

Depression in Parkinson's disease

Depression in Parkinson's disease is common, under recognised and under treated. Depression significantly impairs quality of life and increases the burden on caregivers. This article draws on recent research to update clinicians and aims to improve the recognition and overall management of depression in Parkinson's disease.

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This paper reviews the literature on depression in Parkinson's disease and articles were searched from 1980 till 2011 in medical databases from medline, medscape, pubmed and epub with the key words of depression in Parkinson's disease. Only articles in English were included in the review.

Background

Parkinson's disease (PD) is a neurodegenerative disease primarily of the nigrostriatal system. Research in PD is increasingly focused on non-motor symptoms for example neuropsychiatric and sleep disorders, fatigue, those involving bowel and urinary function. Neuropsychiatric disorders such as depression are common in PD and it is one of the major determinants of health-related quality of life in PD patients and has significant impact on quality of life, independent of the disease severity and medication influence.¹ Clinicians treating patients with PD have difficulty in recognising if they are depressed and if the diagnosis is reached then treatment is challenging. The research base for managing depression is scant hence the need to provide a review to guide clinicians.

Prevalence of depression in PD

Reported prevalence of depression in PD ranges between 2.7% and 90%² but the mean prevalence is about 40%. The marked variability in the prevalence of depression is associated with the use of different definitions of depression, thresholds for identification of a mood disorder, and assessment strategies especially before the standardised rating scales for the diagnosis of depression in PD.²⁻⁵ In a meta-analysis² major depression was recorded as 17% with minor depression as 22% and dysthymia 13%. DSM-IV is used to define and diagnose depression in PD and if

these criteria are not strictly applied then the prevalence of depression in PD is 35%. In a recent hospital based study the prevalence of severe depression in PD was 41.3% and mild to moderate depression 4.3% each, although higher prevalence of severe depression may have resulted from sampling bias of tertiary referral centre and the sample size of the study was small with cross-sectional design.⁶ The overlap between the motor symptoms of PD and those of depression can lead patients, their carers and clinicians to mistake the symptoms of depression as features of their neurodegenerative illness rather than as an associated mood disorder meriting treatment in its own right.⁷

Impact on quality of life

Several studies have shown that depression is a major cause of impairment of quality of life in PD⁸⁻¹¹ and it increases the carer burden.¹²⁻¹³ Other factors such as disability, disease severity and cognitive impairment also affect quality of life.¹⁴ Depression in PD contributes significantly towards patients' disability and depressed PD patients can have rapid disease progression, memory difficulties, cognitive decline and increased mortality.¹⁵ Yamamoto suggested that depression impairs quality of life more than the severity of disease.¹⁶ Care givers burden score will increase with severity of illness and depression in the PD patient¹⁷ and the carers of these depressed PD patients also reported to have high incidence of depression.¹⁸

Symptoms of depression in PD

There are certain characteristic risk factors that are associated with the depression in PD such as female sex, high Hoehn and Yahr score (more severe disease), cognitive impairment, high axial bradykinesia, gait and balance impairment, and previous personal history of depression

can predict the onset of depression in PD.¹⁹⁻²² However, Farabaugh et al in their recent study suggested that duration of PD, younger age, and especially history of depression predicted the prevalence of depression in PD and gender (female) was not a significant risk factor.²³

Depression in PD may manifest as loss of interest and ability to enjoy (anhedonia), a feeling of emptiness, and loss of concentration. There are increased levels of irritability and pessimism but less feelings of guilt and self-blame and a low suicide rate despite some suicidal ideation.^{24,25} However, in a study of more than 5000 patients of PD who underwent deep brain stimulation (DBS) of subthalamic nucleus (STN) and had postoperative depression, suicide rate was increased so caution is advised in the presence of suicidal ideation.²⁶ Depression in older people often present with symptoms of functional and cognitive impairment and it is important to differentiate between depression and executive dysfunction of dementia for the purposes of treatment.²⁷

Leentjen in his study showed that feeling of guilt, anxiety, anhedonia, and lack of interest constituted the most prominent symptoms of depression in PD, and reduced appetite and early morning awakening are two somatic items that discriminate between depressed and non-depressed PD patients.²⁸ Thus the core symptoms and the somatic symptoms of depression were essential in establishing the diagnosis of depression in PD. In another study²⁹ the symptoms that were found to differentiate between depressed and non-depressed PD patients were lack of interest, feeling of worthlessness and hopelessness, feeling blue and self-blame. Studies in the past suggested that depression in PD can co-exist with other psychiatric symptoms such as anxiety, apathy and executive dysfunction.^{30,31} Recently Starkstein et al used Diagnostic and Statistical Manual (4th edition) criteria (DSM-IV) and identified a patient class (severe depression group) with high statistical significance. Using latent class analysis they established a non-depression group and a moderate depression group. Anxiety and apathy were significant comorbid conditions of moderate and severe depression and they suggested that anxiety should be included as an additional diagnostic criterion.³² Another recent trial showed that there is heterogeneity in the affective disturbances in PD, with four classes of either anxiety alone (22%), anxiety with depression (8.6%), depression alone (9%) and the last one with low probability of prominent affective disorders.³³ Diagnosing depression in PD is also challenging as the presence of minor depression and dysthymias can go unnoticed and it was noticed to be present in 30% of patients with PD.³⁴ Dysthymia can, with the emergence of

other symptoms, progress to depression in PD or be the remaining symptom after recovery from depression.³⁵

Pathophysiology of depression in PD

Depression may be the first manifestation of PD even before the development of motor symptoms.^{36,37} Alonso et al have also reported that the risk of PD increases during the first two years of use of antidepressants (both tricyclic antidepressants [TCA] and selective serotonin receptor inhibitors [SSRIs]).³⁸

Deficiencies in serotonin, noradrenaline and dopamine have been implicated as a cause of depression in PD. Earlier studies were more in favour of an imbalance between these neurotransmitters causing depression in PD.³⁹ Serotonergic hypothesis was proposed because post-mortem studies using neurochemical techniques showed decreased serotonin level, reduced CSF level of 5-Hydroxy indoleacetic Acid (5-HIAA) and 5-Hydroxytryptamine 1A (5-HT or serotonin) receptor binding in the depressed patients' brain.^{40, 41} Serotonin inhibits dopamine release hence reduced levels of serotonin will lead to greater dopamine availability.⁴² Braak et al also suggested that degeneration of serotonergic neurons is primary and dopamine degeneration is secondary.⁴³ However, Leentjens et al challenge this serotonergic theory and they suggested that the vulnerability of PD patients for depression was not directly linked to a reduction in serotonin activity.⁴⁴ Similarly, serotonin transporter binding, which is a parameter of integrity of serotonergic projections, was found to be preserved in one recent study of early PD patients but in this study, patients were not depressed hence the correlation is weak.⁴⁵ Tan et al suggested that change in the neural networks within basal ganglia would disrupt 5-HT functioning in the cortical and limbic system through direct and indirect anatomical connections with midbrain raphe and it is an important contributory factor for the development of depression in PD but they suggested a multi-factorial model for 5-HT vulnerability and depression as there was variability in their findings.⁴⁶

One study used [11C]RTI-32 Positron Emission Tomography (PET), an in vivo marker of both dopamine and noradrenaline transporter binding, to localise differences between depressed and non-depressed PD patients. Depressed PD patients had lower [11C]RTI-32 binding in the limbic system and in the locus coeruleus, which is the noradrenergic nucleus than nondepressed PD patients. They suggested that depression in PD might be associated with a loss of dopamine and noradrenaline innervations in

the limbic system.⁴⁷ Dopaminergic pathways are gaining more importance with new evidences emerging and single photon emission computed tomography (SPECT) brain images from patients with depression in PD showed reduced radio signal from striatum and thus deficient dopamine transporter.⁴⁸

The genetic polymorphism of Dopamine (D4) receptors, Dopamine transporter (DAT) and Catechol-o-Methyltransferase (COMT) have been found to be of functional significance with a recent study showing vulnerability for depression⁴⁹ and polymorphism of D3 receptors was the predisposing factor to cause depression in another study.⁵⁰

Despite the above-mentioned discussion cause of depression in PD is multifactorial as the biochemical and genetic theories are deficient in providing explanation for the patients with and without depression with similar biochemical and genetic defects. Schrag et al suggested in their study that along with postural instability and cognitive impairment, the perception of handicap i.e. the impact of disease on their life appears more important than the severity and degree of impairment of PD.⁵¹ Social and personal circumstances can increase or decrease handicap in patients with the same level of disability. MacCarthy & Brown suggested that the best predictors of depression were functional disability, low self-esteem, and avoidant coping. These variables accounted for 46% of the variance in depression. But acceptance of illness and positive affect significantly predicted lower incidence of depression. This study found that disease-related variables (eg, severity and functional disability) do not predict a large portion of the variance in the depression that is experienced in PD, hence the importance of psychosocial variables.⁵² It is also possible that there are other risk factors for depression in PD such as family history, previous history of illness and personality trait. In particular personality trait like harm avoidance is a risk factor for depression in PD although according to this study depression was because of loss of serotonergic activity whereas harm avoidance was due to loss of dopaminergic cells in the striatum.⁵³

Diagnosis and assessment in PD

Diagnosing depression in PD can be challenging because physical symptoms of PD overlap with somatic symptoms of a depressive illness such as on fatigue, hypomimia and psychomotor retardation. The Diagnostic and Statistical Manual of mental disorder IV criteria (DSM-IV) is used as a main tool and gold standard to diagnose depression in

PD but its limitation is that it excludes depression in the background of illnesses such as PD and doesn't discriminate between major, minor depression and dysthymia. Similar limitations were realised in NICE clinical guidelines for depression with chronic physical health problems as DSM-IV includes cognitive, mood and somatic symptoms (significant weight change, sleep disturbance, fatigue or loss of energy and psychomotor retardation or agitation). Somatic symptoms may arise not because of depression but because of the comorbid physical health problem. Guidelines advised clinicians to focus on cognition and mood symptoms in DSM-IV when diagnosing depression in chronic physical health problems.⁵⁴ The National Institute of Neurological Disorders and Stroke/National Institute of Mental Health (NINDS/NIMH) working group on depression and PD was established to review DSM-IV criteria and they suggested DSM-IV TR criteria. It recommended an inclusive approach to all symptom assessment so that all symptoms are taken into account regardless of whether the symptoms could be wholly or partly attributed to PD. They also suggested including sub-syndromal depression in the studies, to be specific in the timing of the assessment of depression in PD if they suffer from motor fluctuations and to use informants in cases of cognitively impaired patients.⁵⁵

In the larger epidemiological studies, generic assessment and rating scales were used for the diagnosis of depression in PD. The Movement Disorder Society commissioned a task force to assess their clinimetric properties and they made clinical recommendations that Beck Depression Inventory (BDI), Hamilton Depression Scale (Ham-D), Hospital Anxiety and Depression Scale (HADS), Geriatric Depression Scale (GDS), Montgomery-Asberg Depression Rating Scale (MADRS) are valid in assessment tools for depression in PD. For screening purposes, the HAM-D, BDI, HADS, MADRS, and GDS are valid in depression in PD. For measurement of severity of depressive symptoms, the Ham-D, MADRS, BDI, and Zung Self-Rating Depression Scale (SDS) scales are recommended. To account for overlapping motor and non-motor symptoms of depression, adjusted instrument cut-off scores may be needed for depression in PD, and scales to assess severity of motor symptoms (eg. UPDRS) should also be included to help adjust for confounding factors.⁵⁶

Treatment of depression in PD

It is important first of all to identify that patient's motor symptoms are well controlled and depression is not occurring in the off period. If depression in PD is occurring in off period then it should be treated by the

optimisation of the anti-parkinsonian medication.

In patients with mild depression psychosocial interventions such as counselling and cognitive behavioural therapy (CBT) should be the first line of treatment.⁵⁷ A recent review of CBT in depression in PD found it to be effective although large randomised controlled studies are needed to answer the questions about the role of CBT in cognitive impairment and in motor and non-motor complications.⁵⁸

Mild or sub-threshold depression should not be treated routinely with antidepressants unless there is significant history of depression in the past or mild depression is persisting for more than two years or after initial interventions.⁵³ Before considering treatment with antidepressants, a dopamine agonist and a MAO-B inhibitor like selegiline should be tried in patients with persisting mild depression or moderate depression.⁵³

Kano et al showed in their study that pramipexole was beneficial in depression in PD and this effect was independent of improvement in motor symptoms.⁵⁹ Recently, a double-blind controlled trial by Barone et al showed the same effect of pramipexole on depression in PD, perhaps through an adjunctive effect on noradrenergic and serotonergic effect.⁶⁰ Pramipexole also reduced the severity of depression in bipolar disorder in non-parkinsonian patient.⁶¹

There are only a few trials on the treatment of depression in PD with antidepressants. Weintraub et al did a literature review and meta-analysis of available studies on the effectiveness of antidepressants in depression in PD and concluded that antidepressants have not been adequately evaluated in this group and treatment effect may be less in elderly depressed patients without PD.⁶² A recent systematic review and meta-analysis of randomised controlled trials of antidepressants for the treatment of depression in neurological disorders by Price et al suggested that evidence is equivocal for the antidepressant use in PD. There is a small and non-statistically significant effect size and the number of studies for depression in PD is few, therefore the statistical power is low.⁶³ Traditional antidepressants such as TCAs have been used in the treatment of depression in PD and a study suggested that the SSRI paroxetine CR is not superior to placebo in depression in PD and may be inferior to nortriptyline.⁶⁴ Another study suggested that the SSRI citalopram was effective but less than desipramine (noradrenergic reuptake inhibitor tricyclic antidepressant).⁶⁵ Antonini suggested that both sertraline or low-dose amitriptyline improved depressive symptoms in PD in their study, even though a significant benefit on quality of life was observed only with sertraline.⁶⁶ In clinical practice SSRI drugs are more used than TCA because of their better side

effect profile but when used in combination with MAO-B inhibitors such as selegiline and rasagiline, there is potential and theoretical risk of serotonin syndrome, so caution is required. NICE recommended using mirtazapine, reboxetine or trazodone in the patients using MAO-B inhibitors.⁵³

Other treatment options include venlafaxine, a selective noradrenaline re-uptake inhibitor (SNRI) and the alpha-2 adrenoreceptor antagonist.⁵³ In a recent study atomoxetine (SNRI) was not effective in clinically significant depression in PD⁶⁷ but on the other hand a small open-label reboxetine study in patients with depression in PD found significant improvement in depression scores with treatment.⁶⁸ However, meta-analysis of antidepressants in general showed that reboxetine is a weak antidepressant, the previous study had publication bias and the drug can be potentially harmful.⁶⁹

Deep brain stimulation was shown to improve depression in a study basically aimed to treat motor symptoms but the change in the scale of depression did not correlate with the improved quality of life so the change in motor symptoms was the main determinant of quality of life.⁷⁰ Electroconvulsive therapy (ECT) has been used in drug resistant depression in PD and it has shown improvement but the effects are transient and ECT needs to be continued over a longer period of time.⁷¹ Repetitive transcranial magnetic stimulation (TMS) is as effective as fluoxetine in the treatment of Parkinson's disease related depression and this has been shown after ECT. TMS may also lead to some improvement of motor symptoms.⁷²

Conclusion

Depression in PD is common and affects the quality of life of the patient and their carer so its importance cannot be overemphasised. Disabling motor symptoms together with cognitive impairment lead to diagnostic difficulties and therefore clinicians must be aware of the other associated symptoms that characterise depression in PD and reach a diagnosis where possible. The absence of an agreed methodology or algorithm remains a problem that must be addressed in the longer term. Treatment of depression in PD improves quality of life for the patient, effects positively on motor symptoms^{66,73} and reduces the burden for care givers. It may postpone the need for other services or long term care.

Conflict of interest: none declared

References available on online version at www.gmjjournal.co.uk