

Depression in Parkinson's Disease.

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Abstract : Depression is one of the commonest non-motor symptoms of Parkinson's disease (PD). Depression has a significant negative impact on the quality of life and outcome of PD patients. Etiopathology of depression in PD is still unclear. The syndrome is often under-recognized and untreated. Treatment of depression in PD is warranted and there are various viable treatment options. In this review we focus on the theories of aetiopathology, clinical diagnosis and management strategies of depression in PD. **Key words:** Depression, Parkinson's disease, Non-motor symptoms, Neuropsychiatry

INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disorder classically described as manifesting with rigidity, tremors, bradykinesia and postural instability. Though the non-motor symptoms were described by James Parkinson himself, it is only recently that much attention has been paid to them. Common non-motor symptoms are apathy, anxiety, depression, and cognitive impairment and they contribute significantly to the suffering of the patients¹.

The relationship between the depression and PD is well known. Depression leads to increased morbidity, poor quality of life, increased health care costs, and also increased mortality of Parkinson's patients. At the same time, it is underestimated and also undertreated². In this review we are discussing the etio-pathology, clinical correlates, and management of depression in Parkinson's disease (dPD).

EPIDEMIOLOGICAL ASPECTS

Studies done to assess the prevalence of dPD have given a wide prevalence range, depending on the study sample and diagnostic tools used. Community based studies have lowest figures. In PRIAMO study, 1072 hospital based patients were assessed and the prevalence of depression was 22.5%³. In their Meta-analysis, Slaughter et al. (2001) reported a prevalence rate of 31%. Depression is also related to fluctuations in the motor symptoms of PD, off-period carrying more risk of depression. Several studies have also revealed that PD patients were more depressed than patients suffering from other neurological illnesses and various medical/surgical conditions. Several risk factors for depression have been described, such as female sex, onset of PD before 40 years of age, cognitive impairment, and history of depression before onset of PD. Depressive symptoms may be encountered during any stage of PD, yet many times they may precede the motor symptoms for years⁴.

AETIOLOGY OF DEPRESSION IN PD

Aetiology of depression in PD is not clearly understood. Both neurobiological and psychosocial theories are put forward, with no conclusive evidences. Both the theories and research evidences supporting them are discussed below.

Psychosocial model postulates that depression is a reaction of the

person to the diagnosis and symptoms of PD, and is related to the duration and severity of the symptoms and the disability due to PD. Some studies have shown a significant relationship between the PD severity and depression, however, many have failed to find any relationship between the duration of PD and depression. Studies correlating the depression in PD with the disability in PD are also not conclusive¹. Interestingly psychosocial variables like amount of social support, coping style are found to be better predictors of depression in PD. Ehmann et al. (1990) in their study found that after controlling for functional disability, PD patients who used avoidant coping style were more depressed than the Rheumatoid Arthritis patients, who used more cognitive coping styles. Moreover, when PD patients used cognitive coping styles, there were significant improvement in depression, disability and social interaction⁵.

Neurobiological model argues that depression may be a manifestation of structural and functional changes of brain in PD. One potential theory is of Monoamine neurotransmitter imbalances. Earlier studies have shown low levels of 5HIAA in PD patients with major depression than those without, however further studies did not agree with the results. Remy et al. (2005) used [¹¹C] RTI-32 PET, an *in vivo* marker of dopamine and noradrenaline transporter binding, to localize the differences between depressed and non-depressed PD patients. Study revealed that the depressed patients had lower binding than non-depressed in limbic system and locus ceruleus. They suggested loss of dopamine and noradrenaline innervations in limbic system as a possible cause of depression in PD patients. Other neuroanatomical studies have shown metabolic abnormalities in PET scans in both caudate and inferior frontal cortices and lower metabolic activity in prefrontal cortex of dPD patients⁶. Criticism against these studies is that they have compared the depressed PD patients with non-depressed PD patients, but not with the patients with major depression without any neurological illness and hence the neuroanatomical changes may be due to depression per se and not a part of PD.

Psychopharmacology has often provided us with the insight into the neurobiology of psychiatric disorders. Tricyclic antidepressants (TCAs) have been shown to reduce both motor and affective symptoms of PD. The improvement in depressive symptoms is due to reuptake inhibition of both nor-adrenaline and serotonin, whereas improvement in motor symptoms is due to the nor-adrenaline mediated, indirect elevation of dopamine levels in basal ganglia¹. Selective Serotonin Reuptake Inhibitors (SSRIs) have also, to some extent proven their efficacy for the treatment of dPD. They are not effective in reducing motor symptoms, as they have no nor-adrenergic

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role⁷. Ropinirole and Pramipexole, dopamine agonists are not only effective for the motor symptoms but also for the depressive symptoms of PD⁸. These evidences from psychopharmacological agents support the role of neurotransmitters and hence the neurobiological hypothesis of dPD.

CLINICAL FEATURES AND ASSESSMENT OF DPD

Diagnosing depression in PD is difficult. Many signs of depression like fatigue, reduced activity, and reduced concentration, lack of sleep and lack of appetite may be caused by PD also. Patients often do not complain of depressive symptoms even when they are suffering with depression. Brod et al. (1998) showed that only 11% of the depressed PD patients considered depression as a health problem. Caregivers also may not report depression, thinking it to be just reaction to the physical problems. Physicians and neurologists are also not sensitive towards the depressive symptoms⁹. In a study by Bouwmans and Weber (2012), neurologists had low sensitivity and high specificity in identifying depression, compared to patients¹⁰. Also, there are no standard diagnostic guidelines specifically designed to diagnose depression in PD. As already emphasised, depression can occur at any stage of PD, sometimes even before the onset of motor symptoms. Depressive symptoms may be more severe in “off” phase, and may improve with “on” phase. The symptoms of depression in PD are different from that of depressive patients without PD. Depressive PD patients experience less guilt and self-reproach. Completed suicide is rare in this group of patients. Agitation, irritability, worry about health are more common¹¹.

DSM-IV TR is the most frequently used diagnostic guideline for the depression in PD, though not specifically designed for this purpose. NINDS/NIMH working group on depression and PD have made following recommendations¹²; I) The diagnosis of dPD should be made according to DSM criteria using an inclusive approach, using all symptoms irrespective of potential aetiological basis, as it has the greatest sensitivity and reliability and does not require clinical judgment; II) subsyndromal depression should be included as a diagnostic category in research studies; III) the timing of assessment should be specified (“on” versus “off”- periods) (it should however be noted that most instruments specify e”2 weeks as a time frame); IV) informants should be used for cognitively impaired patients; and V) anhedonia should only be diagnosed based on loss of pleasure rather than loss of interest (as it overlaps with apathy) for diagnosis of minor depression/subsyndromal depression. However, these modifications need to be validated.

Rating scales are useful tools in diagnosing depression in PD. They can be administered by clinician or can be self-reported. They do not need clinical judgement. Williams et al. (2012) compared the psychometric property of 9 commonly used depression scale, which consisted of 6 self-report scales (Beck Depression Inventory [BDI]-II, Centre for Epidemiologic Studies Depression Rating Scale-Revised [CESD-R], 30-item Geriatric Depression Scale [GDS-30], Inventory of Depressive Symptoms-Patient [IDS-SR], Patient Health Questionnaire-9 [PHQ-9], and Unified Parkinson’s Disease Rating Scale [UPDRS]-Part I) and 3 clinician-rated scales (17-item Hamilton Depression Rating Scale [HAM-D-17], Inventory of Depressive Symptoms- Clinician [IDS-C], and Montgomery-Åsberg Depression Rating Scale [MADRS]). They concluded that, the GDS-30 to be most efficient depression screening scale to use in PD because of its

brevity, favourable psychometric properties, and lack of copyright protection. However, all scales studied, except for the UPDRS Depression, were found to be valid screening tools when PD-specific cut-off scores are used¹³.

MANAGEMENT OF DEPRESSION IN PD

Do we need to treat depression in PD? The question arises because of the diagnostic confusion and lack of evidence based treatment options. Nevertheless, depression is one of the commonest NMS and one of the most important factors that affect the quality of life of PD patients. Hence there is an argument favouring the treatment of depression¹⁴. A treatment algorithm for depression in PD is given n

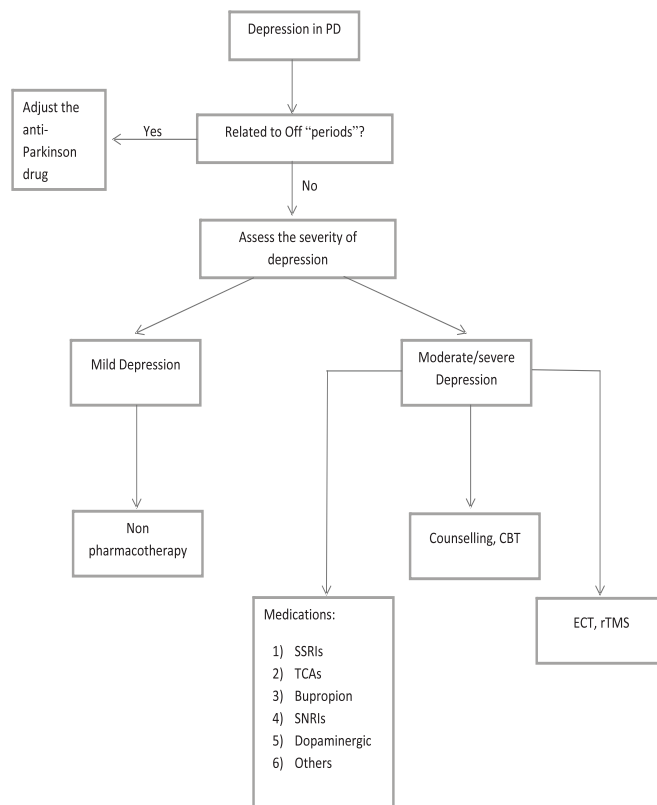


Figure 1: management algorithm of depression in PD.

figure no. I

PHARMACOTHERAPY FOR DEPRESSION IN PD

The research pertaining to the treatment of dPD is sparse. An old meta-analysis by Klaassen et al. (1995)¹⁵, found only 12 well-designed, placebo-controlled, double blind studies, all of which studied the efficacy of TCAs. A recent Cochrane review found only 3 studies eligible for inclusion. The total number of patients in these three studies was 106. Review concluded that, nortriptyline was superior to placebo but citalopram was not¹⁶.

Tricyclic antidepressants (TCAs) have been shown to be effective in management of depression in PD. In a double-blind placebo controlled study, imipramine improved the depressive symptoms for 60% of the patients. This study also found that antidepressant therapy

had a beneficial effect on rigidity, tremors, and akinesia. Desipramine also improved both depressive and motor symptoms of PD in a double-blind, placebo controlled study. The group of patients in whom depression responded to TCAs also had improvement in motor symptoms¹⁷. Hence, it is evident that, TCAs not only improve depression but also motor symptoms of PD. However, side effects of TCAs are frequent and significant. Dry mouth, constipation, urinary retention, sedation, confusion, cardiac arrhythmias, and orthostatic hypotension make them less suitable for many patients.

Selective serotonin Reuptake Inhibitors (SSRIs) have replaced TCAs in management of idiopathic depression due to their tolerability. There are several open labelled clinical studies supporting the use of SSRIs in dPD. Placebo controlled double blind studies are few. In a placebo-controlled trial on PD patients suffering with major depression, citalopram or placebo was administered to an average of 10 subjects in each group over the course of 52 weeks. There were no significant group differences on measures of depression, motor function, or adverse side effects. The fact worth considering is that, at study outset, 60% of the sample consisted of patients with severe recurrent brief depression, which lasted for 2–3 days. Perhaps a treatment effect was not observed because depression would have subsided in the majority of patients after several days. Hence, this trial can be criticized for containing sampling error¹⁸.

Another placebo controlled study, comparing citalopram (n=6) and placebo (n=4), also reported no significant group differences in the measures of depression and motor functions. Because of a very small sample size, the non-significant findings could have been due to lack of statistical power. In another study, Rampello et al. (2002) observed that citalopram improved motor performance for both depressed (n = 18) and non-depressed (n = 14) PD patients relative to a non-depressed placebo (n = 14) control group. Depression was significantly reduced for the depressed PD subgroup¹⁹. There are also rare reports of worsening of motor symptoms with SSRIs.

Bupropion, which is a noradrenergic and dopaminergic antidepressant, is a promising agent. This agent lacks the side effects due to serotonin like drowsiness, sexual dysfunction, weight gain etc. Theoretically, it may also improve the motor symptoms of PD by its dopaminergic actions. However, well designed studies are needed to prove its efficacy. Other antidepressants like mirtazapine, SNRIs, trazodone have not been studied in PD. They can be tried in patients who have shown no or partial response to standard agents²⁰. Dopaminergic agents have also been shown to be effective for the depressive symptoms of PD. D2/D3 agonists like pramipexole and pergolide are found to reduce depression in PD. A prospective study showed that pramipexole along with levodopa significantly improved anhedonia in PD patients²¹.

The American Academy of Neurology recommends amitriptyline for the treatment of depression in PD despite of its tolerability issues. The Brazilian Academy of Neurology recommends nortriptyline, whereas a committee of experts from the Movement Disorders Society considered pramipexole as efficacious and nortriptyline and desipramine were considered probably efficacious²². The choice should be made on the patient profile. In a young patient with good cognition and no tremor, tricyclic antidepressants can be chosen. In older patients with multiple comorbidities SSRIs like citalopram or escitalopram can be better options. Where insomnia is a problem and sedation is desirable, mirtazapine, amitriptyline can be started. Sexual dysfunctions, day time drowsiness warrant the use of bupropion.

BRAIN STIMULATION TECHNIQUES

Apart from drugs, many other treatment modalities have been tried in for treating depression in PD, with varying success. Electro Convulsive Therapy (ECT) was effective in reducing depressive symptoms in 70% of the patients across 21 studies reviewed by Faber and Trimble (1991). ECT also significantly reduced the depressive symptoms in another study which included 25 depressed PD patients. Electrically induced seizures seem to increase the serotonin and norepinephrine levels in brain, improving the depressive symptoms. Norepinephrine in-turn increases the dopamine levels, helping the motor symptoms also. Many trials have shown the improvement in motor symptoms with ECT²³. However there are no double blind, randomised controlled trials on ECT. Treatment with ECT may have some disadvantages. Delirium is one such example. It is not recommended as a first line therapy and is reserved for severely depressive patients, highly suicidal patients and those not responding to drugs.

Repetitive Transcranial Magnetic Stimulation (rTMS) is a novel mode of non-pharmacotherapy of depression. It is safer than ECT and obviates the need for anaesthesia. There is limited evidence of rTMS being effective in treatment of dPD²⁴. Further research is needed to establish the role of rTMS in dPD.

PSYCHOTHERAPIES FOR DEPRESSION IN PD

Various methods of psychotherapies have been applied for treatment of idiopathic depression. A randomised controlled trial compared efficacy of CBT (n=40) versus clinical monitoring (n=40) and reported greater symptom reduction in patients who underwent CBT, suggesting that CBT is a viable option in this group of patients. They concluded that available evidence is encouraging for the effectiveness of CBT in the patients of dPD. They raised concern about the applicability of therapy in patients with patients of cognitive impairment, feasibility in patients with motor and non-motor complications and need for modifications in therapy techniques to suit this population. Relaxation training and individual talks from a multidisciplinary team of therapists reduced the depressive symptoms significantly²⁵.

Psychotherapy is a promising area which needs to be explored further with well-designed studies. CBT has shown promising results in initial studies, many more studies are needed to establish its efficacy. Modifications to suit the need of this special group of patients are also need to be looked into.

FUTURE DIRECTIONS

A little has been understood about the etio-pathology and management of depression in PD, still there is a long way to go. Sensitising the physicians and neurologists to identify the syndrome of depression in PD is the basic need. Understanding the neurobiology, establishing a valid diagnostic guideline are the essential steps. Large number of researches should be dedicated towards identifying the efficacy of antidepressants and brain stimulation techniques. Tailor made, evidence based psychotherapies should be established.

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