

# Depression in Parkinson's disease: diagnosis and treatment

## Depressão na doença de Parkinson: diagnóstico e tratamento

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### ABSTRACT

The prevalence of non-motor symptoms in Parkinson's disease (PD) is high. Depression varies from 20 to 50% of the PD patients, and is associated with increasing disability. The key characteristics of depression are anhedonia and low mood. The recommended scales for screening purposes are: HAM-D, BDI, HADS, MADRS and GDS. As for measurement of severity: HAM-D, MADRS, BDI and SDS. In cases with mild depression, non-pharmacological intervention is the treatment of choice. In moderate depression, antidepressants are required. The choice of an antidepressant should be based mainly on the comorbidities and unique features of the patient. Evidence for antidepressant effectiveness is seen mostly with amitriptyline and nortriptyline, but one should be cautious in elderly patients. Other antidepressants that can be prescribed are: citalopram, escitalopram, sertraline, bupropion, trazodone, venlafaxine, mirtazapine and duloxetine. The dopaminergic agonist pramipexole is a treatment option.

**Key words:** depression, Parkinson disease, non-motor symptoms.

### RESUMO

A prevalência dos sintomas não motores na doença de Parkinson (DP) é considerada elevada. A depressão varia entre 20 e 50% dos pacientes e está associada a maior incapacidade. A presença de anedonia e/ou humor deprimido são os sintomas-chave. As escalas recomendadas para o rastreamento de depressão são: HAM-D, BDI, HADS, MADRS e GDS. Aquelas recomendadas para estimar a gravidade da depressão são: HAM-D, MADRS, BDI e SDS. Nos pacientes com depressão leve, devem ser escolhidas intervenções não farmacológicas. Nos pacientes com sintomas moderados, está indicada a terapia com antidepressivos. A escolha de um antidepressivo deve se basear principalmente nas comorbidades e características de cada paciente. A amitriptilina e nortriptilina são as drogas mais estudadas, porém devem ser prescritas com cautela em pacientes idosos. Outros antidepressivos que podem ser prescritos são: citalopram, escitalopram, sertralina, bupropiona, trazodona, venlafaxina, mirtazapina e duloxetina. O agonista dopaminérgico pramipexole é uma opção para o tratamento.

**Palavras-Chave:** depressão, doença de Parkinson, sintomas não motores.

In recent years, the study of non-motor symptoms (NMS) in Parkinson's disease (PD) has become a major focus of medical care<sup>1-5</sup>. Classically, the diagnosis and treatment of motor symptoms have always been considered of most importance despite the presence of NMS are recognized since its description by James Parkinson in 1817<sup>6</sup>. Recently, with the concept of pathological staging of PD by Braak et al., it was more clearly established the correlation of various non-motor symptoms<sup>7,8</sup>.

The prevalence of NMS is high among patients with PD. The PRIAMO study evaluated 1,072 patients in 55 hospitals<sup>9,10</sup>.

Of PD patients, 98.6% reported NMS, and the most common symptoms were fatigue (58%), anxiety (56%), leg pain (38%), insomnia (37%), urinary urgency and nocturia (35%), excessive salivation, difficulty in maintaining concentration (31%) and depression (22.5%). The average number of NMS was 7.8 per patient (0–32). The psychiatric field was the most commonly affected (67%). The authors reported that the frequency of NMS increases with the duration and severity of the disease. The presence of apathy, cognitive impairment and psychiatric symptoms were associated with worse health-related quality of life. The conclusion was that the NMS have an

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important role in PD and should be measured on outcomes of clinical trials from validated scales for symptoms.

Although it is not the most frequent NMS, depression is the main negative factor that impacts quality of life (QoL) in PD<sup>11-13</sup>. The prevalence of depression in PD varies from 20 to 50% and is frequently associated with greater disability, rapid progression of motor symptoms and increased mortality<sup>14,15</sup>. In the universe of patients diagnosed with depression, 20 to 50% are considered to have major depression. Several risk factors for depression are described, such as severity of cognitive impairment, female sex, onset of parkinsonian symptoms before age 40 and history of depression prior to diagnosis of PD. Depressive symptoms are seen in all stages of severity of PD, and may precede motor symptoms for years<sup>16</sup>.

The depressed mood and anhedonia are the key symptoms, and the presence of at least one of them is needed for clinical diagnosis of depression in PD. Other features may be present in varying combinations, for example, loss of appetite, sleep disturbance, weight gain, loss of libido, loss of concentration and fatigue<sup>2</sup>. However, many of these symptoms may overlap with symptoms of PD themselves, making diagnosis challenging. Conversely, feelings of guilty or worthlessness and suicidal thoughts are not common in PD<sup>17</sup>.

We find various clinimetric tools for the diagnosis of depression, but there is no scale specifically developed for PD. To try to tackle this issue, the Research Committee of the Movement Disorders Society (MDS) was established to evaluate the properties of the main scales of depression and make recommendations on using these for the diagnosis of depression in PD<sup>14,18</sup>. The revised scales were: Beck Depression Inventory (BDI), Hamilton Depression Scale (HAM-D), Hospital Anxiety and Depression Scale (HADS), Zung Self-Rating Depression Scale (SDS), Geriatric Depression Scale (GDS), Montgomery-Asberg Depression Rating Scale (MADRS), Unified Parkinson's Disease Rating Scale (UPDRS) Part I, Cornell Scale for the Assessment of Depression in Dementia (CSDD) and the Center for Epidemiologic Studies Depression Scale (CES-D). The conclusion was that for screening of depression in PD, the scales recommended are: HAM-D, BDI, HADS, MADRS and GDS<sup>14</sup>. To measure severity, the recommended ranges are: HAM-D, MADRS, BDI and SDS. Due to overlapping motor symptoms, NMS and depression, the authors also suggest that studies are proposed to establish the cutoff points of the scales to be applied. The use of depression scales in PD patients is often criticized because of the inclusion of somatic symptoms in some items, which are difficult to differentiate from symptoms themselves (physical) of PD<sup>18,19</sup>. Because of these aspects, the authors found that depression scales should be validated specifically for use in this patient population.

The proposed study consisted of establishing a new cutoff point for the BDI in patients with PD. The instrument consists of 21 items, each graded 0-3, used for the establishment

of depressive symptoms. The authors argued that the BDI instrument was initially created as a tool for evaluating the severity of depressive symptoms, but can currently be used as a tool for screening and diagnosis of depression. The conclusion was that there is no single cutoff point to differentiate depressed from nondepressed PD patients. This problem can be extrapolated to other scales of depression, since they were not specifically developed for the diagnosis of depression in populations of patients with PD.

It is worthwhile to treat depression patients in DP? As previously mentioned, there is no validated diagnostic scale for depression in PD itself, so evaluating the results of any drug is at least controversial. However, because these studies have consistently shown that depression is the most striking quality of life factor, there is consensus that treatment is always indicated<sup>20-22</sup>.

The first aspect to be considered is whether to treat the depressive symptoms if they occur only during off periods (non-motor wearing-off). In this case, adjustment of antiparkinsonian medications is the most appropriate choice. The goal is to decrease the fluctuations of motor and non-motor symptoms<sup>17</sup>.

If depressive symptoms are not associated with fluctuations, the next step is to determine the severity of manifestations. In cases of mild depression, which are the majority, treatment is aimed to non-pharmacological measures as counseling and cognitive behavioral therapy<sup>23</sup>. A systematic review was recently published on the effect of physical activity in patients with PD. Although data regarding the effect on depressive symptoms are sparse or inconclusive, the evidence points to improved overall physical quality of life and gait<sup>23</sup>. In our practice, we recommend regular supervised aerobic physical activity for all patients with parkinsonism. Patients with somatic symptoms, such as insomnia, anxiety and weight loss, can benefit from the use of antidepressants<sup>4,20</sup>.

When depression is considered moderate, pharmacological treatment is indicated. In spite of the high prevalence of depression in PD, there are few controlled trials evaluating the efficacy of antidepressants in this population. The selective serotonin reuptake inhibitors (SSRI) and tricyclic antidepressants are the most studied, but in small or nonrandomized trials<sup>24,25</sup>. The results were generally positive, but showed modest effects<sup>26,27</sup>. A concern related to tricyclic antidepressants is the worsening of cognition and orthostatic hypotension, especially in patients with advanced disease<sup>28</sup>. Our practice is to prescribe tricyclic antidepressants with caution in patients over 65 years.

The SSRI are generally well tolerated despite some reports of worsening of parkinsonian symptoms, especially tremor with the use of sertraline and fluoxetine. Sertraline has been tested in an open study in depressed patients with PD. The drug was effective in decreasing all areas of the UPDRS and the HADS depression scale. Some patients experimented a worsening of

tremor, but the authors conclusion is towards a positive impact of the drug on motor and depressive symptoms<sup>25</sup>. There is no evidence of superiority of one SSRI in particular, but citalopram, escitalopram and sertraline have fewer drug interactions compared with paroxetine and fluoxetine<sup>26</sup>.

Nortriptyline and paroxetine extended-release tablets were tested in a randomized, placebo-controlled trial, in a recent study that lasted eight weeks. Although a relatively small group of patients was randomized, nortriptyline significantly reduced the scores of Hamilton depression scale, compared to placebo, while paroxetine was not superior to placebo. Nortriptyline was also superior to placebo on several secondary endpoints, including quality of sleep, anxiety and social functioning. The tolerability profile was considered good. The group that presented a satisfactory response to medication had a lower relapse of depression compared to placebo<sup>24</sup>.

Bupropion, an antidepressant that has dual mechanism of action, inhibiting the reuptake of norepinephrine and dopamine, seems to be a promising drug for the treatment of depressive manifestations in PD. Due to lack of serotonin action, there is no side effects such as drowsiness, weight gain and sexual dysfunction, a fact that possibly increases the adherence to treatment. Randomized studies are needed to confirm this hypothesis<sup>29</sup>.

Other antidepressants, such as mirtazapine, trazodone, duloxetine and venlafaxine, little studied in PD, can be used in place of other drugs in case of partial response or no response to initial treatment<sup>26</sup>.

The hypothesis that the use of dopamine agonists could lead to improvement of depressive symptoms in PD patients has been tested in clinical trials. A prospective multicenter study has shown that pramipexole in combination with levodopa significantly improved anhedonia in PD patients in advanced stages with major depression<sup>30</sup>.

Another study compared pramipexole with pergolide in reducing depressive symptoms. Both dopamine agonists have demonstrated antidepressant effects, measured by the Zung Depression Scale, but only pramipexole showed significant decrease in scale scores MADRS<sup>31</sup>.

The American Academy of Neurology recommends the use of amitriptyline for the treatment of depression in PD

although this medication is not well tolerated by some patients, especially in the elderly<sup>20</sup>. The Brazilian Academy of Neurology recommends the use of nortriptyline, but emphasizes the lack of sufficient evidence to support or refute the use of other drugs<sup>32</sup>. Recently, a committee of experts from the Movement Disorders Society published recommendations for the treatment of non-motor symptoms in PD. Pramipexole was considered efficacious, and nortriptyline and desipramine were considered probably efficacious. For most of the other interventions there is insufficient evidence to make adequate conclusions on their efficacy. This includes the tricyclic antidepressant amitriptyline, all selective serotonin reuptake inhibitors (SSRIs) reviewed (paroxetine, citalopram, sertraline and fluoxetine) and the newer antidepressants atomoxetine and nefazodone<sup>33</sup>.

The choice of antidepressant in our practice is done taking into account the characteristics and comorbidities of each patient. In younger patients with good cognition and tremor, we chose the tricyclic antidepressants, especially amitriptyline or nortriptyline. In elderly patients, in more advanced stages, who have comorbidities and potential interactions with other drugs, we chose the use of citalopram, escitalopram or sertraline. In patients whose major problem is sleep disturbance, we chose antidepressants with sedative action, including amitriptyline, mirtazapine and trazodone. In the case of chronic pain, we use amitriptyline or venlafaxine. When there is erectile dysfunction, overweight or daytime sleepiness, the drug being considered as the first choice is bupropion. In the case of comorbid anxiety disorder, the initial choice is the use of SSRI. In these cases, we prefer sertraline, citalopram or escitalopram.

Other treatment options are electroconvulsive therapy (ECT) and transcranial magnetic stimulation (TMS). The first, although there was no clinical trial, is reserved for severe and resistant depression and can be a saving measure. The second is promising, but needs further studies to prove its efficacy<sup>17,34</sup>.

We emphasize the importance of depression diagnosis in PD patients, because it is a treatable condition that negatively impacts the quality of life of these patients.

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