms is no solution to the diagnostic problem, because as shown above, these symptoms differ among themselves in terms of diagnostic sensitivity, and some are indeed sensitive symptoms for depression.15

**EPIDEMIOLOGY**

The prevalence of depression in PD is high, but there are large differences in reported prevalences. This may be due to a number of factors. The first of these is the nature of the population under study. In community studies, point prevalences of 2.7% to 7.7% have been reported, which is 2 to 3 times higher than the average prevalence of 1.8% of major depressive disorder in the elderly population.16-18 In outpatient populations, higher prevalences have been reported, ranging from 4% to 90%, with an average of 25% to 40%.1,19 In some cross-sectional studies, point-prevalences are used, whereas in others monthly prevalences are employed, which may lead to different prevalence rates. Next, it matters whether an inclusive or an exclusive approach with regard to physical symptoms is followed. In an inclusive approach, all vital and psychomotor symptoms count toward the diagnosis of depressive disorder, irrespective of their presumed etiology, whereas in an exclusive approach, only symptoms that cannot be attributed to PD count toward this diagnosis. The prevalence of depressive disorder in PD decreases substantially if an exclusive, instead of an inclusive, approach is followed.20 In older studies, a cutoff score on a depression rating scale was often used to establish the diagnosis. Research into the concurrent validity of depression rating scales with the DSM IV diagnostic criteria shows that cutoff points for screening and diagnosis are different for patients with various physical diseases and that higher cutoff scores should be used than those applied to physically healthy persons.21 Lastly, it matters how strict one is in applying diagnostic criteria to syndromes that do not fully meet the criteria of major depressive disorder, such as in dysthymia, coping problems, lability of affect, mood changes in relation to medication intake or on/off periods, anxiety syndromes, and personality changes. It may be difficult to classify these symptoms in terms of DSM criteria.

The different approaches to the assessment of depression and the interpretation of, and adherence to, diagnostic criteria for depression may theoretically result in both overdiagnosis and underdiagnosis. If pharmacological treatment of depression is considered an indicator for diagnosis, then undertreatment constitutes a serious problem in clinical practice. A study by Weintraub et al showed that only 35% of PD patients with depression were receiving treatment with antidepressants.22

**ETIOLOGY**

Often, depression has been considered an understandable reaction to having to cope with a chronic and debilitating disease. However, future PD patients have a 2.4 times higher risk of depression even before the diagnosis of PD is made. Especially in the last 3 years before diagnosis, the incidence of depression rises.23 This supports the hypothesis that PD constitutes a biological risk factor for depression. Apart from (preclinical) PD being a risk factor for depression, 2 studies have shown that depression also predisposes for PD.24,25 This is not a finding that is specific for PD, because depression may also predispose to a number of other diseases, such as Alzheimer’s disease.
cancer, and cardiovascular diseases. A possible explanation for these findings may be found in the hypothesis of “allostatic load.” This hypothesis states that depression is accompanied by an allostatic state, which may lead to atrophy of nerve cells in the brain, which in turn could lead to neurodegenerative diseases.

In patients with PD, the same risk factors for depression apply as in the general population. These general risk factors for depression include female sex, higher age, personal or family history of depression, and comorbid somatic diseases. Research has been directed toward potential disease-specific risk factors for depression in PD. In the search for disease-specific risk factors for depression, there is evidence that an earlier age of onset, more severe disability, the presence of on/off fluctuations, a higher dose of levodopa, and a family history of PD may increase the risk of depression in PD. The value of these findings is uncertain, however, because none of the studies has corrected for the potential confounding influence of general risk factors for depression. Variables that appear to be risk factors in a bivariate approach may not be predictive in a multivariate approach. In a study that followed such a multivariate approach and corrected for general risk factors, the only marker of depression in PD was a right-sided onset of motor symptoms (left-sided cerebral involvement). This marker had only a marginal additional predictive effect over a model that included only the general risk factors.

Although a small effect, it is interesting from an etiological point of view, because an association with left-sided brain pathology has also been described in somatically healthy patients with depression, as well as in stroke patients.

There still is much controversy about the influence of anti-Parkinson medication on mood. Anticholinergics generally improve mood and can even have euphoric effects. Although there are case histories of depressions induced by dopa-agonists, the general consensus is that they improve mood. Recent publications of the antidepressant effect of pramipexole in patients with PD have led to clinical investigations of the usefulness of pramipexole in the treatment of depression in non-PD patients. Levodopa can have both mood-improving and mood-lowering effects.

PATHOPHYSIOLOGY

Several hypotheses try to provide a pathophysiological explanation for the higher prevalence of depression in PD patients, none of which have been empirically tested. The most well-known are the “serotonergic” and the “dopaminergic” hypotheses. The serotonergic hypothesis was formulated by Mayeux et al in 1984 and is based on the finding that serotonergic activity in the cerebrospinal fluid and the brains of PD patients is lowered. As serotonin has the ability to inhibit striatal dopamine release, reduction of serotonergic activity is seen as a functional mechanism compensating for the reduced availability in the striatum. At the same time, it is known that a reduced serotonergic tone is a risk factor for depression. This may explain the higher prevalence of depression in PD and the fact that depression may occur even before the diagnosis. It also explains the exacerbation of extrapyramidal symptoms that may occur during treatment with a selective serotonin reuptake inhibitor (SSRI).

The dopaminergic hypothesis, also described in 1984, considers degeneration of the mesolimbic and mesocortical structures of the dopaminergic system as the cause of depression. These pathways play an important role in the so-called self-reward systems. Compromising these structures would increase the risk of depression. This hypothesis also explains the higher prevalence of depression in PD and the mood-elevating effects of some of the dopamine agonists.

The cholinergic-adrenergic hypothesis is of older date and is less in line with current views on the pathophysiology of depression. In this theory, depression is seen as a state of relative cholinergic overactivity in relation to adrenergic activity. This theory could also be applied to depression in PD. Recently it attracted some new interest after a mood-stabilizing effect of donepezil, a cholinesterase inhibitor, was demonstrated.

Other researchers have followed an approach along the lines of “functional psychopathology” and hypothesized a more direct link between depressive symptoms and altered neurotransmitter activities, rather than propose a higher vulnerability. In both depression and PD, lowered dopaminergic activity in the frontal lobe is associated with psychomotor retardation, reduced noradrenergic activity with anhedonia, and reduced serotonergic activity with depressive symptoms, anxiety, and insomnia. For several reasons, this approach is probably too simplistic. It may be assumed that not the regional absolute activity of one neurotransmitter but the balance of different neurotransmitter activities is responsible for the production of symptoms. The hypothesis also fails to explain why some patients do have and others do not have depressive complaints in spite of similar pathophysiological abnormalities. Furthermore, psychosocial factors, personality, and coping strategies also play a role in the complex interaction of biological and psychological factors. The “vulnerability model” is thus a more appealing hypothesis to explain interindividual differences.

In the past few years, the influence of deep brain stimulation (DBS) of the subthalamic nucleus (STN) on mood has shed a new light on depressive symptoms in PD, but also on mood regulation in general. It has been demonstrated that STN DBS may lead to improved mood, sometimes progressing to pathological laughter or mania. Unintentional stimulation of the substantia nigra, or deeper subthalamic structures, may produce acute depression, with delusions and even suicidality. These find-
ings imply a role for the basal ganglia in mood regulation that yet has to be explored. It will be a challenge to extend existing neuroanatomic hypotheses of the pathophysiology of depression, such as the model of dysfunctional limbic-cortical pathways proposed by Mayberg, with this newly discovered role of the basal ganglia.

TREATMENT

Treatment of depression in PD is important because depression has a negative influence on cognitive performance, activities of daily living, and perceived quality of life in PD patients. In principle, the same guidelines for the treatment of depression apply for PD patients as for somatically healthy patients. In case of mild depression, the treatment of choice is supportive psychotherapy, which addresses problems with accepting the diagnosis, coping strategies, and the emotional consequences for the patient and the partner of having to deal with the diagnosis. Furthermore, it may stimulate the patient to do physical exercise and engage in social activities. In case of more severe depression, pharmacological treatment is warranted. However, the efficacy of antidepressant treatment of depression in PD has never been convincingly established. The only 2 published double-blind, randomized placebo-controlled studies of the efficacy of SSRIs, one with citalopram and one with sertraline, were characterized by very high placebo-responses of up to 80%, with no significant difference in response between the active and placebo conditions. A double-blind, placebo-controlled study of nortriptyline that followed a crossover design also reported a high placebo-response. Unfortunately, the statistical analysis was performed in such a way that no valid conclusions about the efficacy of nortriptyline can be drawn. The place of other antidepressants, such as the reversible monoamine-oxidase-A (MAO-A) inhibitors, also remains uncertain due to lack of evidence. Apart from the SSRIs, the APA treatment guideline advises bupropion, a dopamine reuptake inhibitor, as a first-choice treatment of depression in PD. Although this seems a plausible choice from a theoretical point of view, there is no evidence for its efficacy in PD, apart from one open study and a case report. Moreover, bupropion may precipitate a dopaminergic psychosis in PD. Electroconvulsive therapy (ECT) remains an option for the treatment of depression in PD. A number of case reports and case series describe beneficial effects on depression in PD, without negative side effects, and often even temporary improvement of motor symptoms. Indeed, ECT has been tried as a treatment for motor symptoms in PD patients without depression, with apparent positive results, lasting from several weeks to months.

Looking at the limited number of studies, and their largely negative results, it is not surprising that 2 systematic reviews have concluded that there is insufficient evidence for the efficacy and safety of SSRIs and tricyclic antidepressants (TCAs) in the treatment of depression in PD, with the exception of a possible efficacy of nortriptyline.

The most important consequence of the high placebo-response in the aforementioned double-blind studies is that studies that have not followed a placebo-controlled design will never provide evidence of a superior efficacy of antidepressant treatment. It also has implications for our pathophysiological views on depression in PD, and the possible mechanism of action of antidepressants. In the dopaminergic theory, depression is thought to be caused by deficient self-reward mechanisms, which are located in the mesocortical and mesolimbic dopaminergic structures. Stimulation of the self-reward system can be done by specific interventions, such as treatment with placebo. The expectation of reward may result in actual clinical improvement. The recent finding that PD patients are also susceptible for placebo response in the treatment of motor symptomatology provides additional support for this theory.

There are case reports and case series describing potential side effects and interactions of SSRIs. SSRIs may have a negative influence on motor symptoms. The incidence of this side effect is unknown, but clinically it is not presumed very important. Practice guidelines favor treatment with an SSRI over treatment with TCA because the risk of impairment of motor function is considered less a problem than the potential negative influence on cognition and perception because of the anticholinergic properties of TCAs. Parkinsonism may occasionally occur during the treatment of depression in a patient not known to suffer from PD. In these cases, one should be alert for the possibility that preclinical PD may have become apparent due to the treatment. Both SSRIs and TCAs may give rise to a “serotonergic syndrome” when used in conjunction with selegiline, an irreversible MAO-B inhibitor used in the treatment of motor symptoms of PD. Such a serotonergic syndrome is characterized by tremor, hypertonia, myoclonia, autonomic symptoms, hyperthermia, and hallucinations. In extreme cases, this may lead to death. The incidence of this complication is estimated at 0.24%. Three fatalities have been reported, which were all due to a combination of a TCA with selegiline. In this respect, SSRIs appear to be safer than TCAs.

Having addressed these issues, the question remains how to deal with depressed PD patients in clinical practice. Even in the absence of scientific evidence for the specific therapeutic activity of antidepressant treatment, clinical evidence shows that the patient may still benefit from antidepressant treatment. Thus, in the absence of better options, a trial-treatment with an antidepressant is useful. Both the APA and the American Academy of Neurology (AAN) favor treatment with an SSRI over treatment with a TCA. Once the decision to treat is made, it is important that the patient is treated adequately. This implies increasing the dose in case of poor response, and, if this
still doesn’t have the desired effect, a second trial with an antidepressant of another class. In case the patient does not improve on an SSRI or experiences unacceptable side-effects, treatment with a TCA may be a good second step.\textsuperscript{66,83} Weintraub et al showed that 47% of the PD patients taking antidepressants still showed signs of depression and were not treated adequately.\textsuperscript{22}

CONCLUSION

Depression in PD remains a conceptual, diagnostic, and therapeutic challenge. Due to the overlapping symptomatology of PD and depression, it is often difficult to recognize depression as a separate entity, while the partly shared pathophysiology may make it difficult to specifically treat mood symptoms, without influencing motor or cognitive symptoms. Large placebo-controlled studies are necessary to further evaluate the potential efficacy of antidepressant treatment and to allow the development of evidence-based treatment guidelines. A better understanding of the pathophysiology of depression in PD may also provide valuable information in the pathophysiology of depressive disorder in general.

References


