

## REVIEW ARTICLE

# Drug Choices and Advancements for Managing Depression in Parkinson's Disease

Francesca Assogna<sup>1,#</sup>, Clelia Pellicano<sup>1,2,#</sup>, Cinzia Savini<sup>1</sup>, Lucia Macchiusi<sup>1</sup>, Gaia R. Pellicano<sup>3</sup>, Marika Alborghetti<sup>4</sup>, Carlo Caltagirone<sup>1</sup>, Gianfranco Spalletta<sup>1</sup> and Francesco E. Pontieri<sup>1,4,\*</sup>

<sup>1</sup>Fondazione Santa Lucia, IRCCS, Via Ardeatina, 306-00179 Roma, Italy; <sup>2</sup>Neurology Unit, "Belcolle" Hospital, Str. Sarmartinese-01100 Viterbo, Italy; <sup>3</sup>Dipartimento di Psicologia Dinamica e Clinica, "Sapienza" Università di Roma, Via degli Apuli, 1-00185 Roma, Italy; <sup>4</sup>Dipartimento di Neuroscienze, Salute Mentale e Organi di Senso (NESMOS), "Sapienza" Università di Roma, Via di Grottarossa, 1035-00189 Roma, Italy

**Abstract:** Depression is a frequent non-motor symptom of Parkinson's disease (PD), and may even precede the onset of motor symptoms of parkinsonism. Beyond its negative influence on mood, depression in PD is frequently associated with other neuropsychiatric symptoms and with late-stage complications such as dementia. Despite its profound impact on the quality of life and cognitive functioning in PD, depression in PD is often under-recognized and poorly treated.

## ARTICLE HISTORY

Received: July 01, 2019  
Revised: August 27, 2019  
Accepted: October 15, 2019

DOI:  
10.2174/1570159X17666191016094857

Pathophysiological studies demonstrated that depression in PD is associated with global dysfunction of interactions between discrete brain areas rather than focal structural or functional abnormalities, and that it is sustained by pathological changes of several neurotransmitter/receptor complexes.

In general, all traditional antidepressants and some dopamine agonists have been found to be safe and well-tolerated to treat depressive symptoms in PD, despite initial warning on worsening of parkinsonism. Available data suggest that the time-course of response differs among antidepressants. Efficacy results from clinical trials with antidepressant in PD are, however, rather uncertain, although pooled analysis suggests a moderate benefit. Several issues may critically impact the results of clinical trials with antidepressants in PD, including the correct psychiatric diagnosis, the overlap of symptoms between depression and PD, and the selection of appropriate end-points and rating scales.

**Keywords:** Antidepressants, depression, non-motor symptoms, Parkinson's disease, quality of life, affective disorders.

## 1. INTRODUCTION

The cardinal motor symptoms of Parkinson's disease (PD), bradykinesia, rest tremor and rigidity, depend upon degeneration of dopaminergic neurons of the substantia nigra *pars compacta* (SNpc) in the mesencephalon [1]. Pathological studies demonstrated that the process of neural degeneration in the PD brain extends beyond the SNpc to involve other dopaminergic and non-dopaminergic nuclei [2], thus justifying additional motor and non-motor symptoms (NMS) of the disease [3].

Depression is a frequent NMS in both early and advanced stages of PD [4] and may represent a pre-motor marker of the disease [5]. The occurrence of depression in PD is

associated with increased risk of late-stage complications, such as dementia, falls, and caregiver distress [6, 7].

Prevalence rates for depression in PD range between 10 and 90% of cases [8, 9]. This apparent discrepancy depends on clinical and methodological issues, including the broad spectrum of depressive features and the overlap of symptoms between depression and PD. Strategies chosen to diagnose depression in PD may, indeed, affect prevalence rates. For instance, Hoogendijk and collaborators [10] reported significantly higher prevalence of major depressive disorder (MDD) in a cohort of 100 PD patients when using "inclusive" rather than "exclusive" criteria (23% vs. 13%), the former considering symptoms as related to depression regardless of possible overlap with PD or other medical conditions, and the latter excluding overlap of symptoms between depression and PD. Reijnders and collaborators [9] concluded that use of cut-off levels at rating scales rather than clinical diagnostic criteria for depression, such as those from the Diagnostic and Statistical Manual for Mental Disorders (DSM) (American Psychiatric Association 2000) or the International Classification

\*Address correspondence to this author at the Dipartimento di Neuroscienze, Salute Mentale e Organi di Senso, Sapienza Università di Roma, Via di Grottarossa, 1035-00189 Roma, Italy; Tel: (+39) 06 33775579; Fax: (+39) 06 33775272; E-mail [fe.pontieri@gmail.com](mailto:fe.pontieri@gmail.com)

#These Authors contributed equally to this work

of Diseases (ICD) (World Health Organization 2012), may lead to overestimation of prevalence of depression in PD. Within rating scales, self-reported instruments tended to increase prevalence with respect to observer-rated tools. As to gender differences, several studies demonstrated a higher prevalence of depression among females [11-13], although males affected by PD displayed stronger positive association with MDD and minor depression (MIND) than females [14]. These authors hypothesized that such apparently opposite effects may depend on the higher frequency of the different NMS investigated among females in normal aging cohorts.

Comorbidity with depression has a great negative impact on the quality of life (QoL) of PD patients and significantly affect prognosis [15], being considered a weighty and independent determinant of Health Related Quality of Life (HRQoL) in PD [16]. Despite the profound impact of depressive symptoms on HRQoL and cognitive functioning, depression in PD is often under-recognized and poorly treated [17-19]. Only 20 to 25% of depressed PD patients undergo nursing and antidepressant therapies [18] albeit successful treatment of depression has been shown to improve QoL and reduce disability in PD [20].

## 2. NEUROCHEMISTRY AND PATHOPHYSIOLOGY OF DEPRESSION IN PD

The issue of neurotransmitter/receptor systems involved in depression in PD is still controversial. The mesolimbic dopaminergic pathway and the complex network of interrelated systems, such as serotonergic, noradrenergic and opioid, among others, have been suggested to contribute to the development of depressive symptomatology [21]. Of note, polymorphisms of genes affecting synthesis, degradation, reception and transport of dopamine (*i.e.*, DRD4, DRD2/ANKK1, DAT1, and COMT) have been associated with a state of hypodopaminergia, leading to hedonic tone dysregulation of pleasure-related behaviors [21, 22]. As to PD, however, studies exploring the relationships between polymorphisms of genes related to dopaminergic transmission and depression did not achieve conclusive results [23]. However, there is initial evidence for a possible association between serotonin transporter gene polymorphisms and depression in PD [24, 25]. Furthermore, other genes may be implicated in PD depressive symptomatology, such as glucocerebrosidase gene (GBA) [26] and the dinucleotide repeat REP1 variant of  $\alpha$ -synuclein gene (SNCA-Rep1) [27].

Beyond possible relationships with genetic alterations, a variety of neuroimaging studies support the notion that depression in PD is associated with global dysfunction of interactions between discrete brain areas rather than focal structural or functional abnormalities.

Thus, SPECT and PET studies using tracers for dopamine system provided evidence of degeneration of the mesocorticolimbic dopaminergic projections to the ventral striatum, orbitofrontal cortex (OFCx), anterior cingulate cortex (ACCx) and thalamus in depressed PD subjects [28-31]. Findings on DAT imaging were, however, rather conflicting. Thus, DAT, binding in depressed PD patients was either reduced [32] suggesting greater dopaminergic denervation, or increased [33] as if abnormally high dopamine clearance

may, in turn, drive to reduced dopaminergic activity. Despite these controversies, the involvement of the dopaminergic mesocorticolimbic system in depression associated with PD appears unquestionable. In particular, the association between lower mood and greater D<sub>3</sub> versus D<sub>2</sub> receptor alteration in PD has been shown by PET binding assay [32]. Moreover, the involvement of the dopaminergic system has been demonstrated also in anxiety, suggesting a potentially common mechanism for affective dysfunction in PD patients [31].

The serotonergic system is also altered in depressed PD subjects, particularly in limbic areas, such as the temporal cortex and hippocampus, in frontal regions and in the raphe nuclei [34-36]. PET studies using the serotonin transporter ligand, [<sup>11</sup>C]-DASB, showed increased tracer binding in depressed PD subjects as if, excessive serotonin reuptake would occur [37]. Other PET studies demonstrated decreased postsynaptic 5-HT<sub>1A</sub> receptor density in limbic areas of depressed PD patients [38]. Further, indirect, evidence of the role of serotonergic system in depression in PD came from the observation of persistence of depression related to serotonergic impairment after restoration of dopaminergic innervation in grafted PD patients [31]. Conversely, a large [123I]-FP-CIT SPECT study found no association between serotonergic damage in the raphe nucleus and depression score in early-stage PD patients [39], suggesting that serotonergic involvement in the pathophysiology of depression in PD might be different according to disease progression and in general more pronounced in advanced stages.

Finally, a PET imaging study suggested the link between depression and norepinephrine damage in the locus coeruleus and its projection areas in the limbic system [32]. Because of the limited specificity of the tracer used for norepinephrine transporter this latter finding needs confirmation. In conclusion, alterations of all brainstem aminergic systems have been shown in depressed PD patients.

Brain MRI studies contributed also at identifying the brain anatomical and functional changes associated with depression in PD. As to cortical regions, research focused mostly on frontal and temporal lobes. Within the frontal lobe, several authors [40, 41] reported atrophy of the OFCx, correlating with the severity of depression scores. Other studies demonstrated atrophy of the dorsal portion of the ACCx [36] that plays a fundamental role in motivation, conflict monitoring, response initiation, social behavior and reward encoding, as well as the relationship between activity of the ventral ACCx and depression severity in PD [42], that may contribute at reducing initiative and motivation frequently observed in depressed PD subjects. As to the temporal lobes, atrophy of the amygdala and hippocampus may contribute to mood/emotion learning impairment in depressed PD subjects. The dysfunction of the amygdala may modify the connectivity and activity of fronto-parietal regions [43]. Finally, there is evidence of pathological involvement of subcortical nuclei and cortical-subcortical circuitries in depressed PD subjects. In particular, atrophy and hypoactivity of the limbic portions of the thalamus during emotional perception have been demonstrated [44, 45]. More recently, widespread reduction of connectivity in cortical-

subcortical limbic circuitries and increased connectivity between specific limbic areas (amygdala, limbic thalamus, temporal cortex) have been identified in depressed PD patients [46].

Functional studies on the OFCx in depressed PD patients gave, however, rather contradictory results. Thus, some reports showed hypometabolism and hypoperfusion of the OFCx in depressed PD subjects, as measured by [<sup>18</sup>F]-fluorodeoxyglucose ([<sup>18</sup>F]-FDG) or 99mTc hexamethylpropylene-amine-oxime (99mTc-HMPAO) SPECT [47, 48], whereas other fMRI studies demonstrated the increased resting-state activity of this cortical region [49]. This latter finding, however, may reflect abnormally increased top-down control over limbic and affective circuitries, in turn leading to abnormal behavior in primary depression patients [50]. Interestingly, depression scores in PD patients appear to be related to variations in the amplitude of low-frequency fluctuations measured by MRI at rest both in dorsolateral (DLPFCx) and ventromedial (VMPFCx) prefrontal cortices, as if executive dysfunction and impaired response selection would coexist with alteration in reward, emotion and perception processing in these subjects [51-53].

### 3. CLINICAL FEATURES OF DEPRESSION IN PD

Depression in PD is characterized by elevated degree of dysphoria, irritability and pessimism about future, with low levels of inadequacy and sense of guilt. As anticipated above, the diagnosis of depression in PD may be complicated by overlap of symptoms between the two conditions since they both include fatigue, loss of energy, psychomotor retardation, hypomimia, slowing of intellectual functions, difficulty in concentration, reduced appetite and insomnia. With this respect, Starkstein and colleagues [54] reported that somatic symptoms with the exception of “early morning awakening” and “loss of energy and slowing down” were rather specific of depression in PD. Moreover, “reduced appetite” and “early morning awakening” were somatic items with relatively high feasibility for discriminating between depressed and not depressed subjects, whereas “psychomotor slowdown”, “fatigue”, “physical anxiety” and “insomnia” displayed high prevalence but low discriminating properties. Kostic and colleagues [55] concluded that a quarter of PD patients died and/or had suicidal ideation. Although suicidal ideation is relatively common among PD patients, death by suicide is rare [56] with the possible exception of cases submitted to deep brain stimulation of the subthalamic nucleus [57, 58]. Finally, depressive symptoms in PD are more severe and frequent during the “off” as compared to “on” state [59].

Depression in PD is frequently associated with other psychopathologic symptoms. Alexithymia, defined as the inability to mentalize and symbolize emotions [60] is rather common in PD patients, affecting 18-24% of cases [61]. Significantly higher prevalence [61] and severity [62] of alexithymia were found in PD patients with MDD as compared to those affected by MIND or without depression (NODEP), despite the observation that depression and alexithymia may be independent phenomena [61, 63-65].

The association between apathy, anhedonia and depression is quite complex because of unclear diagnostic criteria

and potential overlap of symptoms among these neuropsychiatric disorders. In particular, there is evidence of the association between depression and apathy in PD, although apathy may occur also in the lack of depression [66-69]. The prevalence of apathy, defined as the lack of feeling, interest, concern and reduced energy, ranges between 17 and 70% of PD patients [67-71]. The prevalence of depression without apathy in PD is lower than apathy without depression [66, 72]. Eventually, anhedonia, defined as the inability to experience pleasure from activities usually found enjoyable [73, 74], is a key symptom of depression and apathy in PD patients. The prevalence of anhedonia in PD patients varies from 10 to 40% [75]. Some studies, however, highlighted the correlation between anhedonia and depression by showing higher levels of anhedonia in depressed PD patients as compared to not depressed cases [76, 77]. In particular, Lemke and colleagues [76, 78] reported a 46% prevalence of anhedonia in a cohort of 657 depressed and not depressed PD patients, that increased to 80% when only depressed cases were considered. Conversely, Isella and collaborators [72] failed to demonstrate significant relationships among anhedonia, depression and apathy, possibly because of the assumption of anhedonia as an independent construct.

### 4. PHARMACOLOGIC APPROACH TO DEPRESSION IN PD

Despite the high prevalence of depression in PD and its significant negative impact on functionality and QoL, studies investigating the tolerability, safety and efficacy of antidepressant drugs in PD patients have been limited for long. The most often studied drugs for depression in PD are selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants (TCA). Fewer studies focused on serotonin/norepinephrine reuptake inhibitors (SNRIs), dopamine agonists, trazodone, memantine, and atomoxetine [79-83].

Early reports showed the potential efficacy of SSRIs for the treatment of depression in PD, together with frequent worsening of motor symptoms of parkinsonism [84,85]. In 1998, Wermuth and colleagues [86] demonstrated the slight reduction of depressive symptomatology by citalopram in a placebo-controlled study in PD patients with clinical diagnosis of MDD and Hamilton Depression Rating Scale (HAM-D) score >13. Avila and colleagues [87] showed the improvement of depressive symptomatology, as measured by the Beck Depression Inventory (BDI) score, by both fluoxetine and nefazodone in PD subjects with MDD or dysthymia. Werneck and collaborators in 2009 [88] investigated the effects of the 5-HT<sub>2A/C</sub> antagonist, trazodone (50 mg, bid), on depression and motor functions in 20 depressed and NODEP PD subjects in a single-blind study. Apparently, trazodone improved depression and ameliorated motor functions in depressed patients solely.

A number of comparative studies were aimed at investigating the therapeutic potentials of antidepressant belonging to different pharmacological classes in PD. Antonini and collaborators in 2006 [89] investigated the tolerability, safety and efficacy of sertraline and low-dose amitriptyline on depression and QoL in 31 patients in a single-blind trial without placebo. Both drugs were safe and significantly reduced the HAM-D score at the end of the 12-week observation pe-

riod. Sertraline, but not amitriptyline, produced a significant positive effect on QoL, as measured by The 39-Item Parkinson's Disease Questionnaire (PDQ-39) scale. Devos and colleagues in 2008 [90] reported the improvement at the Montgomery-Asberg Depression Rating Scale (MADRS) scale by both citalopram and desipramine with respect to placebo in PD patients with MDD. Menza and colleagues (2009) [91] investigated the efficacy of paroxetine controlled-release, nortriptyline and placebo in 52 depressed PD patients. The primary outcomes were the change in the HAM-D and the percentage of responders at 8 weeks. Both drugs were well tolerated. Nortriptyline, but not paroxetine, was superior to placebo. Moreover, patients on nortriptyline significantly gained in physician-rate overall improvement, social functioning, sleep and anxiety. In these studies, however, tricyclic antidepressants, that inhibit the reuptake of serotonin and norepinephrine, were associated with cardiac, dysautonomic and anticholinergic side effects. In a multicenter Randomized Clinical Trial (RCT), Richard and colleagues (2012) [92] evaluated the efficacy and safety of paroxetine, a SSRI, and venlafaxine prolonged-release, a serotonin and norepinephrine reuptake inhibitor (SNRI) in the treatment of depression in 115 PD patients. All subjects met diagnostic criteria for depression (according to the DSM-IV criteria) and scored >12 on the first 17 items of the HAM-D. They were followed for 12 weeks, with maximum daily dosages of 40 mg for paroxetine and 225 mg for venlafaxine. The primary outcome measure was the change at the HAM-D from baseline to the end of the trial. Both treatments reached the endpoint, paroxetine being slightly more efficacious, were generally safe and well-tolerated, and did not affect motor symptoms of parkinsonism. Interestingly, there was a robust improvement in HAM-D score in the placebo group, as in other antidepressant treatment studies.

Weintraub and colleagues in 2010 [79] investigated the antidepressant activity of atomoxetine, a selective norepinephrine reuptake inhibitor. Fifty-five subjects with PD and an Inventory of Depressive Symptomatology Clinician (IDS-C) score  $\geq 22$  were randomized for 8 weeks to either atomoxetine (target dosage = 80 mg/day) or placebo. There was no significant effect on clinically relevant depressive symptoms, although atomoxetine produced a slight improvement in global cognitive performances and daytime sleepiness.

A conspicuous number of studies were oriented at evaluating the potential antidepressant activity of direct dopamine agonists. Rektorova and collaborators in 2003 [93] reported the improvement of MADRS-Zung score by pergolide and pramipexole in PD patients with mild to moderate depression that reached significance only in the pramipexole group, while Navan and collaborators in 2003 [94] demonstrated that either pramipexole or pergolide reduce PD rest tremor and they have beneficial effects on the Unified Parkinson's Disease Rating Scale-part III (UPDRS-III). Barone and colleagues in 2010 [95] further investigated the antidepressant activity of pramipexole (0.125-1.0 mg, t.i.d.) in a large multicenter, double-blind RCT. Mild-to-moderate, not fluctuating PD patients, maintained under stable antiparkinsonian medications and displaying depressive symptoms (15-items Geriatric Depression Scale - GDS score  $\geq 5$  and UPDRS-I depression item score  $\geq 2$ ) were randomized to either

pramipexole (n=139) or placebo (n=148). The primary endpoint was the change in BDI score. The results showed a direct effect of pramipexole on depressive symptoms and the authors interpreted such finding as an indicator of direct antidepressant efficacy of pramipexole in PD, despite the lack of clinical diagnosis of depression in enrolled subjects.

Rasagiline is a mono-amino-oxidase-B-inhibitor with therapeutic efficacy on motor symptoms in the early and advanced stages of PD. In a subset of patients enrolled in the ADAGIO study, Smith and collaborators (2015) [96] investigated the effects of the addition of rasagiline to antidepressant treatment in PD. Depression and cognition scores had a more favorable outcome in the rasagiline group as compared to placebo group. In particular, the effects on depression remained significant after controlling for the improvement in motor symptoms. There was also a not significant trend toward less worsening of apathy. Finally, there were no serious adverse events suggesting the occurrence of serotonin syndrome in the rasagiline-antidepressant group. In the ACCORDO study, Barone and collaborators (2015) [97] investigated the effects of rasagiline on depressive symptoms and cognition in non-demented PD patients displaying depressive symptoms. One-hundred-twenty-three PD patients were randomized to either rasagiline or placebo. Treatment was carried out for 12 weeks, and the primary endpoint was the change of the BDI score. There was no significant difference in the primary efficacy variable neither at any cognitive test.

The cumulative findings from the above studies were the matter of several reviews and meta-analyses. Based on the inconsistency of earlier reports, a Cochrane Review [98] concluded for insufficient data on the efficacy and safety of any antidepressant drug in PD. A further paper by Weintraub and colleagues in 2005 [99] outlined the large effect size of active treatment and placebo in PD patients, and the lack of evidence for the efficacy of antidepressant treatments in PD. In this latter study, increased age and diagnosis of MDD were apparently associated with a better response to treatment. Despite such limits, the meta-analysis concluded that PD patients might benefit from antidepressant drugs, in particular SSRIs.

An early systematic review by Rocha and collaborators 2013 [100] found the risk ratio (RR) for the response to antidepressant compared to placebo to be 1.36 (95% CI 0.98-1.87) across 5 studies in PD patients. Exclusion of studies carrying serious methodological biases allowed to increase RR up to 1.48 (95% CI 1.05-2.10). This latter finding pointed to the relevance of methodological rigor and reduction of biases (in particular, larger sample size, inclusion of patients with different disease severity, placebo-controlled design, longer follow-up periods and comparison of multiple agents) aimed at ensuring the reliability of results. The issue of efficacy and tolerability of SSRIs for the treatment of depression in PD was further reviewed by Skapinakis and collaborators in 2010 [101]. In this review and meta-analysis of the results of 10 RCTs, the authors concluded for a slight, not-significant difference between active treatments and placebo. False negative errors could not be excluded because of the limited number of studies and the small cumulative sam-

ple size. Consistently, the authors admitted insufficient evidence to reject the null hypothesis of no difference in efficacy between SSRIs and placebo.

Eight placebo-controlled RCTs investigating different pharmacological treatment for depression and anxiety in PD were cumulatively reviewed by Troeung and collaborators in 2013 [102]. When pooled across, citalopram, sertraline, desipramine, nortriptyline, paroxetine, and venlafaxine, the standard mean difference (SMD) for antidepressant vs. placebo was 0.69 (95% CI -1.51 to 2.93). When SSRIs were examined separately, the effect size was moderate (SMD 0.44, 95% CI -1.37 to 2.26). Tricyclic antidepressant (TCAs) however, had a stronger effect (SMD 1.36; 95% CI 0.19-2.52). These pooled analyses conclude that more studies with larger sample size and greater methodological rigor to improve the understanding of the effects of pharmacological therapy are needed. Moreover, despite the improvement of depressive symptoms, there is a concern as to the side effects of TCAs. Troeung and collaborators (2013) [102] systematically examined the efficacy of current treatments for depression and anxiety in PD. Nine trials were included. There was only sufficient data to calculate a pooled effect for antidepressant therapies. The pooled effect of antidepressants for depression in PD was moderate but non-significant ( $d = 0.71$ , 95% CI =21.33 to 3.08). The secondary effect of antidepressants on anxiety in PD was large but non-significant ( $d = 1.13$ , 95% CI =2.67 to 2.94). Two single-trials of non-pharmacological treatments for depression in PD resulted in significant large effects: Omega-3-unsaturated fatty acids supplementation, using a dose of 4 g/day of fish oil [103], ( $d=0.92$ , 95% CI=1.15 to 1.69) and cognitive behavioral therapy (CBT) ( $d=1.57$ , 95% CI=1.06 to 2.07), therefore warranting further exploration. Again, the authors concluded that the poverty of controlled trials for both pharmacological and non-pharmacological treatment of depression and anxiety in PD did not allow clear conclusions. While the pooled effects of antidepressant therapies in PD were non-significant, the moderate to large magnitude of each pooled effect was promising. Non-pharmacological approaches showed efficacy for depression in PD (see below). The majority of these studies, however, were classified as high risk of bias.

## 5. NON-PHARMACOLOGIC APPROACH TO DEPRESSION IN PD

The above-mentioned possibility of negative interactions between antidepressant drugs and parkinsonism encouraged research on non-pharmacological treatment of depression in PD [104-106]. Non-pharmacological treatments may either be applied alone or combined with traditional antidepressants [107, 108]. PD patients frequently report interest and positive feelings with such an approach [109].

Preliminary research (*i.e.*, case studies and uncontrolled trials) supported the efficacy of CBT for treating depression in PD [110-117]. The first RCT on CBT for treatment of depression, control group receiving clinical monitoring solely, carried out on 80 PD patients diagnosed with depression according to the DSM-IV criteria [117], demonstrated the significant efficacy (measured by changes at the HAM-D) of a 10-week CBT program that was still present at the

end of a 1-month follow-up. CBT showed also efficacy on secondary outcomes such as the BDI score, anxiety, quality of life, coping and PD symptom measures. A further study by Dobkin and colleagues in 2012 [118] confirmed the efficacy of CBT compared to clinical monitoring (without antidepressant treatment) over a 14-week observation period. In this study, the Clinical Global Impression-Improvement Scale was applied to quantify the improvement, and the authors identified caregiver participation as a factor influencing positively response to depression.

Group treatment offers several advantages for PD patients. Social interaction, mutual support and reciprocal validation may all benefit from group therapy. Furthermore, interactions with subjects experiencing similar difficulties help recognizing shared experiences and the universality of concern [119]. Finally, group treatment is more cost- and time-effective than individual treatment [120]. The results of a recent RCT demonstrated the efficacy of group CBT treatment on depression in PD subjects. These results were consistent with the post-treatment effect reported by Dobkin and colleagues in 2007, 2011 and 2012 [117, 118, 121] for individual CBT in PD. Moreover, Troeung and collaborators showed a delayed effect of CBT [122], full benefit manifesting in the period following completion of treatment. Overall, these results provide preliminary and promising support for the long-term efficacy and utility of CBT in PD.

The physical disability and the need to rely on caregivers for transportation may limit adherence of PD patients to CBT, in particular late along disease course. To overcome these limitations, some authors demonstrated the feasibility of delivering therapy and addressing depression problems in PD through the telephone [117, 123]. Telephone-based CBT was associated with significant improvement of depression, anxiety, negative thoughts, and coping. However, these effects were not coupled with significant benefits in measures of QoL, problem-focused coping, sleep, social support or caregiver burden.

Eventually, Sproesser and collaborators in 2010 [124] demonstrated the efficacy of psychodrama therapy, a psychological approach exploring problems, issues, concerns, desires and relationships between people and groups through dramatic action, on depression in PD patients. Within this setting, each subject in the group can become a therapeutic agent. In general, the benefits acquired during the psychotherapy provided reinforcement of more positive attitudes in relation to the illness and social environment.

## CONCLUSION AND PERSPECTIVES

Depression is one of the most frequent NMS in patients diagnosed with PD, with a significant negative impact on the subjective perception of disability, daily functioning, and QoL. Depressive symptoms may occur at any time along the disease course and may even precede the development of parkinsonism. Despite the high epidemiological impact and the severity of consequences, treatment of depression in PD mostly depends upon subjective feelings, evidence-based guidelines being rather poor. Nevertheless, clinicians keep prescribing medications for more than 20% of patients with depression in PD living at home and 50% living in institutions.

According to a recent Swedish registry study [125], SSRIs are most commonly prescribed, followed by mirtazapine.

The results from a number of studies converge on the observation that, in general, all traditional antidepressants are safe and well-tolerated in PD patients. This somehow contrasts with the initial warning on the worsening of parkinsonian motor symptoms, in particular tremor. Results are, however, rather uncertain as to the efficacy of antidepressants for successfully treating depression in PD.

Efficacy, compared to placebo, has been demonstrated for nortriptyline, venlafaxine extended release, desipramine, citalopram, and paroxetine, although the time course of the antidepressant response has differed. For example, nortriptyline demonstrated superiority to placebo in the short term (*i.e.*, after 8 weeks) [126, 127]. With this respect, identification of the long-term effects of maintenance treatment is critical; antidepressant treatment trials in all populations typically have a prominent placebo response, but the early placebo response is generally not sustained. Most treatment trials lasted 8-12 weeks and were intended to test the superiority of one intervention versus a comparator. By contrast, in clinical practice, patients are advised to expect changes in symptoms over time, with a full antidepressant response taking up to 12 weeks, followed by the continued improvement of any residual symptoms. The intervention is regarded as ineffective for that patient when a response is not observed within 12 weeks and the patient has received the maximum indicated doses. When the clinical response is insufficient, medication adjustments are indicated at any stage, including after the initial 12-week trial, and especially if there are indications of re-emergent depressive symptoms or relapse. This is even more relevant in the case of depression in PD, as the possible overlap of symptoms between the two conditions may further hamper identifying short term responders.

A number of studies recommended considering dopamine agonists for the treatment of depression in PD. A systematic review about the treatment of depressive symptoms in PD, concluded that pramipexole improves mood (as measured by the UPDRS scale) in 63% of patients compared to 45% in the placebo group. The effect was even more pronounced in subjects at advanced disease stage [128]. However, the lack of diagnostic criteria for depression in the majority of these studies and the questionability of the UPDRS to detect depression alone raise concern on these conclusions. Furthermore, the diagnosis of MDD was an exclusion criterion in all these studies. The largest placebo-controlled RCT with pramipexole was a 12-week study showing a significant difference of 1.9 in the BDI score favoring treatment over placebo [95]. Conversely, a recent study failed to demonstrate the improvement of depressive symptoms, as measured by the HAM-D, by rotigotine [129], whereas the other ergot or non-ergot dopamine agonists have been studied in smaller, not placebo-controlled studies, with rather inconsistent results. Finally, levodopa and rasagiline did not show any significant efficacy.

The issue of correct clinical diagnosis of depression is, to our opinion, fundamental for interpreting the results of previous studies as well as designing convincing trials in the future. As discussed earlier, overlap of motor and non-motor

features between depression and PD may seriously hamper precocious identification of neuropsychiatric comorbidity, and use of cut-off scores at rating scales as inclusion criterion may lead to overestimation of prevalence of depression and/or efficacy of therapeutic agents. Furthermore, findings from some studies suggest different neurochemical backgrounds of depression along disease course, with predominant involvement of dopamine system in the early and serotonin system in advanced stages.

Future pharmacological studies should, therefore, focus on more homogeneous cohorts of PD patients, with more strict diagnostic criteria for depression, based on structured psychiatric interviews according to validated international criteria, rating scale scores being only a tool to measure the severity of depressive symptoms.

Eventually, the pharmacological approach to depression in PD has been frequently limited by unimodal approaches aimed at manipulating a single neurotransmitter/receptor system in the brain. In a few instances, drugs acting on two systems (in most cases serotonin and norepinephrine) have been tested with rather inconclusive results. Such an approach clearly contrasts with scientific evidence indicating complex and widespread neurochemical, anatomic and functional changes associated with depression in PD. Thus, dysfunction of all aminergic systems has been shown in depressed PD patients, in turn modifying function of glutamate, GABA, acetylcholine and opiate systems, thus influencing negatively a variety of NMS, such as apathy, cognitive functions (prefrontal executive functions in particular), fatigue, and sleep disturbances. Consistently with this rather complex scenario, evaluation of therapeutic efficacy of antidepressants in PD should include measurement of a number of non-motor (and motor) domains, centered on the effects on QoL of affected subjects.

## CONSENT FOR PUBLICATION

Not applicable.

## FUNDING

This work was supported by grant from Ministero della Salute [GR-2016-02361783] to Francesca Assogna and Clelia Pellicano.

## CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

## ACKNOWLEDGEMENTS

Declared none.

## REFERENCES

- [1] Titova, N.; Padmakumar, C.; Lewis, S.J.G.; Chaudhuri, K.R. Parkinson's: A syndrome rather than a disease? *J. Neural Transm. (Vienna)*, **2017**, *124*(8), 907-914. <http://dx.doi.org/10.1007/s00702-016-1667-6> PMID: 28028643
- [2] Braak, H.; Rüb, U.; Gai, W.P.; Del Tredici, K. Idiopathic Parkinson's disease: Possible routes by which vulnerable neuronal types may be subject to neuroinvasion by an unknown pathogen. *J. Neural Transm. (Vienna)*, **2003**, *110*(5), 517-536.

- http://dx.doi.org/10.1007/s00702-002-0808-2 PMID: 12721813
- [3] Valappil, R.A.; Black, J.E.; Broderick, M.J.; Carrillo, O.; Frenette, E.; Sullivan, S.S.; Goldman, S.M.; Tanner, C.M.; Langston, J.W. Exploring the electrocardiogram as a potential tool to screen for premotor Parkinson's disease. *Mov. Disord.*, **2010**, *25*(14), 2296-2303.  
http://dx.doi.org/10.1002/mds.23348 PMID: 20976736
- [4] Schapira, A.H.V.; Chaudhuri, K.R.; Jenner, P. Non-motor features of Parkinson disease. *Nat. Rev. Neurosci.*, **2017**, *18*(7), 435-450.  
http://dx.doi.org/10.1038/nrn.2017.62 PMID: 28592904
- [5] Pellicano, C.; Benincasa, D.; Pisani, V.; Buttarelli, F.R.; Giovannelli, M.; Pontieri, F.E. Prodromal non-motor symptoms of Parkinson's disease. *Neuropsychiatr. Dis. Treat.*, **2007**, *3*(1), 145-152.  
http://dx.doi.org/10.2147/ndt.2007.3.1.145 PMID: 19300544
- [6] Pfeiffer, R.F. Non-motor symptoms in Parkinson's disease. *Parkinsonism Relat. Disord.*, **2016**, *22*(Suppl. 1), S119-S122.  
http://dx.doi.org/10.1016/j.parkreldis.2015.09.004 PMID: 26372623
- [7] Yapici Eser, H.; Bora, H.A.; Kuruoğlu, A. Depression and Parkinson disease: Prevalence, temporal relationship, and determinants. *Turk. J. Med. Sci.*, **2017**, *47*(2), 499-503.  
http://dx.doi.org/10.3906/sag-1603-101 PMID: 28425238
- [8] Starkstein, S.E.; Merello, M. Psychiatric and cognitive disorders in parkinson's disease. Cambridge University Press, **2002**.
- [9] Reijnders, J.S.; Ehart, U.; Weber, W.E.; Aarsland, D.; Leentjens, A.F. A systematic review of prevalence studies of depression in Parkinson's disease. *Mov. Disord.*, **2008**, *23*(2), 183-189.  
http://dx.doi.org/10.1002/mds.21803 PMID: 17987654
- [10] Hoogendijk, W.J.; Sommer, I.E.; Tissingh, G.; Deeg, D.J.; Wolters, E.C. Depression in Parkinson's disease. The impact of symptom overlap on prevalence. *Psychosomatics*, **1998**, *39*(5), 416-421.  
http://dx.doi.org/10.1016/S0033-3182(98)71300-3 PMID: 9775698
- [11] Barone, P.; Antonini, A.; Colosimo, C.; Marconi, R.; Morgante, L.; Avarello, T.P.; Bottacchi, E.; Cannas, A.; Ceravolo, G.; Ceravolo, R.; Cicarelli, G.; Gaglio, R.M.; Giglia, R.M.; Iemolo, F.; Manfredi, M.; Meco, G.; Nicoletti, A.; Pederzoli, M.; Petrone, A.; Pisani, A.; Pontieri, F.E.; Quatrala, R.; Ramat, S.; Scala, R.; Volpe, G.; Zappulla, S.; Bentivoglio, A.R.; Stocchi, F.; Trianni, G.; Dotto, P.D. The PRIAMO study: A multicenter assessment of nonmotor symptoms and their impact on quality of life in Parkinson's disease. *Mov. Disord.*, **2009**, *24*(11), 1641-1649.  
http://dx.doi.org/10.1002/mds.22643 PMID: 19514014
- [12] Martinez-Martin, P.; Falup Pecurariu, C.; Odin, P.; van Hilten, J.J.; Antonini, A.; Rojo-Abuin, J.M.; Borges, V.; Trenkwalder, C.; Aarsland, D.; Brooks, D.J.; Ray Chaudhuri, K. Gender-related differences in the burden of non-motor symptoms in Parkinson's disease. *J. Neurol.*, **2012**, *259*(8), 1639-1647.  
http://dx.doi.org/10.1007/s00415-011-6392-3 PMID: 22237822
- [13] Guo, X.; Song, W.; Chen, K.; Chen, X.; Zheng, Z.; Cao, B.; Huang, R.; Zhao, B.; Wu, Y.; Shang, H-F. Gender and onset age-related features of non-motor symptoms of patients with Parkinson's disease—a study from Southwest China. *Parkinsonism Relat. Disord.*, **2013**, *19*(11), 961-965.  
http://dx.doi.org/10.1016/j.parkreldis.2013.06.009 PMID: 23849500
- [14] Nicoletti, A.; Vasta, R.; Mostile, G.; Nicoletti, G.; Arabia, G.; Iliceto, G.; Lamberti, P.; Marconi, R.; Morgante, L.; Barone, P.; Quattrone, A.; Zappia, M. Gender effect on non-motor symptoms in Parkinson's disease: are men more at risk? *Parkinsonism Relat. Disord.*, **2017**, *35*, 69-74.  
http://dx.doi.org/10.1016/j.parkreldis.2016.12.008 PMID: 28017549
- [15] Weintraub, D.; Moberg, P.J.; Duda, J.E.; Katz, I.R.; Stern, M.B. Effect of psychiatric and other nonmotor symptoms on disability in Parkinson's disease. *J. Am. Geriatr. Soc.*, **2004**, *52*(5), 784-788.  
http://dx.doi.org/10.1111/j.1532-5415.2004.52219.x PMID: 15086662
- [16] Balestrino, R.; Martinez-Martin, P. Neuropsychiatric symptoms, behavioural disorders, and quality of life in Parkinson's disease. *J. Neurol. Sci.*, **2017**, *373*, 173-178.  
http://dx.doi.org/10.1016/j.jns.2016.12.060 PMID: 28131182
- [17] Shulman, L.M.; Taback, R.L.; Rabinstein, A.A.; Weiner, W.J. Non-recognition of depression and other non-motor symptoms in Parkinson's disease. *Parkinsonism Relat. Disord.*, **2002**, *8*(3), 193-197.  
http://dx.doi.org/10.1016/S1353-8020(01)00015-3 PMID: 12039431
- [18] Weintraub, D.; Moberg, P.J.; Duda, J.E.; Katz, I.R.; Stern, M.B. Recognition and treatment of depression in Parkinson's disease. *J. Geriatr. Psychiatry Neurol.*, **2003**, *16*(3), 178-183.  
http://dx.doi.org/10.1177/0891988703256053 PMID: 12967062
- [19] Pachana, N.A.; Egan, S.J.; Laidlaw, K.; Dissanayaka, N.; Byrne, G.J.; Brockman, S.; Marsh, R.; Starkstein, S. Clinical issues in the treatment of anxiety and depression in older adults with Parkinson's disease. *Mov. Disord.*, **2013**, *28*(14), 1930-1934.  
http://dx.doi.org/10.1002/mds.25689 PMID: 24123116
- [20] Menza, M.; Dobkin, R.D.; Marin, H.; Mark, M.H.; Gara, M.; Buy-ske, S.; Bienfait, K.; Dicke, A. The impact of treatment of depression on quality of life, disability and relapse in patients with Parkinson's disease. *Mov. Disord.*, **2009**, *24*(9), 1325-1332.  
http://dx.doi.org/10.1002/mds.22586 PMID: 19412944
- [21] Gold, M.S.; Blum, K.; Febo, M.; Baron, D.; Modestino, E.J.; Elman, I.; Badgaiyan, R.D. Molecular role of dopamine in anhedonia linked to reward deficiency syndrome (RDS) and anti-reward systems. *Front. Biosci. (Schol. Ed.)*, **2018**, *10*, 309-325.  
http://dx.doi.org/10.2741/s518 PMID: 29293435
- [22] Blum, K.; Gondré-Lewis, M.C.; Baron, D.; Thanos, P.K.; Braverman, E.R.; Neary, J.; Elman, I.; Badgaiyan, R.D. Introducing precision addiction management of reward deficiency syndrome, the construct that underpins all addictive behaviors. *Front. Psychiatry*, **2018**, *9*, 548.  
http://dx.doi.org/10.3389/fpsy.2018.00548 PMID: 30542299
- [23] Lim, E.W.; Tan, E.K. Genes and nonmotor symptoms in Parkinson's disease. *Int. Rev. Neurobiol.*, **2017**, *133*, 111-127.  
http://dx.doi.org/10.1016/bs.irm.2017.05.029 PMID: 28802918
- [24] Burn, D.J.; Tiangyou, W.; Allcock, L.M.; Davison, J.; Chinnery, P.F. Allelic variation of a functional polymorphism in the serotonin transporter gene and depression in Parkinson's disease. *Parkinsonism Relat. Disord.*, **2006**, *12*(3), 139-141.  
http://dx.doi.org/10.1016/j.parkreldis.2005.11.005 PMID: 16459126
- [25] Menza, M.A.; Palermo, B.; DiPaola, R.; Sage, J.I.; Ricketts, M.H. Depression and anxiety in Parkinson's disease: possible effect of genetic variation in the serotonin transporter. *J. Geriatr. Psychiatry Neurol.*, **1999**, *12*(2), 49-52.  
http://dx.doi.org/10.1177/089198879901200202 PMID: 10483924
- [26] Beavan, M.; McNeill, A.; Proukakakis, C.; Hughes, D.A.; Mehta, A.; Schapira, A.H.V. Evolution of prodromal clinical markers of Parkinson disease in a GBA mutation-positive cohort. *JAMA Neurol.*, **2015**, *72*(2), 201-208.  
http://dx.doi.org/10.1001/jamaneurol.2014.2950 PMID: 25506732
- [27] Dan, X.; Wang, C.; Zhang, J.; Gu, Z.; Zhou, Y.; Ma, J.; Chan, P. Association between common genetic risk variants and depression in Parkinson's disease: A dPD study in Chinese. *Parkinsonism Relat. Disord.*, **2016**, *33*, 122-126.  
http://dx.doi.org/10.1016/j.parkreldis.2016.09.029 PMID: 27745782
- [28] Kostić, V.S.; Agosta, F.; Petrović, I.; Galantucci, S.; Spica, V.; Jecmenica-Lukic, M.; Filippi, M. Regional patterns of brain tissue loss associated with depression in Parkinson disease. *Neurology*, **2010**, *75*(10), 857-863.  
http://dx.doi.org/10.1212/WNL.0b013e3181f11c1d PMID: 20686125
- [29] Frosini, D.; Unti, E.; Guidoccio, F.; Del Gamba, C.; Puccini, G.; Volterrani, D.; Bonuccelli, U.; Ceravolo, R. Mesolimbic dopaminergic dysfunction in Parkinson's disease depression: Evidence from a 123I-FP-CIT SPECT investigation. *J. Neural Transm. (Vienna)*, **2015**, *122*(8), 1143-1147.  
http://dx.doi.org/10.1007/s00702-015-1370-z PMID: 25613061
- [30] Wei, L.; Hu, X.; Yuan, Y.; Liu, W.; Chen, H. Abnormal ventral tegmental area-anterior cingulate cortex connectivity in Parkinson's disease with depression. *Behav. Brain Res.*, **2018**, *347*, 132-139.  
http://dx.doi.org/10.1016/j.bbr.2018.03.011 PMID: 29530489
- [31] Thobois, S.; Prange, S.; Sgambato-Faure, V.; Tremblay, L.; Brossolle, E. Imaging the etiology of apathy, anxiety, and depression in Parkinson's disease: Implication for treatment. *Curr. Neurol. Neurosci. Rep.*, **2017**, *17*(10), 76.  
http://dx.doi.org/10.1007/s11910-017-0788-0 PMID: 28822071
- [32] Remy, P.; Doder, M.; Lees, A.; Turjanski, N.; Brooks, D. Depression in Parkinson's disease: loss of dopamine and noradrenaline innervation in the limbic system. *Brain*, **2005**, *128*(Pt 6), 1314-1322.  
http://dx.doi.org/10.1093/brain/awh445 PMID: 15716302

- [33] Felicio, A.C.; Moriyama, T.S.; Godeiro-Junior, C.; Shih, M.C.; Hoexter, M.Q.; Borges, V.; Silva, S.M.; Amaro-Junior, E.; Andrade, L.A.; Ferraz, H.B.; Bressan, R.A. Higher dopamine transporter density in Parkinson's disease patients with depression. *Psychopharmacology (Berl.)*, **2010**, *211*(1), 27-31. <http://dx.doi.org/10.1007/s00213-010-1867-y> PMID: 20495790
- [34] Stark, A.J.; Smith, C.T.; Petersen, K.J.; Trujillo, P.; van Wouwe, N.C.; Donahue, M.J.; Kessler, R.M.; Deutch, A.Y.; Zald, D.H.; Claassen, D.O. [<sup>18</sup>F]fallypride characterization of striatal and extrastriatal D<sub>23</sub> receptors in Parkinson's disease. *Neuroimage Clin.*, **2018**, *18*, 433-442. <http://dx.doi.org/10.1016/j.nicl.2018.02.010> PMID: 29541577
- [35] Politis, M.; Wu, K.; Loane, C.; Turkheimer, F.E.; Molloy, S.; Brooks, D.J.; Piccini, P. Depressive symptoms in PD correlate with higher 5-HTT binding in raphe and limbic structures. *Neurology*, **2010**, *75*(21), 1920-1927. <http://dx.doi.org/10.1212/WNL.0b013e3181feb2ab> PMID: 21098407
- [36] Maillet, A.; Krack, P.; Lhommée, E.; Météreau, E.; Klingler, H.; Favre, E.; Le Bars, D.; Schmitt, E.; Bichon, A.; Pelissier, P.; Fraix, V.; Castrioto, A.; Sgambato-Faure, V.; Broussolle, E.; Tremblay, L.; Thobois, S. The prominent role of serotonergic degeneration in apathy, anxiety and depression in de novo Parkinson's disease. *Brain*, **2016**, *139*(Pt 9), 2486-2502. <http://dx.doi.org/10.1093/brain/aww162> PMID: 27538418
- [37] Boileau, I.; Warsh, J.J.; Guttman, M.; Saint-Cyr, J.A.; McCluskey, T.; Rusjan, P.; Houle, S.; Wilson, A.A.; Meyer, J.H.; Kish, S.J. Elevated serotonin transporter binding in depressed patients with Parkinson's disease: A preliminary PET study with [11C]DASB. *Mov. Disord.*, **2008**, *23*(12), 1776-1780. <http://dx.doi.org/10.1002/mds.22212> PMID: 18661545
- [38] Ballanger, B.; Klingler, H.; Eche, J.; Lerond, J.; Vallet, A.E.; Le Bars, D.; Tremblay, L.; Sgambato-Faure, V.; Broussolle, E.; Thobois, S. Role of serotonergic 1A receptor dysfunction in depression associated with Parkinson's disease. *Mov. Disord.*, **2012**, *27*(1), 84-89. <http://dx.doi.org/10.1002/mds.23895> PMID: 21994070
- [39] Pasquini, J.; Ceravolo, R.; Brooks, D.J.; Bonuccelli, U.; Pavese, N. Progressive loss of raphe nuclei serotonin transporter in early Parkinson's disease: A longitudinal 123I-FP-CIT SPECT study. *Parkinsonism Relat Disord.*, **2019**, *S1353-8020*(19), 30185-3.
- [40] Mayberg, H.S.; Starkstein, S.E.; Sadzot, B.; Preziosi, T.; Andrezejewski, P.L.; Dannals, R.F.; Wagner, H.N., Jr; Robinson, R.G. Selective hypometabolism in the inferior frontal lobe in depressed patients with Parkinson's disease. *Ann. Neurol.*, **1990**, *28*(1), 57-64. <http://dx.doi.org/10.1002/ana.410280111> PMID: 2375634
- [41] Luo, C.; Song, W.; Chen, Q.; Yang, J.; Gong, Q.; Shang, H.F. Cortical thinning in drug-naive Parkinson's disease patients with depression. *J. Neurol.*, **2016**, *263*(10), 2114-2119. <http://dx.doi.org/10.1007/s00415-016-8241-x> PMID: 27485171
- [42] Huang, P.; Xuan, M.; Gu, Q.; Yu, X.; Xu, X.; Luo, W.; Zhang, M. Abnormal amygdala function in Parkinson's disease patients and its relationship to depression. *J. Affect. Disord.*, **2015**, *183*, 263-268. <http://dx.doi.org/10.1016/j.jad.2015.05.029> PMID: 26042728
- [43] Cardoso, E.F.; Maia, F.M.; Fregni, F.; Myczkowski, M.L.; Melo, L.M.; Sato, J.R.; Marcolin, M.A.; Rigonatti, S.P.; Cruz, A.C. Jr.; Barbosa, E.R.; Amaro, E. Jr. Depression in Parkinson's disease: Convergence from voxel-based morphometry and functional magnetic resonance imaging in the limbic thalamus. *Neuroimage*, **2009**, *47*(2), 467-472. <http://dx.doi.org/10.1016/j.neuroimage.2009.04.059> PMID: 19398020
- [44] Li, W.; Liu, J.; Skidmore, F.; Liu, Y.; Tian, J.; Li, K. White matter microstructure changes in the thalamus in Parkinson disease with depression: A diffusion tensor MR imaging study. *AJNR Am. J. Neuroradiol.*, **2010**, *31*(10), 1861-1866. <http://dx.doi.org/10.3174/ajnr.A2195> PMID: 20705702
- [45] Hu, X.; Song, X.; Yuan, Y.; Li, E.; Liu, J.; Liu, W.; Liu, Y. Abnormal functional connectivity of the amygdala is associated with depression in Parkinson's disease. *Mov. Disord.*, **2015**, *30*(2), 238-244. <http://dx.doi.org/10.1002/mds.26087> PMID: 25545969
- [46] Kim, Y.D.; Jeong, H.S.; Song, I.U.; Chung, Y.A.; Namgung, E.; Kim, Y.D. Brain perfusion alterations in depressed patients with Parkinson's disease. *Ann. Nucl. Med.*, **2016**, *30*(10), 731-737. <http://dx.doi.org/10.1007/s12149-016-1119-2> PMID: 27566684
- [47] Liang, P.; Deshpande, G.; Zhao, S.; Liu, J.; Hu, X.; Li, K. Altered directional connectivity between emotion network and motor network in Parkinson's disease with depression. *Medicine (Baltimore)*, **2016**, *95*(30), e4222. <http://dx.doi.org/10.1097/MD.0000000000004222> PMID: 27472694
- [48] Kerestes, R.; Davey, C.G.; Stephanou, K.; Whittle, S.; Harrison, B.J. Functional brain imaging studies of youth depression: A systematic review. *Neuroimage Clin.*, **2013**, *4*, 209-231. <http://dx.doi.org/10.1016/j.nicl.2013.11.009> PMID: 24455472
- [49] Feldmann, A.; Illes, Z.; Kosztołanyi, P.; Illes, E.; Mike, A.; Kover, F.; Balas, I.; Kovacs, N.; Nagy, F. Morphometric changes of gray matter in Parkinson's disease with depression: A voxel-based morphometry study. *Mov. Disord.*, **2008**, *23*(1), 42-46. <http://dx.doi.org/10.1002/mds.21765> PMID: 17973326
- [50] Wen, X.; Wu, X.; Liu, J.; Li, K.; Yao, L. Abnormal baseline brain activity in non-depressed Parkinson's disease and depressed Parkinson's disease: A resting-state functional magnetic resonance imaging study. *PLoS One*, **2013**, *8*(5), e63691. <http://dx.doi.org/10.1371/journal.pone.0063691> PMID: 23717467
- [51] Luo, C.; Chen, Q.; Song, W.; Chen, K.; Guo, X.; Yang, J.; Huang, X.; Gong, Q.; Shang, H.F. Resting-state fMRI study on drug-naive patients with Parkinson's disease and with depression. *J. Neurol. Neurosurg. Psychiatry*, **2014**, *85*(6), 675-683. <http://dx.doi.org/10.1136/jnnp-2013-306237> PMID: 24227759
- [52] Starkstein, S.E.; Preziosi, T.J.; Forrester, A.W.; Robinson, R.G. Specificity of affective and autonomic symptoms of depression in Parkinson's disease. *J. Neurol. Neurosurg. Psychiatry*, **1990**, *53*(10), 869-873. <http://dx.doi.org/10.1136/jnnp.53.10.869> PMID: 2266368
- [53] Kostić, V.S.; Pekmezović, T.; Tomić, A.; Jecmenica-Lukić, M.; Stojković, T.; Spica, V.; Svetel, M.; Stefanova, E.; Petrović, I.; Džoljić, E. Suicide and suicidal ideation in Parkinson's disease. *J. Neurol. Sci.*, **2010**, *289*(1-2), 40-43. <http://dx.doi.org/10.1016/j.jns.2009.08.016> PMID: 19737673
- [54] Cummings, J.L. Depression and Parkinson's disease: a review. *Am. J. Psychiatry*, **1992**, *149*(4), 443-454. <http://dx.doi.org/10.1176/ajp.149.4.443> PMID: 1372794
- [55] Myslobodsky, M.; Lalonde, F.M.; Hicks, L. Are patients with Parkinson's disease suicidal? *J. Geriatr. Psychiatry Neurol.*, **2001**, *14*(3), 120-124. <http://dx.doi.org/10.1177/089198870101400304> PMID: 11563434
- [56] Funkiewiez, A.; Ardouin, C.; Caputo, E.; Krack, P.; Fraix, V.; Klingler, H.; Chabardes, S.; Foote, K.; Benabid, A.L.; Pollak, P. Long term effects of bilateral subthalamic nucleus stimulation on cognitive function, mood, and behaviour in Parkinson's disease. *J. Neurol. Neurosurg. Psychiatry*, **2004**, *75*(6), 834-839. <http://dx.doi.org/10.1136/jnnp.2002.009803> PMID: 15145995
- [57] Storch, A.; Schneider, C.B.; Wolz, M.; Stürwald, Y.; Nebe, A.; Odin, P.; Mahler, A.; Fuchs, G.; Jost, W.H.; Chaudhuri, K.R.; Koch, R.; Reichmann, H.; Ebersbach, G. Nonmotor fluctuations in Parkinson disease: severity and correlation with motor complications. *Neurology*, **2013**, *80*(9), 800-809. <http://dx.doi.org/10.1212/WNL.0b013e318285c0ed> PMID: 23365054
- [58] Bagby, R.M.; Parker, J.D.; Taylor, G.J. Dimensional analysis of the MMPI Alexithymia scale. *J. Clin. Psychol.*, **1991**, *47*(2), 221-226. PMID: 2030127
- [59] Assogna, F.; Palmer, K.; Pontieri, F.E.; Pierantozzi, M.; Stefani, A.; Gianni, W.; Caltagirone, C.; Spalletta, G. Alexithymia is a non-motor symptom of Parkinson disease. *Am. J. Geriatr. Psychiatry*, **2012**, *20*(2), 133-141. <http://dx.doi.org/10.1097/JGP.0b013e318209de07> PMID: 22273734
- [60] Costa, A.; Peppe, A.; Carlesimo, G.A.; Pasqualetti, P.; Caltagirone, C. Alexithymia in Parkinson's disease is related to severity of depressive symptoms. *Eur. J. Neurol.*, **2006**, *13*(8), 836-841. <http://dx.doi.org/10.1111/j.1468-1331.2006.01216.x> PMID: 16879293
- [61] Costa, A.; Peppe, A.; Carlesimo, G.A.; Salamone, G.; Caltagirone, C. Prevalence and characteristics of alexithymia in Parkinson's disease. *Psychosomatics*, **2010**, *51*(1), 22-28. [http://dx.doi.org/10.1016/S0033-3182\(10\)70655-1](http://dx.doi.org/10.1016/S0033-3182(10)70655-1) PMID: 20118437
- [62] Poletti, M.; Frosini, D.; Pagni, C.; Lucetti, C.; Del Dotto, P.; Tognoni, G.; Ceravolo, R.; Bonuccelli, U. The association between mo-



- tor subtypes and alexithymia in de novo Parkinson's disease. *J. Neurol.*, **2011**, *258*(6), 1042-1045.  
<http://dx.doi.org/10.1007/s00415-010-5878-8> PMID: 21188407
- [63] Poletti, M.; De Rosa, A.; Bonuccelli, U. Affective symptoms and cognitive functions in Parkinson's disease. *J. Neurol. Sci.*, **2012**, *317*(1-2), 97-102.  
<http://dx.doi.org/10.1016/j.jns.2012.02.022> PMID: 22503136
- [64] Kirsch-Darrow, L.; Fernandez, H.H.; Marsiske, M.; Okun, M.S.; Bowers, D. Dissociating apathy and depression in Parkinson disease. *Neurology*, **2006**, *67*(1), 33-38.  
<http://dx.doi.org/10.1212/01.wnl.0000230572.07791.22> PMID: 16832074
- [65] Dujardin, K.; Sockeel, P.; Devos, D.; Delliaux, M.; Krystkowiak, P.; Destée, A.; Defebvre, L. Characteristics of apathy in Parkinson's disease. *Mov. Disord.*, **2007**, *22*(6), 778-784.  
<http://dx.doi.org/10.1002/mds.21316> PMID: 17290451
- [66] Pedersen, K.F.; Alves, G.; Aarsland, D.; Larsen, J.P. Occurrence and risk factors for apathy in Parkinson disease: a 4-year prospective longitudinal study. *J. Neurol. Neurosurg. Psychiatry*, **2009**, *80*(11), 1279-1282.  
<http://dx.doi.org/10.1136/jnnp.2008.170043> PMID: 19864662
- [67] Drijgers, R.L.; Dujardin, K.; Reijnders, J.S.; Defebvre, L.; Leentjens, A.F. Validation of diagnostic criteria for apathy in Parkinson's disease. *Parkinsonism Relat. Disord.*, **2010**, *16*(10), 656-660.  
<http://dx.doi.org/10.1016/j.parkreldis.2010.08.015> PMID: 20864380
- [68] Aarsland, D.; Larsen, J.P.; Lim, N.G.; Janvin, C.; Karlsen, K.; Tandberg, E.; Cummings, J.L. Range of neuropsychiatric disturbances in patients with Parkinson's disease. *J. Neurol. Neurosurg. Psychiatry*, **1999**, *67*(4), 492-496.  
<http://dx.doi.org/10.1136/jnnp.67.4.492> PMID: 10486397
- [69] Pluck, G.C.; Brown, R.G. Apathy in Parkinson's disease. *J. Neurol. Neurosurg. Psychiatry*, **2002**, *73*(6), 636-642.  
<http://dx.doi.org/10.1136/jnnp.73.6.636> PMID: 12438462
- [70] Isella, V.; Melzi, P.; Grimaldi, M.; Iurlaro, S.; Piolti, R.; Ferrarese, C.; Frattola, L.; Appollonio, I. Clinical, neuropsychological, and morphometric correlates of apathy in Parkinson's disease. *Mov. Disord.*, **2002**, *17*(2), 366-371.  
<http://dx.doi.org/10.1002/mds.10041> PMID: 11921125
- [71] Snaith, R.P.; Hamilton, M.; Morley, S.; Humayan, A.; Hargreaves, D.; Trigwell, P. A scale for the assessment of hedonic tone the Snaith-Hamilton Pleasure Scale. *Br. J. Psychiatry*, **1995**, *167*(1), 99-103.  
<http://dx.doi.org/10.1192/bjp.167.1.99> PMID: 7551619
- [72] Lemke, M.R.; Fuchs, G.; Gemende, I.; Herting, B.; Oehlwein, C.; Reichmann, H.; Rieke, J.; Volkmann, J. Depression and Parkinson's disease. *J. Neurol.*, **2004**, *251*(Suppl 6), VI/24-7.  
<http://dx.doi.org/10.1007/s00415-004-1606-6> PMID: 15675721
- [73] Miura, S.; Kida, H.; Nakajima, J.; Noda, K.; Nagasato, K.; Ayabe, M.; Aizawa, H.; Hauser, M.; Taniwaki, T. Anhedonia in Japanese patients with Parkinson's disease: Analysis using the Snaith-Hamilton pleasure scale. *Clin. Neurol. Neurosurg.*, **2012**, *114*(4), 352-355.  
<http://dx.doi.org/10.1016/j.clineuro.2011.11.008> PMID: 22137783
- [74] Lemke, M.R.; Brecht, H.M.; Koester, J.; Kraus, P.H.; Reichmann, H. Anhedonia, depression, and motor functioning in Parkinson's disease during treatment with pramipexole. *J. Neuropsychiatry Clin. Neurosci.*, **2005**, *17*(2), 214-220.  
<http://dx.doi.org/10.1176/jnp.17.2.214> PMID: 15939976
- [75] Fujiwara, S.; Kimura, F.; Hosokawa, T.; Ishida, S.; Sugino, M.; Hanafusa, T. Anhedonia in Japanese patients with Parkinson's disease. *Geriatr. Gerontol. Int.*, **2011**, *11*(3), 275-281.  
<http://dx.doi.org/10.1111/j.1447-0594.2010.00678.x> PMID: 21241445
- [76] Lemke, M.R.; Brecht, H.M.; Koester, J.; Reichmann, H. Effects of the dopamine agonist pramipexole on depression, anhedonia and motor functioning in Parkinson's disease. *J. Neurol. Sci.*, **2006**, *248*(1-2), 266-270.  
<http://dx.doi.org/10.1016/j.jns.2006.05.024> PMID: 16814808
- [77] Weintraub, D.; Mavandadi, S.; Mamikonyan, E.; Siderowf, A.D.; Duda, J.E.; Hurtig, H.I.; Colcher, A.; Horn, S.S.; Nazem, S.; Ten Have, T.R.; Stern, M.B. Atomoxetine for depression and other neuropsychiatric symptoms in Parkinson disease. *Neurology*, **2010**, *75*(5), 448-455.  
<http://dx.doi.org/10.1212/WNL.0b013e3181ebdd79> PMID: 20679638
- [78] Costa, F.H.; Rosso, A.L.; Maultasch, H.; Nicaretta, D.H.; Vincent, M.B. Depression in Parkinson's disease: diagnosis and treatment. *Arq. Neuropsiquiatr.*, **2012**, *70*(8), 617-620.  
<http://dx.doi.org/10.1590/S0004-282X2012000800011> PMID: 22899034
- [79] Bomasang-Layno, E.; Fadlon, I.; Murray, A.N.; Himelhoch, S. Antidepressive treatments for Parkinson's disease: A systematic review and meta-analysis. *Parkinsonism Relat. Disord.*, **2015**, *21*(8), 833-842.  
<http://dx.doi.org/10.1016/j.parkreldis.2015.04.018> PMID: 26037457
- [80] Zhuo, C.; Xue, R.; Luo, L.; Ji, F.; Tian, H.; Qu, H.; Lin, X.; Jiang, R.; Tao, R. Efficacy of antidepressive medication for depression in Parkinson disease: a network meta-analysis. *Medicine (Baltimore)*, **2017**, *96*(22), e6698.  
<http://dx.doi.org/10.1097/MD.0000000000006698> PMID: 28562526
- [81] Vanle, B.; Olcott, W.; Jimenez, J.; Bashmi, L.; Danovitch, I.; IsHak, W.W. NMDA antagonists for treating the non-motor symptoms in Parkinson's disease. *Transl. Psychiatry*, **2018**, *8*(1), 117.  
<http://dx.doi.org/10.1038/s41398-018-0162-2> PMID: 29907742
- [82] Jiménez-Jiménez, F.J.; Tejero, J.; Martínez-Junquera, G.; Cabrera-Valdivia, F.; Alarcón, J.; García-Albea, E. Parkinsonism exacerbated by paroxetine. *Neurology*, **1994**, *44*(12), 2406.  
<http://dx.doi.org/10.1212/WNL.44.12.2406> PMID: 7991139
- [83] Simons, J.A. Fluoxetine in Parkinson's disease. *Mov. Disord.*, **1996**, *11*(5), 581-582.  
<http://dx.doi.org/10.1002/mds.870110517> PMID: 8866503
- [84] Wermuth, L.; Sorensen, P.S.; Timm, B.; Utzon, N.P.; Boas, J.; Dupont, E.; Magnussen, I.; Mikkelsen, B.; Worm-Petersen, J.; Lauritzen, L.; Bayer, L.; Bech, P. Depression in idiopathic Parkinson's disease treated with citalopram: a placebo-controlled trial Nordic. *J. Psychiatry*, **1998**, *52*(2), 163-169.  
<https://doi.org/10.1080/08039489850139049>
- [85] Avila, A.; Cardona, X.; Martín-Baranera, M.; Maho, P.; Sastre, F.; Bello, J. Does nefazodone improve both depression and Parkinson disease? A pilot randomized trial. *J. Clin. Psychopharmacol.*, **2003**, *23*(5), 509-513.  
<http://dx.doi.org/10.1097/01.jcp.0000088908.24613.db> PMID: 14520130
- [86] Werneck, A.L.; Rosso, A.L.; Vincent, M.B. The use of an antagonist 5-HT<sub>2a/c</sub> for depression and motor function in Parkinson' disease. *Arq Neuropsiquiatr.*, **2009**, *67*(2B), 407-12.  
<http://dx.doi.org/10.1590/s0004-282x2009000300007> PMID: 19623435
- [87] Antonini, A.; Tesi, S.; Zecchinelli, A.; Barone, P.; De Gaspari, D.; Canesi, M.; Sacilotto, G.; Meucci, N.; Mariani, C.; Pezzoli, G. Randomized study of sertraline and low-dose amitriptyline in patients with Parkinson's disease and depression: Effect on quality of life. *Mov. Disord.*, **2006**, *21*(8), 1119-1122.  
<http://dx.doi.org/10.1002/mds.20895> PMID: 16637039
- [88] Devos, D.; Dujardin, K.; Poirot, R.; Moreau, C.; Cottencin, O.; Thomas, P.; Destée, A.; Bordet, R.; Defebvre, L. Comparison of desipramine and citalopram treatments for depression in Parkinson's disease: A double-blind, randomized, placebo-controlled study. *Mov. Disord.*, **2008**, *23*(6), 850-857.  
<http://dx.doi.org/10.1002/mds.21966> PMID: 18311826
- [89] Menza, M.; Dobkin, R.D.; Marin, H.; Mark, M.H.; Gara, M.; Buy-ske, S.; Bienfait, K.; Dicke, A. A controlled trial of antidepressants in patients with Parkinson disease and depression. *Neurology*, **2009**, *72*(10), 886-892.  
<http://dx.doi.org/10.1212/01.wnl.0000336340.89821.b3> PMID: 19092112
- [90] Richard, I.H.; McDermott, M.P.; Kurlan, R.; Lyness, J.M.; Como, P.G.; Pearson, N.; Factor, S.A.; Juncos, J.; Serrano Ramos, C.; Brodsky, M.; Manning, C.; Marsh, L.; Shulman, L.; Fernandez, H.H.; Black, K.J.; Panisset, M.; Christine, C.W.; Jiang, W.; Singer, C.; Horn, S.; Pfeiffer, R.; Rottenberg, D.; Slevin, J.; Elmer, L.; Press, D.; Hyson, H.C.; McDonald, W. A randomized, double-blind, placebo-controlled trial of antidepressants in Parkinson disease. *Neurology*, **2012**, *78*(16), 1229-1236.  
<http://dx.doi.org/10.1212/WNL.0b013e3182516244> PMID: 22496199

- [91] Rektorová, I.; Rektor, I.; Bares, M.; Dostál, V.; Ehler, E.; Fanfardlová, Z.; Fiedler, J.; Klajblová, H.; Kulist'ák, P.; Ressler, P.; Svátová, J.; Urbánek, K.; Velísková, J. Pramipexole and pergolide in the treatment of depression in Parkinson's disease: a national multicentre prospective randomized study. *Eur. J. Neurol.*, **2003**, *10*(4), 399-406. <http://dx.doi.org/10.1046/j.1468-1331.2003.00612.x> PMID: 12823492
- [92] Navan, P.; Findley, L.J.; Jeffs, J.A.; Pearce, R.K.; Bain, P.G. Double-blind, single-dose, cross-over study of the effects of pramipexole, pergolide, and placebo on rest tremor and UPDRS part III in Parkinson's disease. *Mov. Disord.*, **2003**, *18*(2), 176-180. <http://dx.doi.org/10.1002/mds.10320> PMID: 12539211
- [93] Barone, P.; Poewe, W.; Albrecht, S.; Debieuvre, C.; Massey, D.; Rascol, O.; Tolosa, E.; Weintraub, D. Pramipexole for the treatment of depressive symptoms in patients with Parkinson's disease: a randomised, double-blind, placebo-controlled trial. *Lancet Neurol.*, **2010**, *9*(6), 573-580. [http://dx.doi.org/10.1016/S1474-4422\(10\)70106-X](http://dx.doi.org/10.1016/S1474-4422(10)70106-X) PMID: 20452823
- [94] Smith, K.M.; Eyal, E.; Weintraub, D. Combined rasagiline and antidepressant use in Parkinson disease in the ADAGIO study: effects on nonmotor symptoms and tolerability. *JAMA Neurol.*, **2015**, *72*(1), 88-95. <http://dx.doi.org/10.1001/jamaneurol.2014.2472> PMID: 25420207
- [95] Barone, P.; Santangelo, G.; Morgante, L.; Onofri, M.; Meco, G.; Abbruzzese, G.; Bonuccelli, U.; Cossu, G.; Pezzoli, G.; Stanzione, P.; Lopiano, L.; Antonini, A.; Tinazzi, M. A randomized clinical trial to evaluate the effects of rasagiline on depressive symptoms in non-demented Parkinson's disease patients. *Eur. J. Neurol.*, **2015**, *22*(8), 1184-1191. <http://dx.doi.org/10.1111/ene.12724> PMID: 25962410
- [96] Shabnam, G.N.; Th, C.; Kho, D.; H, R.; Ce, C. Therapies for depression in Parkinson's disease. *Cochrane Database Syst. Rev.*, **2003**, (3)CD003465. PMID: 12917968
- [97] Weintraub, D.; Morales, K.H.; Moberg, P.J.; Bilker, W.B.; Balderston, C.; Duda, J.E.; Katz, I.R.; Stern, M.B. Antidepressant studies in Parkinson's disease: a review and meta-analysis. *Mov. Disord.*, **2005**, *20*(9), 1161-1169. <http://dx.doi.org/10.1002/mds.20555> PMID: 15954137
- [98] Rocha, F.L.; Murad, M.G.; Stumpf, B.P.; Hara, C.; Fuzikawa, C. Antidepressants for depression in Parkinson's disease: systematic review and meta-analysis. *J. Psychopharmacol. (Oxford)*, **2013**, *27*(5), 417-423. <http://dx.doi.org/10.1177/0269881113478282> PMID: 23427193
- [99] Skapinakis, P.; Bakola, E.; Salanti, G.; Lewis, G.; Kyritsis, A.P.; Mavreas, V. Efficacy and acceptability of selective serotonin reuptake inhibitors for the treatment of depression in Parkinson's disease: a systematic review and meta-analysis of randomized controlled trials. *BMC Neurol.*, **2010**, *10*, 49. <http://dx.doi.org/10.1186/1471-2377-10-49> PMID: 20565960
- [100] Troeung, L.; Egan, S.J.; Gasson, N. A meta-analysis of randomised placebo-controlled treatment trials for depression and anxiety in Parkinson's disease. *PLoS One*, **2013**, *8*(11), e79510. <http://dx.doi.org/10.1371/journal.pone.0079510> PMID: 24236141
- [101] da Silva, T.M.; Munhoz, R.P.; Alvarez, C.; Naliwaiko, K.; Kiss, A.; Andreatini, R.; Ferraz, A.C. Depression in Parkinson's disease: a double-blind, randomized, placebo-controlled pilot study of omega-3 fatty-acid supplementation. *J. Affect. Disord.*, **2008**, *111*(2-3), 351-359. <http://dx.doi.org/10.1016/j.jad.2008.03.008> PMID: 18485485
- [102] Leo, R.J. Movement disorders associated with the serotonin selective reuptake inhibitors. *J. Clin. Psychiatry*, **1996**, *57*(10), 449-454. <http://dx.doi.org/10.4088/JCP.v57n1002> PMID: 8909330
- [103] Cole, K.; Vaughan, F.L. The feasibility of using cognitive behaviour therapy for depression associated with Parkinson's disease: a literature review. *Parkinsonism Relat. Disord.*, **2005**, *11*(5), 269-276. <http://dx.doi.org/10.1016/j.parkreldis.2005.03.002> PMID: 15970452
- [104] Oehlberg, K.; Barg, F.K.; Brown, G.K.; Taraborelli, D.; Stern, M.B.; Weintraub, D. Attitudes regarding the etiology and treatment of depression in Parkinson's disease: a qualitative study. *J. Geriatr. Psychiatry Neurol.*, **2008**, *21*(2), 123-132. <http://dx.doi.org/10.1177/0891988708316862> PMID: 18474721
- [105] Veazey, C.; Aki, S.O.; Cook, K.F.; Lai, E.C.; Kunik, M.E. Prevalence and treatment of depression in Parkinson's disease. *J. Neuro-psychiatry Clin. Neurosci.*, **2005**, *17*(3), 310-323. <http://dx.doi.org/10.1176/jnp.17.3.310> PMID: 16179652
- [106] Frisina, P.G.; Borod, J.C.; Foldi, N.S.; Tenenbaum, H.R. Depression in Parkinson's disease: health risks, etiology, and treatment options. *Neuropsychiatr. Dis. Treat.*, **2008**, *4*(1), 81-91. PMID: 18728814
- [107] Gupta, R. Treatment of depression in an elderly Asian Indian male: a cognitive behavioural approach. *Clin. Gerontol.*, **2000**, *22*(1), 87-90.
- [108] Heinrichs, N.; Hoffman, E.C.; Hofmann, S.G. Cognitive-behavioral treatment for social phobia in Parkinson's disease: A single-case study. *Cognit. Behav. Pract.*, **2001**, *8*(4), 328-335. [http://dx.doi.org/10.1016/S1077-7229\(01\)80005-5](http://dx.doi.org/10.1016/S1077-7229(01)80005-5) PMID: 16770438
- [109] Feeney, F.; Egan, S.; Gasson, N. Treatment of depression and anxiety in Parkinson's disease: a pilot study using group cognitive behavioural therapy. *Clin. Psychol.*, **2005**, *9*(1), 31-38. <http://dx.doi.org/10.1080/13284200500048240>
- [110] Dobkin, R.D.; Allen, L.A.; Menza, M. A cognitive-behavioral treatment package for depression in Parkinson's disease. *Psychosomatics*, **2006**, *47*(3), 259-263. <http://dx.doi.org/10.1176/appi.psy.47.3.259> PMID: 16684945
- [111] Farabaugh, A.; Locascio, J.J.; Yap, L.; Growdon, J.; Fava, M.; Crawford, C.; Matthews, J.; McCutchen, J.; Buchin, J.; Pava, J.; Alpert, J.E. Cognitive-behavioral therapy for patients with Parkinson's disease and comorbid major depressive disorder. *Psychosomatics*, **2010**, *51*(2), 124-129. <http://dx.doi.org/10.1176/appi.psy.51.2.124> PMID: 20332287
- [112] Mohlman, J.; Reel, D.H.; Chazin, D.; Ong, D.; Georgescu, B.; Tiu, J.; Dobkin, R.D. A novel approach to treating anxiety and enhancing executive skills in an older adult with Parkinson's disease. *Clin. Case Stud.*, **2010**, *9*(1), 74-90. <http://dx.doi.org/10.1177/1534650109351305> PMID: 20419071
- [113] Dobkin, R.D.; Menza, M.; Allen, L.A.; Gara, M.A.; Mark, M.H.; Tiu, J.; Bienfait, K.L.; Friedman, J. Cognitive-behavioral therapy for depression in Parkinson's disease: a randomized, controlled trial. *Am. J. Psychiatry*, **2011**, *168*(10), 1066-1074. <http://dx.doi.org/10.1176/appi.ajp.2011.10111669> PMID: 21676990
- [114] Dobkin, R.D.; Rubino, J.T.; Allen, L.A.; Friedman, J.; Gara, M.A.; Mark, M.H.; Menza, M. Predictors of treatment response to cognitive-behavioral therapy for depression in Parkinson's disease. *J. Consult. Clin. Psychol.*, **2012**, *80*(4), 694-699. <http://dx.doi.org/10.1037/a0027695> PMID: 22409644
- [115] Lewinsohn, P.M.; Clarke, G.N. Psychosocial treatments for adolescent depression. *Clin. Psychol. Rev.*, **1999**, *19*(3), 329-342. [http://dx.doi.org/10.1016/S0272-7358\(98\)00055-5](http://dx.doi.org/10.1016/S0272-7358(98)00055-5) PMID: 10097874
- [116] Oei, T.P.; Dingle, G. The effectiveness of group cognitive behaviour therapy for unipolar depressive disorders. *J. Affect. Disord.*, **2008**, *107*(1-3), 5-21. <http://dx.doi.org/10.1016/j.jad.2007.07.018> PMID: 17716745
- [117] Dobkin, R.D.; Allen, L.A.; Menza, M. Cognitive-behavioral therapy for depression in Parkinson's disease: a pilot study. *Mov. Disord.*, **2007**, *22*(7), 946-952. <http://dx.doi.org/10.1002/mds.21455> PMID: 17377926
- [118] Troeung, L.; Egan, S.J.; Gasson, N. A waitlist-controlled trial of group cognitive behavioural therapy for depression and anxiety in Parkinson's disease. *BMC Psychiatry*, **2014**, *14*, 19. <http://dx.doi.org/10.1186/1471-244X-14-19> PMID: 24467781
- [119] Veazey, C.; Cook, K.F.; Stanley, M.; Lai, E.C.; Kunik, M.E. Telephone-administered cognitive behavioral therapy: a case study of anxiety and depression in Parkinson's disease. *J. Clin. Psychol. Med. Settings*, **2009**, *16*(3), 243-253. <http://dx.doi.org/10.1007/s10880-009-9167-6> PMID: 19404724
- [120] Sproesser, E.; Viana, M.A.; Quagliato, E.M.; de Souza, E.A. The effect of psychotherapy in patients with PD: A controlled study. *Parkinsonism Relat. Disord.*, **2010**, *16*(4), 298-300. <http://dx.doi.org/10.1016/j.parkreldis.2009.08.008> PMID: 19864172
- [121] Ryan, M.; Eatmon, C.V.; Slevin, J.T. Drug treatment strategies for depression in Parkinson disease. *Expert Opin. Pharmacother.*, **2019**, *20*(11), 1351-1363. <http://dx.doi.org/10.1080/14656566.2019.1612877> PMID: 31120798

- [122] Haasum, Y.; Fastbom, J.; Johnell, K. Use of antidepressants in Parkinson's disease: A Swedish register-based study of over 1.5 million older people. *Parkinsonism Relat. Disord.*, **2016**, *27*, 85-88. <http://dx.doi.org/10.1016/j.parkreldis.2016.04.015> PMID: 27117031
- [123] Marsh, L. Depression and Parkinson's disease: current knowledge. *Curr. Neurol. Neurosci. Rep.*, **2013**, *13*(12), 409. <http://dx.doi.org/10.1007/s11910-013-0409-5> PMID: 24190780
- [124] Mills, K.A.; Greene, M.C.; Dezube, R.; Goodson, C.; Karmarkar, T.; Pontone, G.M. Efficacy and tolerability of antidepressants in Parkinson's disease: A systematic review and network meta-analysis. *Int. J. Geriatr. Psychiatry*, **2018**, *33*(4), 642-651. <http://dx.doi.org/10.1002/gps.4834> PMID: 29235150
- [125] Dobkin, R.D.; Menza, M.; Bienfait, K.L.; Gara, M.; Marin, H.; Mark, M.H.; Dicke, A.; Friedman, J. Depression in Parkinson's disease: symptom improvement and residual symptoms after acute pharmacologic management. *Am. J. Geriatr. Psychiatry*, **2011**, *19*(3), 222-229. <http://dx.doi.org/10.1097/JGP.0b013e3181e448f7> PMID: 20808132
- [126] Whitlock, M.E.; Woodward, P.W.; Alexander, R.C. Is high placebo response really a problem in depression trials? A critical re-analysis of depression studies. *Innov. Clin. Neurosci.*, **2019**, *16*(7-08), 12-17. PMID: 31832258
- [127] Li, F.; Nasir, M.; Olten, B.; Bloch, M.H. Meta-analysis of placebo response in adult antidepressant trials. *CNS Drugs*, **2019**, *33*(10), 971-980. <http://dx.doi.org/10.1007/s40263-019-00662-y> PMID: 31573058
- [128] Barone, P. Treatment of depressive symptoms in Parkinson's disease. *Eur. J. Neurol.*, **2011**, *18*(Suppl. 1), 11-15. <http://dx.doi.org/10.1111/j.1468-1331.2010.03325.x> PMID: 21255198
- [129] Chung, S.J.; Asgharnejad, M.; Bauer, L.; Ramirez, F.; Jeon, B. Evaluation of rotigotine transdermal patch for the treatment of depressive symptoms in patients with Parkinson's disease. *Expert Opin. Pharmacother.*, **2016**, *17*(11), 1453-1461. <http://dx.doi.org/10.1080/14656566.2016.1202917> PMID: 27322571