# DEPRESSION IN PARKINSON'S DISEASE

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**DEPRESSZIÓ PARKINSON-KÓRBAN**
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The prevalence of major and minor depression in Parkinson's disease is around 30–40% but, unfortunately, depression remains frequently underrecognized and often undertreated. However, recognition and appropriate treatment of depression in patients with Parkinson's disease is essential for improving the cross-sectional picture and longitudinal course. This review focuses on the epidemiology, pathophysiology and different treatment modalities of depression in Parkinson's disease.

***Keywords:*** *depression, Parkinson's disease, risk factors, epidemiology*

A major és minor depresszió prevalenciája Parkinson-kórban szenvedők között körülbelül 30-40%, ugyanakkor a depresszió ebben a betegcsoportban aluldiagnosztizált és alulkezelt kórkép. A depresszió diagnózisának és az adekvát kezelésének elmaradása nemcsak a depressziós tünetek perzisztálásához, de csökkent életminőséghez, az alapbetegség súlyosabb tüneti képéhez és kedvezőtlenebb prognózisához is vezetnek. Összefoglaló tanulmányunkban a Parkinson-kórban megjelenő depresszió epidemiológiai, patofiziológiai és terápiás vonatkozásait tárgyaljuk.

***Kulcsszavak:*** *depresszió, Parkinson-kór, rizikófaktor, epidemiológia*

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Parkinson's disease (PD) is among the most common and serious neurological disorders of later life (median age of onset is 60 years), with an estimated lifetime risk of 1.5%. The incidence of PD increases as the age of the investigated population is higher (50–59 yrs: 17.4/100 000/year; 70–79 yrs: 93.1/100 000/year)[1–3].

The typical neurological manifestations of PD (4–6 Hz rest tremor, muscular rigidity, hypo- and bradykinesia and postural instability) as well as other associated symptoms (festinant gait; marked fatigue; masklike/expressionless face; dementia; monotonous and slightly slurred speech; dysautonomia etc.) lead to a serious disability and/or reduced quality of life (QoL), particularly in the late stage of the illness[1]. PD is a true neuropsychiatric disorder since various psychiatric symptoms as well as well-defined ICD–10 or DSM–IV psychiatric syndromes (depressive disorders, anxiety, dementia and psychotic disorders) can be seen in a substantial proportion of patients[1, 4–6].

The most common psychiatric illness associated with PD is depression. Comorbid depression worsens the cross-sectional clinical picture and outcome and makes the treatment of PD more difficult. Unfortunately, depression in PD patients is frequently unrecognised and untreated. However, depression associated with PD is treatable and the successful treatment enhances not only the QoL of the patients but also the patients' compliance with

the therapy and the adaptive coping strategies with the medical illness[7–13].

The unipolar or bipolar nature of depression in patients with PD is not clear. Well-designed epidemiological studies on the distribution of unipolar major depression and bipolar depression in such patients are still lacking. Since only a few case reports may be found in the literature on the bipolar nature of mood disorder in PD patients it is probable that the vast majority of PD patients with depressive symptoms suffer from unipolar depression[14–16]. It is interesting to note that some case-histories reported on remission of Parkinsonian symptoms when patients become manic[15, 16]. Another point where bipolar phenomenology is also linked to PD based on clinical observations on the appearance of maniac symptoms in some cases after using some pharmacological agents (levodopa; bromocriptine; selegiline, pramipexole) or deep brain stimulation of the subthalamic nucleus (STN-DBS; a widely used therapy for PD)[7, 17, 18].

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

PD and depression co-occur together much more frequently than it would 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%)[9]. Considering only the nine studies published between 1987 and 1990, the rate of depression ranged from 25 to 70%, and the mean figure was 43%[9]. Cummings also noted that the lowest reported figures were found in studies that were done before standardised methodology or operationalised diagnostic criteria were in general use[9]. Most recent reviews also show that major depression associated with PD is quite frequent and affects 17–40% of the patients and frequently antedates the movement disorder and if minor depression or dysthymic disorder are also considered the rate of depression in PD raises up to 50 percent[13, 19–22]. Authors of one of these recent reviews of prevalence studies observed that prevalences were significantly lower in population studies than in studies conducted in outpatient or inpatient samples and that those studies measuring the prevalence of major depressive disorder (MDD) with (semi)structured interviews to establish DSM criteria reported higher prevalences than those employing DSM criteria without a structured interview[7, 19]. Depressive symptoms probably are even more prevalent (in some studies above 75%) among patients with PD and concomitant dementia[7, 23].

*Even* and *Weintraub* (2012) identified three potential subtypes of depression in PD. Authors took as a basis the 19% prevalence rate of major depression in PD – a figure comes from studies using a (semi) structured interview to establish DSM criteria and reported by the systematic review by *Reijnders* et al.[19] – and other sources of prevalence data and calculated that 10.2% of depression cases is specifically associated with PD (i.e. these are those cases which are directly related to the pathophysiology of PD). Another 6.8% of depression cases observed among patients with PD are the consequence of the chronic/debilitating nature of PD (in other words these cases would be depressed if they have another disabling comorbid medical illness). A third proportion (2%) of cases consists those depressed subject who would be depressed even if they would not suffer from PD[24].

The majority of depressed patients with PD do not receive antidepressant treatment, accordingly we may state that depression is undertreated in this patient population[6, 25].

However, depressive symptoms frequently preceed the onset of motor signs of PD (discussed below), in patients with already diagnosed PD the onset of depression follows a bimodal distribution (one peak in close proximity at the time of PD diagnosis and a second peak during the late course of PD)[7].

The distribution of the two main types of depression encountered in PD are: (1) about half of depressed patients with PD meet the criteria for major depressive episode (almost in all cases unipolar major depression), and (2) another half have minor depressive disorder or its chronic form called dysthymic disorder[8–10].

The diagnosis of depression in PD can be difficult owing to the overlap of symptoms between depression, parkinsonism and cognitive symptoms, and due to psychological reactions to the movement disorder (e.g. fatigue may occur in both MDD and PD; masklike/expressionless face may be interpreted as affective blunting; bradykinesia may be interpreted as psychomotor retardation, a DSM criterion for major depressive episode)[1, 22, 23, 26]. It is important that the assessment of depression in patients with motor fluctuations should be conducted during "on" states. It should be remarked – apropos of this issue – that, those patients with motor fluctuations who have depressive symptoms only during the "off" phases can be classified as having subsyndromal depression and the treatment of their depressive symptoms should be initated with the adjustment

of antiparkinsonian medications[6, 13, 27, 28]. 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, marked fluctuations of mood and psychotic features as well as attempted suicide and completed suicide are rare[9, 10, 26, 28]. Besides the detailed interview based on ICD-10 or unmodified DSM-IV criteria, the Geriatric Depression Scale (15-item version) may be optimal because it is short, reliable and less dependent on physical symptoms[4, 23, 26].

There are several *consequences* of depression in PD. Accordingly, depression in PD patients is associated with declining motor symptoms, cognitive impairment, reduced QoL, increased disability, elevated levels of psychiatric and medical comorbidity (and consequential higher mortality), greater health-care utilization, poorer adherence to treatment, increased stress on caregivers, etc.[6, 7, 19, 23, 29]. It is important to emphasize that the impact of depression on QoL of subjects with PD seems to be bigger than the impact of the motor aspects of the illness[29, 30].

## Risk factors for depression in PD and depression as a risk factor for PD

The most common risk factors for depression in patients with PD include female gender, previous history of depressive illness, hypo- or bradykinesis, gait instability, greater functional disability, greater degree of left hemisphere involvement, and an earlier age of onset of PD. However, the role of family history of depressive and other psychiatric disorders and the current age of the patient are ambiguous[9, 10, 30–32]. Findings of other studies suggest that general risk factors of depression are able to predict 75% of depression cases in PD and from neurological signs only the inclusion of the right-sided onset of PD symptoms was able to enhance the efficacy of prediction. Accordingly it was concluded that there is a substantial overlap between established risk factors for depression in the general population and risk factors for depression among patients with PD[7]. Results of a very recent study also suggest that non-PD specific risk factors for depression are in a 3-times-stronger association with depression in PD than PD-specific risk factors. Accordingly, they found that six non-PD specific risk factors (female sex, history of anxiety and/or depression, family history of depression, worse functioning on activities of daily living, and worse cognitive status) and three PD-specific variables (increased disease duration, more severe motor symptoms, the use of levodopa) were associated with depression[30].

It is important to note that in about 25% of cases patients had already been depressed before the onset of PD[21, 33].

On the other hand, it has been also shown that either depression could be a risk factor for PD or PD and depression may have a common biological/genetic root. Results of a large-scale retrospective study from general practice suggested that depression itself might also be a risk factor for PD: 19 out of the 1358 depressed patients (1.39%) later developed PD, while the same figure among the 67.570 nondepressed subjects was 259 (0.38%) indicating that the development of PD in depressed patients was about three times more frequent than in the case of nondepressed primary care patients[11]. Several other studies also found that depression was more frequent among those who later became ill with PD than among those who did not[7]. A recently published, large-scale, retrospective, matched cohort study found that among patients with depression the risk of developing PD is higher than among control subjects and this association remained significant even after the exclusion of those patients whose depression was diagnosed 'shortly' (2-5 years) before the onset of PD. This result further suggests that depression is an independent risk factor for PD[34]. In addition, increased risk of depression in first-degree relatives of PD patients suggests that depression may share familial susceptibility factors (genetic or nongenetic) with PD[35, 36].

## Pathophysiology of depression in patients with PD

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 neurological or orthopaedic causes (hemiplegia, paraplegia, arthritis etc.) and others – with some exceptions[28] – also reported higher levels of depression among patients with PD than among individuals with other serious disorders of the CNS (e.g. stroke) or other chronic and disabling disorders[5 ,6, 24, 37, 38]. These findings refute the above mentioned ("psychological reaction") hypothesis

and strongly suggests that depression (or at least the bigger part of depression cases—see Even and Weintraub, 2012) is a more integrant 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[9, 10, 12, 21]. 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 also cannot be ruled out.

It is well known that a variety of subcortical structures (substantia nigra pars compacta, ventral tegmental area, nucleus basalis of Meynert, raphe nuclei, locus coeruleus, etc.) which are also the major sources of some neurotransmitters – those very ones play an important role in the pathophysiological background of primary depressive disorders – are affected in PD. The pathological involvement of these subcortical structures leads to altered neurotransmitter (mainly dopamine, norepinephrine, serotonin and acethylcholine) signaling at sites remote from these nuclei resulting in various changes in levels of neurotransmitter metabolites, receptors and transporters – in a somewhat similar manner to those changes described consistently in primary depressive disorders without any medical comorbidity – and ultimately in depression[1, 7, 26, 36, 39, 40–42]. However it seems that results on changes of the serotonergic system in PD-associated depression are less consistent (or more contradictory) than in primary depressive disorders[24, 26, 36]. This is consonant with those results which indicated that efficacy of SSRI therapy in PD-associated depression is limited (if it has any effect at all)[29, 36].

In PD the neuropathological changes in areas implicated in depression including the raphe nuclei and the locus coeruleus may precede the loss of dopaminergic neurons which may explain the phenomena discussed above that some non-motor symptoms of PD (including depression) frequently occur prior to the appearance of motor symptoms[5, 43, 44].

## Therapy of depression in PD

### ANTIPARKINSONIAN DRUGS

It has been demonstrated that some *antiparkinsonian drugs* as dopamine-receptor agonists (especially demonstrated in case of pramipexole and less for bromocriptine) and MAO-B inhibitors (selegiline and rasagiline), when administered in the recommended dose-range for the treatment of PD exert limited antidepressant efficacy in patients with PD. The effects of other antiparkinson medications on depressive symptoms are contradictiory. For example, there are results on both mood improving and mood deteriorating effects of L-DOPA. Mood effects of anticholinergic drugs and amantadine are considered as not clinically significant[7, 9, 10, 25, 26, 44–47]. *Therefore, manipulation of these drugs is recommended as the first step in the pharmacological treatment of depression in PD, and, if ineffective, specific antidepressive pharmacotherapy is indicated (see below).*

Selegiline (l-deprenyl), a selective MAO-B inhibitor, is employed as a 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 nonselective MAO-I, inhibiting the degradation not only of dopamine, but also of serotonin and noradrenaline and works as an effective antidepressant[48, 49]. Of course dietary restrictions are highly recommended if selegiline is administered in higher doses than the dose indicated in the labeling.

### ANTIDEPRESSANTS AND OTHER PSYCHOTROPIC AGENTS

Although depression in PD is very frequent and it has deteriorating impact on QoL of the patient as well as on the course of PD there is a scarcity of well-designed treatment studies with antidepressants in this patient population [7]. Furthermore, results of studies are frequently contradictory and – accordingly – conclusions of meta-analyses are also disillusioning[29, 50].

The most prescribed subfamily of antidepressants in PD is *SSRIs*[24, 36]. Earlier a few *uncontrolled* studies[14, 51–53] indicated that SSRI treatment is effective in the treatment of PD-associated depression[7]. Until recently there was only limited and ambiguous evidence from *placebo-controlled* studies relating to the efficacy of SSRIs (e.g. citalopram, sertralin and paroxetine) in this patient population[36]. However, a recent randomized, double-blind, placebo-controlled study by *Richard* et al. with 12 weeks duration compared the SSRI *paroxetine*, the SNRI *venlafaxine XR* and placebo for patients with PD with DSM-IV defined major or minor depression (n=115) and found that both medications have significant benefits compared to placebo, without worsening the motor symptoms[36, 54, 55]. At the same time, results of the most recent meta-analysis – which also includes the study by *Richard* et al.[54] – on efficacy of SSRIs in this patient population are not convincing[29]. They also mentioned that antidepressants in general and SSRIs in particular showed statistically significant higher rates of dropouts than placebo, but they appended that "in general antidep-

ressant medications were well tolerated"[29]. However there is a concern about the possible negative effect on SSRIs on PD-related motor symptoms (since serotonin has an inhibitory effect on the dopamine release in the striatum) data are reassuring in this regard[7, 23, 29, 51, 53, 56].

Traditional *tricyclic antidepressants (TCAs)*, such as amitriptyline, imipramine, desipramine, nortriptyline have all been shown to be effective in the treatment of depression in patients with PD (according to some opinions the efficacy of desipramine and nortriptyline is more strongly confirmed than the efficacy of the remaining TCA agents). There are some evidences that TCAs are more effective than SSRIs for the treatment of depression in PD[6, 8–10, 23, 25, 29, 57, 58]. At the same time, due to their anticholinergic properties TCAs have the propensity to impair some PD-related symptoms such as cognitive and autonomic dysfunctions so they should be used with caution[5, 7, 26].

However, – from a theoretical point of view – great caution and close monitoring are advised when a MAO inhibitor (selegiline, rasagiline) is coadministered with an agent with serotonin reuptake inhibitory properties (e.g. SSRI; SNRI; TCA), current results suggest a very low frequency of consequential serotonin syndrome[5, 7, 14, 57, 59].

*Mirtazapine, atomoxetine* and – interestingly – *buproprion*, a norepinephrine-dopamine reuptake inhibitor antidepressant, are not effective (or yet little studied) in treating depression in patients with PD [4,7,13,23,36]. A double-blind, placebo-controlled study of 31 subjects reported that *fish oil* (omega-3-fatty acid) was effective in the treatment of major depression comorbid with PD. Because of the safe nature of fish oil this option may be a useful addition to treatment, but further confirmation of this single result is required by investigations with larger sample sizes[23, 58, 60].

### OTHER THERAPEUTIC MODALITIES

*Electroconvulsive therapy (ECT)* might also be an effective treatment of depressed patients with PD, particularly in drug intolerant or drug resistent cases[7, 9]. In addition, ECT has beneficial effects on motor symptoms of PD which are independent of its impacts on depressive symptoms and occurred well before these[7, 61].

Some findings also suggest that the use of ECT is probably safe in patients with STN-DBS electrodes in place. This may be of great importance, since depression with an increased risk of suicide is frequent following DBS surgery[7, 62].

Results on the impact of *deep brain stimulation (DBS)* – an intervention with well-established efficacy in alleviating motor dysfunction and drug-associated motor side effects and allowing dopaminergic dose reduction in PD – on depression in PD are ambiguous: while some findings suggest that *STN-DBS* (the only treatment modality of PD which – according to recent preliminary data – seems to improve survival of patients) amends depressive symptoms associated with PD (moreover it leads to mania in some cases) others found that it is also associated with depression and substantially elevated risk of suicide postoperatively[5, 7, 25, 63, 64]. However, DBS treatment of some other targets than subthalamic nuclei (e.g. globus pallidus) has been rarely reported to be associated with mood-changes[6, 6–67].

According to our best knowledge so far only a few studies investigated the efficacy of *repetitive transcranial magnetic stimulation (rTMS)* – a noninvasive brain stimulation method, which has already been proven effective for the treatment of idiopathic major depression – among patients with depression and PD. These studies provided promising results and found that treatment is well-tolerated in this patient population but further multi-centered studies involving larger samples and using double-blinded, sham-controlled design are needed before rTMS become an established treatment for depression associated with PD[36, 68–70].

The efficacy of *cognitive behavioural therapy (CBT)* was evaluated recently by two studies in Parkinson's disease depression[71, 72]. In the first study authors used an RCT setting and found that CBT (modified to meet the unique needs of patients with PD) administred for 10 weeks was associated with a significantly greater reduction in depression scores than clinical monitoring only (i.e. the placebo condition). Furthermore, the CBT group also reported greater improvements on secondary outcome measures (e.g. QoL, coping and anxiety as well as motor symptoms)[4, 23, 71]. The same authors confirmed their results in a second uncontrolled pilot study using telephone-based CBT intervention (which may be especially valuable in this population because of their difficulties in movement). Results of this study are also promosing[23, 72].

Other antidepressant treatments, such as *sleep deprivation* as well as *light therapy* are not well studied in PD and warrant further investigations.

## Discussion

Depression is a common nonmotor feature of PD which frequently remains unrecognised and untreat-

ed. Adverse impacts of comorbid depression in patients with PD are well-known. For instance, depression has detrimental effects on QoL, leads to increased disability of patients and elevated levels of caregiver burden and also to declining motor symptoms and cognitive impairments. Several possible explanations, e.g. overlapping neurochemical changes and the familiar clustering of PD and depression (which suggest shared genetic backround of the two illnesses) were put forward to interprete the comorbidity between the two conditions. Treatment of depression in PD should be individually tailored. Optimal adjustment of antiparkisonian medication, initiation of treatment with an antiparkisonian agents with antidepressants properties (e.g. pramipexole), initiation of antidepressant treatment and use of non-pharmacological treatment modalities (e.g. ECT and CBT) are all parts of treatment possibilities for depression in patients with PD.

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*CONFLICT OF INTEREST*

*The authors have no conflict of interest to declare related to this manuscript.*

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