

Psychiatric aspects of Parkinson's disease

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ABSTRACT

Parkinson's disease (PD) is essentially characterized by the motor symptoms in the form of resting tremor, rigidity and bradykinesia. However, over the years it has been recognized that motor symptoms are just the "tip of the iceberg" of clinical manifestations of PD. Besides motor symptoms, PD characterized by many non-motor symptoms, which include cognitive decline, psychiatric disturbances (depression, psychosis and impulse control), sleep difficulties, autonomic failures (gastrointestinal, cardiovascular, urinary, thermoregulation) and pain syndrome. This review evaluates the various aspects of psychiatric disorders including cognitive decline and sleep disturbances in patients with PD. The prevalence rate of various psychiatric disorders is high in patients with PD. In terms of risk factors, various demographic, clinical and treatment-related variables have been shown to be associated with higher risk of development of psychiatric morbidity. Evidence also suggests that the presence of psychiatric morbidity is associated with poorer outcome. Randomized controlled trials, evaluating the various pharmacological and non-pharmacological treatments for management of psychiatric morbidity in patients with PD are meager. Available evidence suggests that tricyclic antidepressants like desipramine and nortriptyline are efficacious for management of depression. Among the antipsychotics, clozapine is considered to be the best choice for management of psychosis in patients with PD. Among the various cognitive enhancers, evidence suggest efficacy of rivastigmine in management of dementia in patients with PD. To conclude, this review suggests that psychiatric morbidity is highly prevalent in patients with PD. Hence, a multidisciplinary approach must be followed to improve the overall outcome of PD. Further studies are required to evaluate the efficacy of various other measures for management of psychiatric morbidity in patients with PD.

Key words: Non-motor symptoms, Parkinson's disease, psychiatric manifestations

Introduction

James Parkinson is attributed with rendering the first cogent description of Parkinson's disease (PD). He identified the hallmark features of the illness through descriptions of cases observed in the streets of London as well as his own patients.^[1] Over time, PD or idiopathic PD has replaced the original term, paralysis agitans, for the clinical syndrome characterized by resting tremor, rigidity, bradykinesia in association with the specific pathological findings of depigmentation of the substantia nigra as a result of loss of melanin-laden dopaminergic neurons containing eosinophilic cytoplasmic inclusions (Lewy bodies).^[1] PD is the second

most common chronic neurodegenerative condition in older people especially beyond the age of 60. A number of studies have estimated the prevalence of PD in different countries and the findings of prevalence have varied widely. Studies suggest an incidence and prevalence rate of 1% in people aged above 65 years.^[2] Data suggests that the occurrence of PD is significantly lower in Chinese, Japanese and African populations compared to those from Western countries.^[3] There is no nationwide epidemiological data on the incidence and prevalence of PD from India. Data from door to door surveys in three different regions of India suggest a low prevalence rate of PD among Indians compared to Western studies.^[4] Studies from India also suggest that prevalence of PD is high among Parsi population^[5] and prevalence rate is higher in males, in those with family history of PD, in those with history of depression of more than 10 years prior to PD.^[6]

Although the definition of PD is based on the presence of motor features, these are just the "tip of the iceberg." It is now known that in addition to the typical motor symptoms

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of PD, the clinical picture includes many non-motor symptoms, with behavior problems often being the most common.^[7] Many non-motor symptoms have been described that include cognitive declines, psychiatric disturbances (depression, psychosis and impulse control), autonomic failures (gastrointestinal, cardiovascular, urinary, sexual dysfunction, thermoregulation), sleep difficulties, and pain syndrome.^[8] In fact it is suggested that in advanced PD, non-motor symptoms dominate the clinical picture and are associated with severe disability, impaired quality of life, and shortened life expectancy.^[1,7] Non-motor symptoms like depressive disorders, anxiety disorders, cognitive decline, pain, fatigue, insomnia, and autonomic dysfunction are shown to be associated with poor health-related quality of life of individuals with PD.^[4] Although non-motor symptoms greatly influence the health-related quality of life of PD patients, more than 50% of existing non-motor symptoms are not identified in clinical practice.^[9] In the advanced stages of disease, non-motor symptoms are major determinants of loss of independence, caregiver strain, and nursing home placement.^[10] Among the various non-motor symptoms, psychiatric comorbidity is quite common and disabling. In terms of etiopathogenesis, it is suggested that the non-motor symptoms have the common etiopathogenesis as that of PD or it may be due to medications used for management of PD or as a reaction to the physical illness and its consequences. In most cases it is more often than not multifactorial in origin.^[11] In terms of common etiopathogenesis, hypothesis involving various neurotransmitters like dopamine, serotonin and acetylcholine/noradrenaline have been reported for various psychiatric disorders. However, some of the researchers suggest that attempting to understand the etiopathogenesis on the basis of single neurotransmitter may be too simplistic and development of various neuropsychiatric manifestations is related to alteration in many neurotransmitters.^[11]

This review attempts to look at the existing information on various psychiatric conditions, like depression, psychosis, anxiety disorders, sleep disturbances and cognitive deficits in patients with PD. The data is organized in the form of epidemiology, risk factors and management of these conditions in patients with PD. For this review we searched the electronic databases of PUBMED, Google Scholar, PsychINFO, Scopus and Ovid. Cross-searches of electronic and hand search of key references yielded other relevant material. To carry out the electronic searches we used the terms of PD, prevalence, incidence, epidemiology, depression, mania, anxiety, psychosis, sleep disturbances, insomnia, hypersomnia, excessive daytime sleepiness, restless leg syndrome, sleep related movement disorders, parasomnias, dementia,

mild/minimal cognitive impairment, non-motor symptoms, psychiatric morbidity, impulse dyscontrol, compulsive behavior, dopamine dyscontrol, apathy, anhedonia, suicide, suicidal behavior in various combinations. All the relevant articles were reviewed and the relevant data were extracted. Then the data was organized to mainly understand the epidemiology, risk factors and management of various psychiatric manifestations in patients with PD.

Risk of Parkinson's disease in patients with psychiatric disorders

The influence of mental illness early in life on the subsequent risk of PD and its clinical picture remain obscure. Several studies have identified certain psychiatric illnesses, particularly anxiety, depression and schizophrenia as risk factors for PD.^[12] Anxiety has been suggested to be one of the earliest manifestations of PD in several case-control and cohort studies.^[13,14]

Depression in Parkinson's disease

Depression has been reported to be very common in patients with PD. In fact the relationship of depression and PD follows a vicious cycle, with the presence of either increasing the risk of other disorder. The risk of PD in patients with depressive disorders have been reported to be more than that seen in general population.^[15,16] A large sample retrospective study of a matched cohort of 23,180 participants (4,634 patients with depression and 18,544 control patients), reported that patients with depression were 3.24 times more likely to develop PD compared with the control patients.^[17] Another register-based study that had data of 105,416 subjects evaluated the history of depression in patients diagnosed with PD and reported a life time prevalence of depression prior to onset of PD to be 9.2% compared to 4% in the control population and the difference between the two groups was statistically significant and the odds of having depression in patients with PD was 2.5.^[18] Few studies have evaluated the incidence of depression in patients with PD and reported the incidence rate to be 1.86-5.1% per year.^[19,20]

Overall many studies have evaluated the prevalence of depression in patients with PD.^[21-76] Most of these studies are clinic based,^[21-26,39-71] limited to outpatient of single study site,^[22-36,40-59,61-68,73-75] cross-sectional in design^[21-44,46-74] and have evaluated 28-353 patients.^[21-40,42-73] Other studies have also evaluated the prevalence of depressive disorders in patients with PD in the inpatient setting^[21,67] and in population-based study samples.^[27,30-37,43,63,69] One multicentric study included 1072 patients from 55 hospitals and evaluated the prevalence of depressive disorders.^[76] Many of these

studies are based on evaluation of patients for depression by using various structured interview schedules like Composite International Diagnostic Interview (CIDI),^[35] structured clinical interview for DSM-III-R,^[29-31,36-38,44,52-54] or have used DSM-IV criteria,^[55,58,60,67-69] to evaluate the prevalence of depressive disorders. Some studies have relied only on rating scales like Beck Depression Inventory,^[40,46,47,50,51,65] Center for Epidemiologic studies – depression scale,^[28,45] Hospital Anxiety and depression scale,^[49] Zung self-rated depression scale^[62] and Geriatric depression rating scale.^[39,56,63,66] Although studies have varied in the reporting of depression, these studies have reported prevalence rates of major depression, minor depression, dysthymia and clinically relevant depressive symptoms. The prevalence rates have varied from 2.7% to 55.6%^[25-38,42-44,52-59,67-73] for major depression, 13% to 34.5%^[25,26,54,67,70-72] for minor depression and 2.2% to 31.3%^[22,29,34-36,52,57,58,72] for dysthymia. The prevalence rate of clinically significant depressive features has varied from 2.7% to 89%.^[21-43,46-69,72-74] The very high rate, i.e. 89% was reported in one of the old studies involving the inpatients.^[26] In general prevalence rates in the community samples have been in the lower range, varying between 2.7% and 13%,^[27,30-33,35,37,43,63] but these are still higher than the rates seen in reference population. One meta-analysis that included 10 studies reported the prevalence rate for major depression (24.8%), minor depression (36.6%) and dysthymia (22.5%).^[72]

Various risk factors for development of depression in patients with PD include advanced/more severe disease,^[34,49,56,69-72] anxiety,^[72] cognitive impairment,^[23-32,39,56,62,67,69-73] psychosis,^[32,60,72] longer duration of illness,^[69-71] early and late stage of disease,^[25] motor disability,^[32,34] bradykinesia,^[36,39,73] akinetic-rigid type of PD,^[36] dystonia,^[57] presence of tremor,^[23] presence of motor fluctuations,^[32,69] more evidence of atypical parkinsonism,^[32] gait and balance impairment,^[31,39,73] more alexithymia,^[67] younger age,^[32] higher daily doses of levodopa,^[23,32,48] presence of sleep disorders,^[32,33,48] restless leg syndrome^[55] and female gender.^[56] When compared to drug naïve patients those on antiparkinsonian medications have higher rates of depression (75.5% versus 59.2%).^[76] In term of impact of depression, studies have consistently shown deterioration of scores on activities of daily living.^[25,26,32,34,69]

With regards to treatment of depression in patients with PD, few randomized controlled trials (RCTs) have evaluated the efficacy of various antidepressant medications. The various RCTs have evaluated the efficacy of selective serotonin reuptake inhibitors (sertraline, citalopram, fluoxetine, paroxetine, and fluvoxamine), tricyclic antidepressants (TCAs), pramiprexole and

repetitive transcranial magnetic stimulation (rTMS). One meta-analysis, which included 10 RCTs (6 compared SSRIs with placebo; 5 compared SSRIs with TCAs, 1 compared with rTMS and 1 compared SSRIs with pramiprexole) reported that the response rate for SSRIs to be 36%, which was not different from that seen with placebo (34%). When the response rate of SSRIs was compared with TCAs, the response rate for TCAs was higher than SSRIs (57% versus 41%).^[77] Another recent meta-analysis that included 11 RCTs calculated the odds ratio for the efficacy of various agents. In this meta-analysis when TCAs were used as the comparison arm, the odds ratio for efficacy of SSRIs was -0.69 (95% CI -1.28 to -0.10). The odds ratio for pramiprexole was -0.73 (95% CI -1.71 to -0.26), pergolide was -1.97 (95% CI -3.67 to 0.27) and for serotonin nor-epinephrine reuptake inhibitors (SNRIs) was SNRIs -0.86 (95% CI -1.86 to 0.15) and that of placebo was -1.24 (95% CI -1.99 to -0.50). When compared with placebo the odds ratio for TCAs was 1.24 (95% CI 0.50 -1.99), SSRIs was 0.55 (95% CI -0.03 to 1.13), pramiprexole 0.51 (95% CI -0.12 to 1.15), pergolide -0.73 (95% CI -0.25 to 0.80) and that of SNRIs 0.38 (95% CI -0.42 to 1.19). On the basis of these findings, the authors concluded that the evidence does not support the use of SSRIs, pramiprexole, pergolide and SNRIs as antidepressants in patients with PD. In this meta-analysis when the acceptability of various antidepressants was evaluated, the authors found that TCAs, pramiprexole, pergolide and SNRIs are more tolerated than the SSRIs. Accordingly the authors suggested that TCAs should preferably be used for management of depression in patients with PD.^[78] Data also supports the use of ECT for depression in patients with PD. A review of studies published during 1975 to 1990 reported that in 21 studies, 70% of PD patient's showed improvement in psychiatric disturbances (including depression) and 50% patients showed improvement in PD symptoms too.^[79] Reports published after 1990 also have reported the beneficial effect of ECT in both symptoms of depression and PD *per se*.^[80,81] However, these studies suggest high rates of transient inter-treatment delirium necessitating the postponement/termination.^[80,81] An occasional open-label study has also evaluated the beneficial effect of cognitive behavior therapy for management of depression in patients with CBT and report significant improvement in the Hamilton Depression Rating Scale scores.^[82-85] Other studies have shown that caregiver participation and executive functioning predict the response to CBT in patients with PD.^[85] A recent meta-analysis evaluated the effect of deep brain stimulation (DBS) on depressive and anxiety symptoms in PD patients. The authors concluded that DBS, especially that is focused on the subthalamic nucleus (STN) is useful in management of depressive symptoms in short term; however, the effect wanes off

with time.^[86] There is some evidence to support the use of rTMS for management of depression in patients with PD.^[87]

Based on available evidence for depression in patients with PD and that for management of depression *per se* some of the authors have suggested certain steps in the management of depression. At the first step, whenever a patient with PD presents with depression there is a need to assess the relationship of depression with medications used for the management of PD and if required dose of anti-parkinsonian medications should be adjusted. If this does not help then based on the severity of depressive symptoms, treatment strategies must be selected. If a patient has only mild depression, use of psychotherapeutic interventions like supportive psychotherapy or cognitive behavior therapy should be used as the first-line treatment. For moderate depression one of the antidepressants or CBT can be considered and in patients with severe depression additionally ECT should be considered as an option.^[88] Although TCAs are found to be most efficacious, some authors recommend cautious use of TCAs because of the anticholinergic side effects. However, the recent Movement Disorder Society (MDS) Task Force on Evidence-Based Medicine (EBM) Review of Treatments for PD suggests that new studies have not suggested any safety concerns with regards to use of TCAs in patients with PD.^[89] In general, it is suggested that TCAs antidepressants with least sedative properties and little anticholinergic effects, like desipramine and nortriptyline, should be used, as the evidence supports their efficacy in patients with PD.^[89,90] ECT is recommended in patients with severe depression who are suicidal and those who cannot wait for the required time for the treatment response through medications.^[90]

Anxiety disorders in Parkinson's disease

Anxiety disorders are also highly prevalent in patients with PD with a range of 19.8% to 67%.^[91] In general studies that have relied upon rating scales/questionnaire^[92-94] report higher prevalence of anxiety disorders, compared to those that are based on the structured clinical interviews.^[58,95,96] Studies that have compared the prevalence of clinically significant anxiety symptoms with age-matched controls have reported significantly higher prevalence in those with PD.^[97] Some authors have attempted to categorize anxiety symptoms/disorders in patients with PD into primary anxiety disorder, anxiety secondary to other psychiatric comorbidities (e.g. depression, psychosis), anxiety secondary to the use of antiparkinsonian medications (e.g. levodopa, pergolide etc), anxiety secondary to fluctuation of motor symptoms (on/off periods), anxiety as a prodromal symptom

of PD and anxiety secondary to the impairment and limitations caused by PD.^[98] The most common anxiety disorders in patients with PD are panic disorder,^[58] generalized anxiety disorder, and social phobia.^[58,95] However, some authors suggest that anxiety disorder not otherwise specified (NOS) to be the most common type of anxiety disorder in patients with PD.^[98] Although few studies suggest a correlation of higher level of anxiety with left-sided lesions, but most studies report no relationship between severity of motor symptoms and levels of anxiety.^[99,100] Other risk factors reported for anxiety disorder/symptoms in patients with PD include female gender,^[93] younger age,^[93] young onset PD,^[95] more depressive symptoms,^[93] worst sleep quality,^[93] severity of PD,^[96] postural instability,^[96] gait dysfunction,^[96] higher rates of motor fluctuations,^[95] morning dystonia,^[95] symptom clustering and experience of dyskinesia.^[96]

There are no controls or definitive studies that have evaluated various antianxiety medications for management of anxiety disorders in patients with PD. However, studies that have evaluated the effect of antidepressants and other modalities in patients with depression have assessed the effect of these interventions on anxiety symptoms. Thus, the recommendations are usually based on the data available for elderly populations without PD. However, certain issues must be kept in mind while evaluating and managing anxiety in patients with PD. Since some antiparkinsonian medications may be associated with the presence or variations of anxiety symptoms, it is extremely important to adjust the dose and to be aware of the effects of the medications used for the treatment of PD, with replacement of the medication when the anxiety symptoms are not tolerated. In addition, the control of motor fluctuations is indispensable for a better evaluation of anxiety symptoms. Specific anxiety disorders should be investigated based on the clinical characteristics of the anxiety symptoms, since different anxiety disorders have peculiarities that should be considered both at diagnosis and during treatment. In patients who suffer panic attacks during off periods, treatment should be directed at reducing time off by adjusting the dose of the antiparkinsonian medication. Among the various antianxiety medications, SSRIs are considered to be the first line of treatment. Other options include TCAs and benzodiazepines. However, in general it is suggested to avoid these medications in elderly and when used should be used for the minimum possible period of time and at the lowest possible dose. Benzodiazepines are known to increase the risk of falls and fractures in the elderly population and are associated with a greater cognitive decline at high doses. Further, benzodiazepines may

be related to the worsening of parkinsonian symptoms and they may also lead to abuse and dependence.^[101] Non-pharmacological measures like psychoeducation, relaxation practices, sleep hygiene, and social measures for adaptation to PD can also be tried. There is some evidence to suggest the usefulness of cognitive behavior therapy, DBS and rTMS in management of anxiety symptoms associated with depression in patients with PD.^[83-87,102]

Psychosis in Parkinson's disease

Psychosis is generally not considered as a primary symptom of idiopathic PD, although there are case reports of psychosis in patients with PD from the pre-levodopa era.^[103] The inability to reliably discriminate post-encephalitic Parkinsonism from idiopathic PD and the lack of recognition of the numerous parkinsonian disorders that are not idiopathic PD make these reports suspect. In fact some authors suggest that the occurrence of psychotic symptoms in an untreated PD patient constitutes an "atypical" feature and cast doubt on the diagnosis.^[104]

However, in recent times many studies have evaluated the prevalence of psychosis in patients with PD.^[105-117] The time frames that have been considered by these studies have varied from last 1 week to last 6 months.^[104,106-111,114-117] Some of these studies have concentrated just on evaluation of hallucination^[50,105,108,112,114,117] whereas others evaluated other psychotic symptoms also along with hallucinations.^[104,116,109,110,115,116] Some of the studies have relied on questionnaires like hallucination questionnaire,^[105] Queen Square Visual Hallucination Inventory,^[116] University of Miami Parkinson's disease hallucinations questionnaire^[117] to evaluate the prevalence of psychosis, whereas some have used DSM-IV criteria to study the prevalence of psychosis.^[104,110,112,115] The sample size of these studies has varied from 70 to 422 subjects^[104,105,107-112,114-117] and most of these studies have a followed-up prospective study design^[93-100,102-105] with an occasional retrospective study.^[104,108] Most of these studies recruited participants from the patient population attending the movement disorder clinics^[104-112,114-117] with occasional studies based on the community-based population.^[50,108] The prevalence of psychosis (or visual hallucinations) in these studies has varied from 15.8% to 75%.^[104-117] A 12-year longitudinal follow-up study that evaluated PD-associated psychosis (PDP) on the basis of rating of 2 or more on the Unified Parkinson Disease Rating Scale thought disorder (UPDRS-TD) item 2 or those taking antipsychotic drugs reported development of hallucinations and delusions in 60% of patients. The incidence rate of PDP was 79.7 per 1000 person-years.^[118] Among the various psychiatric symptoms, visual hallucinations have been

reported to be the most common symptoms with a prevalence rate of 16-38%.^[104-110,115-117] Studies that have evaluated other symptoms have reported prevalence of auditory hallucinations to be 0-22%,^[104-111,114-117] delusions to be 1-14%^[104,106,110,115] and other minor psychotic symptoms to be 17.4-72%.^[109,115,116] The risk factors associated with development of psychosis/hallucinations in patients with PD include cognitive decline (dementia, Mini-Mental State Examination scores of ≤ 24 , global cognitive impairment),^[104-112,114,115] age,^[105,108,115] age of onset of motor symptoms,^[112] longer duration of disease,^[105,109,115,116] history of depression,^[105] or history of sleep disorder,^[105] modified Hoehn-Yahr stage of ≥ 4 ,^[116] postural instability,^[106] rapid progression of the motor component of the disease,^[106] severity of motor symptoms,^[115] treated with a direct-acting dopamine receptor agonist,^[106] higher depressive score,^[108-110] comorbid affective disorders,^[104] daytime somnolence,^[109] worse visual acuity,^[110] higher severity of illness,^[110] positive family history of dementia^[114] and presence of REM (rapid eye movement) sleep behavior disorders.^[115] In the longitudinal follow-up study risk factors for development of psychosis were higher age at onset, higher baseline levodopa-equivalent doses, probable REM sleep behavior disorder (RBD) at baseline, and follow-up time were independent risk factors of incident PDP.^[118]

In terms of management of psychosis in patients with PD, first step involves evaluation for delirium and relationship of psychosis with antiparkinsonian medications. If the patient does not have delirium and the psychosis is possibly related to use of antiparkinsonian medications then efforts should be made to reduce these medications. In this regard, if the patient is on multiple antiparkinsonian agents, efforts should be made to reduce the drugs to the lowest effective dose, in the order of anticholinergics, selegiline, amantadine, dopamine receptor agonists, catechol-O-methyltransferase inhibitors and lastly levodopa. However, if reduction in anti-PD medications to the lowest dose tolerable without exacerbation of motor symptoms doesn't improve psychosis, use antipsychotic medications is warranted. Studies have evaluated the efficacy of various atypical antipsychotic, i.e. clozapine, olanzapine, risperidone and quetiapine in patients with PD (for review see).^[89] Based on the evidence, clozapine is considered to be the best choice for management of psychosis in patients with PD.^[89]

Cognitive deficits in Parkinson's disease

Dementia is quite common in PD, especially in the late stages.^[119] Cognitive impairment of a lesser severity is also common in patients with PD without dementia, designated as mild cognitive impairment (MCI) of PD, or PD-MCI.^[120,121] Patients with PD with MCI have

an increased risk of developing dementia, compared with those without.^[119,120] Many studies have evaluated the prevalence of MCI in patients with PD.^[119,120,122-126] However, these studies have differed in the definition of MCI. Further some of these studies have evaluated the incident cohorts^[119,122,123,125] and other has evaluated MCI in prevalence cohorts^[120,124-126] in samples drawn from community population,^[119,122,123,124] with occasional clinic-based studies.^[120,124-126] Sample sizes of these studies has varied from 72 to 1346^[119,120,122-126] and the prevalence rate of MCI has varied from 18.9% to 55%.^[119,120,122-126] The risk factors identified in these studies to be related to MCI were male gender,^[125] increasing age,^[124,125] higher UPDRS motor scores,^[120,122,125] higher disease severity,^[124,125] lower premorbid intelligence quotient,^[122] lower educational level,^[123] longer duration of illness,^[120,126] use of anti-anxiety medications,^[124] increasing severity of daytime sleepiness,^[124] depression,^[125] higher postural instability and gait disorder.^[126]

As with other abnormalities, the prevalence rate of dementia in PD is also variable.^[119,121,127-134] In a systematic review of literature, authors reported the point prevalence of dementia in PD to be 31.3% and the incidence rate is increased four to six times as compared to controls. The cumulative prevalence is very high with at least 75% of PD patients who survive for more than 10 years developing dementia. The mean time from onset of PD to dementia is approximately 10 years.^[119] The most established risk factors for early dementia are old age,^[119,121,125,127-133] severity of motor symptoms,^[127,128] in particular postural and gait disturbances,^[119,127,128] MCI^[119,121,125,127,128-133] and visual hallucinations.^[119,127,128]

Data suggests that the cognitive profile of PD dementia may be different from that of Alzheimer's dementia. Patients with PD dementia have higher dysfunction in the domains of attention, executive and visuo-spatial functioning with lesser involvement of memory and language. Many of the cognitive deficits observed in PD patients resemble impairments demonstrated by patients with damage to the frontal lobes.^[121,128]

Management of dementia associated with PD involves making the correct diagnosis after excluding the other causes of dementia. In terms of treatment, studies have evaluated the efficacy of donepezil, rivastigmine, galantamine and memantine.^[89] Of these agents, only rivastigmine has been conclusively found to be efficacious in dementia associated with PD.^[89]

Sleep disorders in Parkinson's disease

Sleep disorders are very common in patients with PD and have a significant negative impact on their quality of life.^[135]

The sleep-related problems in patients with PD can be broadly classified into daytime manifestations, nocturnal sleep disturbance, sleep-related movement disorders and parasomnias. The daytime sleep manifestations include excessive daytime sleepiness (EDS). The nocturnal sleep disturbances include insomnia and obstructive sleep apnea. The common sleep-related movement disorder include restless leg syndrome. The common parasomnias include RBD. As with depression and anxiety disorders, sleep disorders are also reported to increase the risk of development of PD in the later life.^[136-141] A longitudinal population-based prospective study reported increased risk of PD in patients with EDS. This risk persists after controlling for various confounders like mid-life cigarette smoking and coffee drinking, bowel movement frequency, cognitive functions, depressed mood, and insomnia. Overall, EDS was associated with a three-fold increase in the risk of developing PD.^[137] Clinic-based studies that have looked at the risk of developing PD in patients with sleep disorder have mainly focused on RBD and these studies suggest that when the patients with RBD are followed over the period, 16-65% of patients develop PD^[138-141] and the incidence of PD increases with longer follow-up duration.^[138-141]

Many population-based studies have evaluated the incidence of sleep disorders in patients with PD.^[142-145] These studies suggest that about 50% of patients have insomnia,^[142,144] 14.7% have RBD^[142] and 8% have EDS.^[145] When the cohorts were followed up, it was seen that the incidence of sleep disorders increased with progress and increasing duration of PD.^[74,146-149] Among the various types of sleep disorders, usually the frequency of EDS and RBD increases^[142,144-146,149] but that of insomnia is reported to be relatively stable.^[74,143] However, clinic-based studies have not come up with such consistent findings.^[150-153] The risk factors that have been reported to be associated with onset of sleep disorder in patients with PD include older age,^[144,145,152] male gender,^[142,145] use of higher doses of dopaminergic drugs,^[142,144,152] presence of cognitive impairment^[144,145] and presence of hallucinations.^[142,144,148]

Studies that have evaluated the prevalence of various sleep disorders in patients with PD have come up with varying rates, mainly because of different methods of ascertainment. Some of these studies are population based,^[142-145] whereas others have focused on clinic attending population.^[45,146-153] These studies suggest that the prevalence of EDS vary from 15% to 87%,^[45,146-148,150,151,153] insomnia vary from 40% to 50%,^[143,153] restless leg syndrome vary from 0% to 50%^[144,145,153] and that of RBD varies from 25% to 50% in patients with PD.^[142,146,149]

The presence of sleep disorder, especially multiple sleep disorders is known to predict other symptoms of PD.^[154] A cross-sectional study suggested that the presence of at least two sleep disorders predicted significantly higher more overall non-motor symptoms, higher scores on the individual measures of multiple symptoms, quality of life, fatigue, depression and cognitive decline.^[146] Studies also suggest that the presence of subjective insomnia is independently associated with depressed mood (odds ratio [OR] =1.79), autonomic symptoms (OR = 1.77), fatigue (OR = 1.19), and age (OR = 0.61). Subjective daytime sleepiness is reported to be associated with dosage of dopaminergic medication (OR = 1.74) and fatigue (OR = 1.14).^[155]

Management of sleep disorders involves proper diagnosis. Accordingly, for proper diagnosis it is important to obtain a proper history from the patient and the bed partner. Besides this patient may have to undergo investigations like polysomnography, actigraphy and multiple sleep latency test.^[156-158] Once the diagnosis is made there is a need to look for the cause that involves review of patient's medications, comorbid conditions and sleep hygiene. It is important to know that in small doses, levodopa may improve the sleep, however, in higher doses it may be associated with impairment in sleep. Other antiparkinsonian agents have also been implicated in development of confusion that may exacerbate sleep problems. Excessive daytime sedation can be caused by dopaminergic drugs – with dopamine agonists than with levodopa that is dose dependent. EDS may occur when dopamine agonist dose is increased. Dopaminergic agents have also been shown to influence the REM sleep.^[156]

Once the diagnosis is made, depending on the sleep disorder, sleep hygiene should be used as the first line of treatment. In terms of pharmacological management although the studies have evaluated the efficacy of dopaminergic agents, pergolide, eszopiclone, and melatonin, etc., the evidence is not sufficient to recommend these medications.^[89] For EDS, studies have evaluated the usefulness of modafinil, but these studies do not suggest that modafinil is more efficacious than placebo.^[89] Clonazepam is recommended as the first-line agent for management of RBD, although there are no RCTs for the use of the same.^[156] For RLS too, there is lack of data from the RCTs. However, there is some evidence to support the use of long-acting dopamine agonist like cabergoline that may be effective.^[159,160]

Anhedonia in Parkinson's disease

Although anhedonia is understood as a symptom of depression in patients with PD, studies suggest that it

may be characteristic of PD itself which could be due to the dysfunction of the dopamine reward pathway in the mesolimbic area.^[161] Studies that have evaluated the prevalence of anhedonia have reported a range of 7% to 45.7%. With regards to the prevalence of anhedonia and depression, studies suggest a strong correlation between the two; however, in many patients anhedonia is present in the absence of depression.^[162-167] Studies also suggest an association between anhedonia and apathy.^[164] Studies are inconclusive with regard to the relationship of anhedonia with severity of motor symptoms.^[168] With regards to management of anhedonia, which is independent of depression, no studies have specifically evaluated the efficacy of any pharmacological agent.

Apathy in Parkinson's disease

Apathy is understood as a *“reduced interest and participation in normal purposeful behavior, lack of initiative with problems in initiation or sustaining an activity to completion, lack of concern or indifference and a flattening of affect.”*^[169] Many studies have evaluated the prevalence of apathy in patients with PD using different scales and have reported a prevalence rate of 16.5-70%, depending on the assessment procedure and the study population.^[164,169-174] Evidence suggests that apathy in PD is not related to depression, anxiety, severity of motor symptoms.^[164,169] However, some of the recent studies suggest high level of comorbidity between apathy and depression in patients with PD.^[175] However, some studies suggest that apathy may be a side effect of DBS^[176,177] and other suggest that apathy in PD is determined by the level of cognitive impairment.^[178] Recent evidence suggests that in non-depressed non-demented patients, apathy may in fact be a predictor of cognitive decline and dementia in PD.^[178]

Impulsive-compulsive disorders in PD

Many studies have reported high rate of impulsive compulsive disorders (ICD) in patients with PD. These disorders are suggested to arise from aberrant or excessive dopamine receptor stimulation. Recent studies that have reported the cumulative life time prevalence of Impulsive compulsive disorders in patients with PD have reported a prevalence rate of 35.9 to 60%.^[178,179] These rates are much higher than those reported for individual disorders in the older studies as reviewed by Evans, et al.^[180] The prevalence of various ICD in patients with PD has been reviewed by Evans, et al.^[180] and the rates for pathological gambling has been reported to be 2.3% to 9.3% and that of hypersexuality is reported to vary from 0.9% to 13%. Evidence also suggests that the rates of ICDs are higher in those receiving dopaminergic agents, especially direct D2/D3 dopamine agonists and reduction

or resolution of ICDs with reduction or discontinuation of dopaminergic agents.^[181]

The factors associated with pathological gambling include younger age of onset, higher scores on impulsive sensation seeking personality traits, personal or immediate family history of alcohol use disorders, use of dopamine agonist agents, dose of dopamine agonists and duration of dopamine agonist therapy.^[178,180] The risk factors for hypersexuality in PD include male gender, early age of onset, use of dopamine agonist agents and depression.^[180] The rate for compulsive buying has been reported to vary from 0.4% to 5.7% and that of Binge eating disorder to be 4.3%.^[180] The rates of punting have varied from 1.4% to 8%.^[180] The risk factors that have been identified to be associated with punting include younger age of onset for PD, high impulsivity, poor quality of life and use of dopamine receptor agonists.^[180]

Dopamine dysregulation syndrome

Data suggest that few patients of PD develop addiction to dopamine agonist drugs. This is known as dopamine dysregulation syndrome (DDS). The prevalence for this syndrome is reported to be 3-4% among patients attending specialist PD centers.^[180] Problems with decision making are thought to be responsible for addictive behaviors. The risk factors for DDS include younger age of onset, longer duration of illness, use of higher dose of dopaminergic agents, history of past experimental drug use, higher depressive symptoms, high level of impulsivity and history of alcohol intake.^[181] Studies also suggest that DDS, ICDs and punting often coexist in PD receiving dopaminergic agents.^[181,182]

Suicidal behavior in Parkinson's disease

Suicidal behavior includes suicidal ideations, suicidal gestures, attempted suicide and completed suicide. Compared to other aspects, little information is available about suicidal behavior in patients with PD. A longitudinal follow-up study of 8 years duration reported the risk of death in patients with PD due to suicide to be 5.3 times higher than expected.^[183] Studies that have evaluated suicidal behaviors have reported rates of suicidal ideations/death in patients with PD to vary from 22.7% to 30%.^[183-185] The risk factors for suicidal ideations/death include depression, anxiety, hopelessness, level of education level, age of onset of PD, duration of illness, and history of impulse-control disorder (ICD).^[183] The odds ratio for suicidal ideation/death in patients with PD for different risk factors are 4.6 to 5.9 (depression), 2.45 to 19.2 (psychosis), 1.2 (hopelessness), 2.92 (severity of depression) and 4.97 to 6.08 (impulse control disorder)

in various studies.^[183,185] Other studies have reported increased risk for suicidal ideations with increasing severity of depression with odds ratio of 2.92.^[185]

Conclusion

Existing data suggest that PD should not be considered only as a motor disorder. In addition to the motor symptoms, patients with PD have very high prevalence of non-motor symptoms. Among the various non-motor symptoms, psychiatric manifestations are very common and are associated with impairment in quality of life and higher treatment costs. Hence, there is a need to identify these symptoms and treat them adequately to optimize the outcome of patients with PD. Comprehensive management of PD calls for an inter-disciplinary approach that should include mental health professionals. From the psychiatrist point of view, it is important to understand that various psychiatric manifestations in patients with PD may be due to the same neuro-degenerative process that is responsible for the motor symptoms; additionally the psychiatric symptoms may be associated with the medications used for management of motoric symptoms of PD. In terms of future research, there is a need to improve understanding about some of the phenomena like ICDs, apathy and anhedonia. Existing data also suggest that there are only very few RCTs that have evaluated the efficacy of various psychotropics and various psychological treatments in the management of various psychiatric manifestations of PD and there is an urgent need to expand the literature.

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