

# PARKINSON'S DISEASE AND DEPRESSION

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## PARKINSON BETEGSÉG ÉS DEPRESSZIÓ

A Parkinson-kóros betegek körülbelül 40%-a szenved egyidejűleg depresszióban is, de sajnos a depresszió az ilyen állapotokban viszonylag ritkán kerül felismerésre és így a megfelelő antidepresszív terápia gyakran elmarad. A klinikai gyakorlatban a Parkinson-kóros betegek depressziójának felismerése és megfelelő kezelése igen fontos. Jelen áttekintés célja a Parkinson-betegséghez társuló depresszió epidemiológiájának, patofiziológiájának és kezelésének összefoglalása.

**KULCSSZAVAK:** depresszió, Parkinson-betegség, antidepresszívumok, gyógyszeres kezelés

## SUMMARY

The prevalence of depression in Parkinson's disease is around 40%, but, unfortunately, such depression is frequently unrecognized and untreated. However, recognition and appropriate treatment of depression in patients with Parkinson's disease is essential for clinical practice. This review focuses on the epidemiology, pathophysiology and treatment of depression associated with Parkinson's disease

**KEYWORDS:** depression, Parkinson's disease, antidepressants, drug-treatment

## INTRODUCTION

Parkinson's disease (PD) is among the most common and serious neurological disorders of later life, with an estimated prevalence of one percent. The typical neurological manifestations of PD (pill-rolling tremor, muscular rigidity and hypokinesia), as well as other associated symptoms (bradykinesia/akinesia, slowness in initiating movement, postural changes, festinant gait, merked fatigue etc.), lead to serious disability and reduced life quality, particularly in the late stage of the illness.

PD is really a neuropsychiatric disorder, since various psychiatric symptoms as well as defined psychiatric disorders (depressive disorders, dementias and psychotic disorders) can be seen in a substantial proportion of patients.

## DEPRESSION IN PARKINSON'S DISEASE

The most common psychiatric illness associated with PD is depression (Starkstein et al., 1990; Cummings, 1992; Robertson, 1997; Schuurman et al., 2002). Comorbid depression worsens the outcome and makes the treatment of PD more difficult. Unfortunately, depression in PD patients is frequently unrecognized and not treated. How-

ever, depression associated with PD is highly treatable, and the successful treatment enhances the patients' compliance with therapy and their adaptive coping strategies with the medical illness.

### *Prevalence and clinical characteristics of depression in Parkinson's disease*

Parkinson's disease and depression co-occur much more frequently than it could be expected by chance. Reviewing 26 studies published between 1922 and 1990, Cummings (1992) reported that a mean rate of depression in PD was 40% (range: 4-70%). He also noted that the lowest reported figures were found in studies done before standardized methodology or operationalized diagnostic criteria came to be used generally. Considering only the 9 studies published between 1987 and 1990, the rate of depression ranged from 25 to 70%, and the mean figure was 43%. A recent review by Okun and Watts (2002) also shows that depression associated with PD is quite frequent and affects 25-40% of the patients.

Two main types of depression are encountered in PD: (1) about half of depressed patients with PD met the criteria for major depressive episode (almost in all cases unipolar major depression), and (2) the other half had minor depressive disorder.

der or its chronic form called dysthymic disorder (Starkstein et al. 1990; Cummings, 1992; Robertson, 1997).

Depression associated with PD shows some clinical differences from primary major depressive episode; in the comorbid cases, there are high levels of dysphoria, anxiety, pessimism, irritability and suicidal ideation. However, on the other hand, guilt, self-blaming and psychotic features as well as attempted suicide and completed suicide are rare (Cummings, 1992; Robertson, 1997).

### *Risk factors of depression in Parkinson's disease*

The most common risk factors of depression in patients with PD are the following: female gender, previous history of depressive illness, hypo- or bradykinesia, gait instability, greater functional disability, greater degree of left brain involvement, and an earlier age of onset of PD. On the other hand, family history of depressive and other psychiatric disorders and current age of the patient do not correlate with the presence of depression (Cummings, 1992; Robertson, 1997). It is important to note that in about 25% of cases patients had already been depressed before the onset of PD (Mayeux, 1981). A recent retrospective study from general practice showed that depression itself might also be a risk factor for PD: 19 out of the 1,358 depressed patients (1.39%) later developed PD, while the same figure among the 67,570 non-depressed subjects was 259 (0.38%). In other words, the development of PD in depressed patients was about three times more frequent than in the case of non-depressed primary care patients (Schuurman et al., 2002).

### **PATHOPHYSIOLOGY OF DEPRESSION IN PARKINSON'S DISEASE**

The pathophysiology of depression in PD is complex and multicausal. Earlier aetiological models have suggested that the development of depression in PD was mainly a simple psychological reaction to the severe physical disability caused by the movement disorder. However, Robins (1976) reported much higher rates of depression among patients with PD than in a group of age- and sex-matched patients with the same level of physical disability of peripheral causes (hemiplegia, paraplegia, arthritis etc.). This finding refutes the above-mentioned ("psychological reaction") hypothesis, and strongly suggests that depression is a

more integral part of PD, indicating that the mood disturbance might be more closely related to the brain (neurotransmitter) pathology, i.e. that depression is the direct result of underlying biochemical changes caused by the disease process (Cummings, 1992; Robertson, 1997). The exact cause of depression in PD is still unknown, but it is very likely that the aetiology is multifactorial and the role of psychosocial factors cannot also be ruled out.

The well-known hypothesis of PD involve a variety of subcortical nuclei (substantia nigra, ventral tegmental area, nucleus basalis, hypothalamus, dorsal raphe nucleus, locus ceruleus, caudate nucleus etc.) that are the major sources of neurotransmitters. The pathological process of these subcortical structures leads to neurochemical depletion remote from these nuclei. A moderate to marked depletion (i.e. 40–90% reduction) of dopamine, norepinephrine, and serotonin in these nuclei has been reported in PD (Cummings 1992). On the other hand, as in the cases of primary major depression, several studies have found lower levels of CSF 5-hydroxyindoleacetic acid (5-HIAA) in patients with PD and major depression than in those without mood disturbance (Goodwin and Jamison, 1990; Mayeux, 1990). Therefore, the pathophysiology of depression in PD might be primarily related to these neurotransmitter abnormalities (and to the accompanying receptor changes), since disturbance of central serotonin, norepinephrine and dopamine metabolism is consistently demonstrated in primary depressive disorders without any medical comorbidity (Goodwin and Jamison 1990). Neurobiological studies also show that mood disturbance in PD may be mediated by dysfunction in mesocortical and prefrontal reward, motivational and stress-response systems (Cummings, 1992).

### **PHARMACOTHERAPY OF DEPRESSION IN PARKINSON'S DISEASE**

It has been demonstrated that antiparkinsonian drugs, when administered in the recommended dose-range for the treatment of PD, exert limited (dopamine-receptor agonists, selegiline) or no clinically significant (anticholinergic drugs, l-dopa, amantidine, carbidopa) antidepressant efficacy in patients with PD (Cummings, 1992; Robertson, 1997). Moreover, some of them (amantidine, carbidopa, levodopa) may also precipitate depression (Cummings 1992; Wise and Taylor 1990). Therefore, manipulation of these drugs is recommended

as the first step, and, if ineffective, specific antidepressive pharmacotherapy is indicated.

Selegiline (l-deprenyl), a selective MAO-B inhibitor, is employed as part of the treatment of PD, but it does not appear to have a marked effect on depression in doses at which this selectivity is present (less than 15 mg/day). However, in higher doses (25 mg/day or above), selegiline loses its MAO-B selectivity and starts to act as a non-selective MAO-I, inhibiting the degradation not only of dopamine, but also of serotonin and noradrenaline, and works as an effective antidepressant (Mann et al., 1989).

Traditional antidepressants (tricyclics and others) such as imipramine, desipramine, nortriptyline and bupropion have all been shown to be effective in the treatment of depression in patients with PD (Cummings 1992; Robertson 1997; Kennedy and Frazier, 1999). However, because of their safer nature and lower interaction potential, selective serotonin re-uptake inhibitors (SSRIs) and other newer antidepressants (venlafaxine, mirtazapine, nefazodon), as well as moclobemide (a reversible MAO-A inhibitor), have become recently the first-choice agents (Caley and Friedman, 1992; Cunningham, 1994; Robertson, 1997; Greenblatt et al., 1998; Kennedy and Frazier, 1999; Rihmer et al., 2000).

Since a significant association has been reported between low CSF 5-HIAA and depression in Parkinson's patients (Mayeux 1990), SSRIs seem to be potentially excellent drugs for treating depression in patients with PD. In contrast with the suggestions of some previous case histories, Caley and Friedman (1992) found that fluoxetine, in doses up to 40 mg/day, did not exacerbate parkinsonian symptoms in 23 depressive outpatients with PD. A recent open-label prospective study including more than 50 depressed patients with PD also showed that SSRIs (citalopram, fluoxetine, fluvoxamine and sertraline) were effective in treating depression, and they did not worsen PD (Dell'Agnello et al. 2001). Parkinson's patients

are often on selegiline therapy (5–15 mg/day) because of their movement disorder. The incidence of serotonin syndrome while combining a low dose of selegiline with antidepressants seems to be very low (Kennedy and Frazier, 1999). Citalopram, the most selective SSRI with very favourable side-effect and interaction profile, is a potentially promising drug in this respect. A recent 8-week-long open clinical study evaluated the effectiveness and safety of a selegiline+ citalopram combination for major depression in 8 outpatients whose mild or moderate PD had previously been treated with a low dose of selegiline (5–10 mg/day) and who were still on selegiline during the citalopram treatment. The majority of the patients (6/8) responded well to citalopram (20 mg/day) and no adverse events occurred. The findings suggest that combination of low-dose selegiline and citalopram (and probably other SSRIs) is an effective and safe method in the treatment of major depression of patients with PD (Rihmer et al., 2000).

Investigating 18 depressed and 28 non-depressed patients with PD, Rampello et al. (2002) found that, when combined with levodopa, citalopram was effective and safe in the treatment of depression and induced an improvement of motor performance both in depressed and non-depressed patients.

Electroconvulsive therapy might also be an effective treatment in depression with PD, particularly in drug-intolerant or drug-resistant cases (Cummings, 1992). Other antidepressant treatments, such as sleep deprivation, light therapy as well as transcranial magnetic stimulation, are not well studied in PD and warrant further investigation.

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