MILD COGNITIVE IMPAIRMENT, DEMENTIA, AND PSYCHIATRIC SYMPTOMS IN PARKINSON'S DISEASE

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Nonmotor manifestations, particularly neuropsychiatric problems, in Parkinson's disease (PD) are common and substantially affect patient outcomes and quality of life. In recent years, there has been greater recognition of PD-related problems affecting cognition, mood, and behavior, with increasing attention directed towards improved screening for them, understanding their mechanisms, and developing interventions for symptomatic treatment. Taken together as a group, neuropsychiatric issues can be found throughout the whole course of their PD, from early in the disease, potentially even in its premotor stage, or at the time of diagnosis, to later in the course with more advanced disease. In the comprehensive care of PD patients, their recognition is critical. Patient management frequently requires a multi-disciplinary approach with collaboration of neurologists with neuropsychologists, psychologists, psychiatrists, and other allied health professionals.

Cognitive disorders: Mild cognitive impairment (PD-MCI) and Dementia (PDD)
Cognitive impairment in PD is frequent and greatly impacts patients and their caregivers. Longitudinal studies illustrate that dementia in PD is frequent. In the Sydney longitudinal study of PD patients, cognitive decline occurred in 84% and dementia in 48% of the remaining patients at 15 and 20 years of longitudinal follow up.[1] In a longitudinal cohort of prevalent PD cases in Norway, 52% were demented after 4 years and 78% were demented after 8 years.[2] Cognitive disturbances in PD can be difficult to treat, and it is recognized that these non-motor symptoms are typically non-levodopa responsive symptoms and predominate at 15-20 years of the disease. Furthermore, PDD is associated with poor outcomes including increased morbidity, nursing home placement, falls, and mortality. A systematic literature review by a MDS Task Force reported a prevalence of 19-38% of PD-MCI (mean of 27%).[3] Moreover, PD-MCI has now been recognized as its own frequent, distinct entity, not only in more advanced and treated PD populations, but also in incident cohorts.

Clinical features and definitions
Clinical features of PD cognitive impairment may be noted by the patient, caregiver, or observed by the clinician. Most commonly, these symptoms affect cognitive domains of attention, working memory, executive function, memory, and visuospatial function. Symptoms endorsed include slowed thinking, trouble with paying attention and concentration, problems with multi-tasking or planning, difficulty switching tasks or starting new ones, forgetfulness or short-term memory problems, or difficulty with one's sense of direction. While language (i.e., confrontational naming) is generally less affected, PD patients often report difficulty finding the "right words." Cognitive deficits vary in their severity from mild to marked and as significantly affecting activities of daily living such as in PDD. In addition, cognitive deficits may occur in isolation (single domain) and in combination with multiple cognitive domains impaired. Some studies suggest that there may be two different phenotypes of cognitive impairment in PD with one reflecting frontostriatal-based deficits, such as seen on the attention and executive function tasks, and the other, representing "posterior cortical" deficits, such as evidenced on semantic fluency, memory, and visuospatial tasks.[4, 5] Other categorizations illustrate the presence of greater non-amnestic deficits (e.g., attention, executive function, visuospatial abilities), compared to amnestic or memory deficits, though the frequency of these deficits varies across different studies, classification of neuropsychological tests, and definitions of cognitive impairment used.[3, 6-8]

Two Task Forces of the Movement Disorder Society (MDS) have developed diagnostic criteria for PDD and PD-MCI.[9, 10] The MDS PDD criteria, in contrast to older definitions such as the Diagnostic Statistical Manual (DSM) III or IV versions, emphasize that memory does not have to be impaired in PD and that dementia can be present if other cognitive domains (e.g., executive function, visuospatial function) are affected and that behavioral problems (e.g., psychosis, sleep disturbances, mood disturbances) are common in PD dementia. The PD-MCI criteria complement those for PDD and include recommendations for determining impairment as well as in the context of comprehensive vs. limited neuropsychological testing availability.[9]
PD cognitive impairment also can be thought of in terms of its time course and relationship to PD motor symptoms and diagnosis. These stages may be considered with respect to the premotor, early motor, and

middle/late motor stages, as linked to Braak's pathological staging system and involvement of different neuroanatomical regions, neurochemistry, and neuropathologies.[11, 12] Cognitive impairment in PD is no longer just a late stage phenomenon but rather can occur early in the motor time course of PD. There is increasing evidence for cognitive deficits in premotor PD or in cohorts "at risk" or relatives of PD patients, who also may be "at risk." Several studies demonstrate that rapid eye movement (REM) behavior disorder (RBD) is associated with cognitive deficits in domains such as executive function, memory, and visuospatial abilities, as are particularly affected in PD, and the development of synucleinopathies and MCI.[13, 14] The Parkinson Associated Risk Study (PARS), which screened a large number of PD relatives and non-relatives to detect early signs that may predict an increased risk of PD, revealed that healthy relatives of PD patients who had hyposmia and decreased dopamine transporter uptake on imaging scans had lower scores on verbal fluency measures (phonemic and semantic fluency), tests of attention/executive function (Trail Making Test), and slower processing speed.[15]

Cognitive decline, conversion to PD dementia, and risk factors

Cognitive deficits or PD-MCI also occurs in newly diagnosed PD patients, as evidenced by several epidemiological studies of incident PD cohorts with estimates of about 20-40%. In a United Kingdom population study of new cases of PD (CamPaIGN study), cognitive impairment occurred in 36%, as defined by MMSE > 24 and either poor scores on a pattern recognition memory task or the Tower of London task, measures of temporal lobe function and working memory, respectively.[16] In the Norway ParkWest study, 196 newly diagnosed and untreated PD patients were evaluated, and 18.9% were found to have PD-MCI, defined as an observed z-score falling > –1.5 standard below the expected z-score in at least one cognitive domain.[17] Among the PD-MCI patients, nearly two-thirds had a non-amnestic MCI subtype and one third had an amnestic MCI subtype. Using MDS PD-MCI diagnostic criteria, the ICICLE study from the United Kingdom found a frequency of PD-MCI in 42.5% of the newly diagnosed, incident cases. Memory was most commonly impaired, and depression scores were higher in the cognitively impaired group.[18] In the Parkinson's Progression Markers Initiative (PPMI) study of de novo, untreated PD patients, baseline data of 423 PD patients revealed that 22% had cognitive impairment as defined by screening cutoffs on the Montreal Cognitive Assessment (MoCA), but much fewer (9%) met PD-MCI criteria using a detailed but limited battery of neuropsychological tests.[19] Early PD patients can have cognitive deficits, and it is important to ask patients and caregivers about cognitive symptoms even at this stage. Furthermore, PD cognitive symptoms can be clinically heterogeneous, with some patients manifesting greater problems with executive functions or attention, and others with greater memory impairment. Various factors including neurochemical and neuropathological changes, biological markers including genetics, and co-morbid non-motor symptoms may influence the phenotypic differences and possibly also the conversion of mild cognitive impairment to dementia.

Several studies report over 10 year longitudinal data on the risk of dementia from incident cohorts. Of note, that despite differences in PD dementia definitions, geographical regions, and populations, the frequency of developing dementia in PD is fairly common across studies from the United Kingdom, Australia, China, and Europe.[1, 20-22] While there is evidence that many, and possibly most, PD patients go on to develop a dementia syndrome, it does not appear that all patients necessarily do so. Risk factors associated with PDD include older age; older age at PD onset; greater motor severity and more advanced disease; akinetic-rigid PD motor phenotype; longer PD duration; co-morbid neuropsychiatric symptoms such as psychosis, depression, daytime sleepiness; and potentially different genetic profiles.[5, 10] In addition, baseline cognitive impairment and also different neuropsychological profiles such as greater "posterior cortical" cognitive deficits (e.g., impaired semantic fluency, memory, and visuospatial functions) may be risk factors for developing PD dementia.[20] Studies of PD-MCI patients demonstrate that after 3-5 years, many of them have converted to PD dementia.[23 24] However, studies also show that some PD-MCI revert to normal cognition on follow-up testing or remain stable, thereby suggesting that PD cognitive impairment may fluctuate and that there may be other contributing factors to consider, whether related to cognitive performance, co-morbid non-motor features, medication use, or underlying neuropathology and other biomarkers.

Treating PD cognitive impairment

First, and on a practical front, a physician faced with a PD patient with cognitive issues especially if acute should exclude other potential causes of cognitive impairment and pursue additional clinical, laboratory, and imaging investigations, if needed. These include infections (e.g., urinary tract infection, pneumonia), metabolic derangements, dehydration, new neurological problems (e.g., stroke, subdural hematoma), new medical problems (e.g., B12 deficiency, thyroid disorders), or medication effects (e.g., pain, bladder, sedating

medications). It is important to inquire about other co-morbid neuropsychiatric problems including poor night-time sleep, excessive daytime sleepiness, psychosis, depression, anxiety, and apathy, which may play a role in cognitive deficits. A careful review of medication lists including PD medications with anticholinergics and dopamine agonists should be undertaken to stop or reduce agents that could contribute to impaired cognition. Detailed bedside cognitive testing and formal neuropsychological evaluations can be helpful to ascertain the severity and characteristics of the cognitive deficits. One also should discuss driving and home safety issues.

To date, only one medication has been approved by the FDA for the treatment of PDD, namely rivastigmine, a cholinesterase inhibitor that has both acetylcholinesterase and butyrylcholinesterase inhibition. A recent review highlights clinical trials of pharmacological and non-pharmacological agents for PDD and PD-MCI, from 2013-2015.[25] Other cholinesterase inhibitors including donepezil and galantamine and the NMDA antagonist memantine have been studied in PD dementia in double-blind, placebo-controlled trials with varying sample sizes and durations – and varying results. In the EXPRESS study, rivastigmine was studied in a large double-blind, placebo-controlled study at 3-12 mg/daily for 24 weeks in mild to moderate PDD patients and using the AD Assessment Scale-Cognitive (ADAS-Cog) subscale as the primary outcome.[26] Of the 541 PD patients who were enrolled, 410 completed the study (76% completion). There was a modest (2.1 point) improvement on ADAS-Cog in the rivastigmine group and a small worsening in the placebo group. Adverse events were mainly related to cholinergic effects including nausea, vomiting, and tremor. Donepezil (5 or 10 mg/d for 24 weeks) was studied in an equally large double-blind, placebo-controlled trial with ADAS-Cog and the Clinician's Interview-Based Impression of Change plus caregiver input (CIBIC+; global function) as primary outcomes.[27] ADAS-Cog mean changes from baseline to week 24 were not significant for donepezil in the intention to treat model, but after removing a treatment-by-country interaction (due to imbalance in enrollment across different countries), there was a significant, though modest, dose-dependent benefit with donepezil vs. placebo. On the CIBIC+, there was improvement in the 10 mg/d but not the 5 mg/d group. Similar side effects for cholinesterase inhibitors were seen. There have been several recent studies with memantine and PD dementia or DLB but results have been mixed.[28] Overall, benefits of cholinesterase inhibitors and memantine have been modest in clinical trials of PDD.[29]

More recently, cholinesterase inhibitors have been studied in PD-MCI with several trials underway (clinicaltrials.gov) and one small study with rivastigmine reporting negative results (p=0.096).[30] Other agents focused on the noradrenergic (e.g., atomoxetine) or dopaminergic systems (e.g., rasagiline) have been investigated in PD-MCI or PD-related executive dysfunction, and some trials have recently completed. While many studies to date are limited by small sizes, methodological issues, or open label designs, there is a growing interest in exploring the potential roles for cognitive training, physical exercise, combined mental and physical exercises, and deep brain stimulation techniques (DBS) or neuromodulation (e.g., transcranial magnetic stimulation) in treating PD cognitive impairment.[31] Improved symptomatic treatments for PD-MCI and PDD features as well as disease-modifying agents to stop or slow down cognitive decline in PD are greatly needed.

Mood disorders: Depression and Anxiety

Mood symptoms are frequent in PD, with depression and anxiety most commonly encountered. Neurodegenerative and neurochemical changes in mesocortical and mesolimbic dopaminergic neurons, brainstem serotonergic and noradrenergic neurons, and cortical-subcortical and limbic circuits suggest an intrinsic neurobiological basis for depression and anxiety in PD. Reactive depression and situational stressors may also occur, whether at the time of PD diagnosis, advancing symptoms, or other circumstances. Mood changes may occur as effects of medical or surgical interventions such as with dopamine agonists and mania/hypomania; post-operative depression, suicidal ideation, or mania have been reported after DBS for PD.

Depression

Estimates of depression in PD in the literature range from 2.7-90%, but it is thought that about 40-50% of PD patients have clinically significant depression.[32, 33] Depression in PD is likely underdiagnosed due to the definitions and criteria used for identifying depression and failure of PD patients to meet DSM-IV or V criteria for major depression. PD patients rather may experience milder, minor forms of depression; subsyndromal depression; or situational depression. Clinical symptoms of depression in PD, similar to its occurrence in a non-PD population, include mood changes (i.e., depressed mood, decreased interest and pleasure) as well as somatic and vegetative features. Some features of major depression, however, may overlap with PD motor, somatic, vegetative, sleep, and cognitive symptoms. Anxiety and apathy can also accompany depression in PD, though these may also be separate, distinct entities.[33, 34] PD patients with depression are less likely to have excessive guilt; feelings of worthlessness, hopelessness, or helplessness; delusions; or suicidality. A unique aspect of

depression in PD, along with anxiety, is its occurrence as a non-motor fluctuation, occurring at the nadir of dopaminergic stimulation or "off" period.[35] Much like motor fluctuations with the return of increased tremor, bradykinesia, or gait difficulty while wearing off or "off," PD patients can exhibit depressed mood, tearfulness, anxiety or panic symptoms in the "off" period. Recognition of the timing or cyclical occurrence of mood symptoms in this context is important as treatment strategies may target wearing off or "off" periods.

Like the cognitive symptoms, depressive symptoms can occur throughout the disease course in PD, from premotor to advanced stages, and contribute to reduced quality of life and daily function. Neurobiological and epidemiological data support the hypothesis that depression, along with anxiety, may represent a prodromal feature of PD, particularly with Braak's pathological staging of PD involving the locus ceruleus and dorsal raphe nuclei. Epidemiological studies support over 2-fold increased prevalences of depression diagnosis in patients later diagnosed with PD.[36] Depression is also commonly reported in early, de novo or untreated PD patients, along with other non-motor symptoms, such that de novo PD patients experienced significantly more depression, fatigue, apathy, and anxiety than healthy controls at baseline and over two years of follow-up.[37] Depression may be associated with longer disease duration, younger onset age, worsened motor severity and motor complications, more advanced disease stage, greater disability, and the postural instability gait disturbance phenotype as well as other neuropsychiatric co-morbidities affecting cognition, psychosis, and sleep.[38]

Treating PD depression

The treatment of PD depression involves both pharmacologic and non-pharmacologic approaches. The pharmacologic rationale is rooted in neurochemical alterations of serotonin, norepinephrine, and to some degree, dopamine associated with depression. Antidepressants in PD, however, have limited evidence base, due to few large, randomized, double-blind, placebo-controlled studies performed.[34, 39, 40] Typical medications used for PD depression include: Selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), tricyclic-related drugs (e.g., trazadone), presynaptic alpha-2 adrenoreceptor antagonist mirtazapine, and the noradrenaline**–**dopamine reuptake inhibitor (NDRI) bupropion. SSRIs are frequently used since they are better tolerated than other antidepressant classes such as TCAs. In one randomized, controlled study (SAD-PD) comparing paroxetine, venlafaxine, and placebo, both drug treatment groups were similarly effective in improving HAM-D scores at 12 weeks.[41] Two other randomized controlled trials, compared SSRIs and TCAs (one with desipramine vs. citalopram; the other with paroxetine CR vs. nortriptyline); in both studies, the drug treatment groups did better than placebo but TCAs were superior to SSRIs.[42, 43] TCAs should be used with caution, particularly in the elderly due to risk of confusion, hallucinations, and arrhythmias as well as in those with sedation and orthostatic hypotension. Dopamine agonists (e.g., pramipexole) improved depressive symptoms in some studies, along with providing motor benefit. Other medications such as mirtazapine, buproprion, atomoxetine, and newer antidepressants await further study. Serotonin syndrome is a rare risk with SSRIs and SNRIs when combined with MAOB-inhibitors. Non-pharmacological therapies such as cognitive behavioral therapy (CBT) demonstrated greater improvement in HAM-D scores as well as modest gains in verbal memory and executive function scores in a randomized controlled study of CBT vs. clinical monitoring.[44, 45] Transcranial magnetic stimulation, counseling, and psychotherapy may have roles as non-pharmacological treatments of PD depression, though require further study.

Anxiety

Anxiety is a common neuropsychiatric issue in PD, occurring in 20-50%.[34, 46] Similar to PD depression, it is likely under-recognized and undertreated. Anxiety in PD can occur in several different contexts – by itself or a specific anxiety state, but also as part of depression. Specific anxiety states in PD include: generalized anxiety disorder, panic disorder, phobias (e.g., social, agoraphobia), obsessive-compulsive disorder, and situational or stress-related. Non-motor fluctuations can occur with anxiety as the primary symptom. PD patients with extreme anxiety when wearing off or in "off" periods can have panic attacks, with marked anxiety, shortness of breath, diaphoresis, and autonomic and gastrointestinal symptoms, which can even lead to emergency room visits and evaluations for cardiopulmonary reasons. Some symptoms of anxiety also overlap PD symptoms with muscle tension, poor concentration, fatigue, sleep problems (insomnia), and autonomic dysfunction (cardiovascular, respiratory, gastrointestinal) among those. PD patients may have situational anxiety related to their tremors, experiencing freezing or turning "off," fear of falling, or in social situations. Similar also to depression in PD, DSM criteria fail to capture many PD patients who have anxiety disturbances.[47]

Anxiety in PD may relate to the underlying PD-related neurochemical alterations and neurodegeneration in the brainstem and subcortical regions.[46] Anxiety symptoms can occur throughout the disease course, from premotor phases to advanced stages. Anxiety also has been proposed as a risk factor for PD, with a 1.5-fold increased risk of PD associated with phobic anxiety and anti-anxiety medication prescriptions. Also, the concept of a "PD personality-type" has been proposed over the years, with a more anxious, lower novelty seeking, and higher harm avoidance personality type.[48] Anxiety symptoms have been endorsed by over 50% of PD patients on non-motor symptom surveys.[49]

Treating PD anxiety

To date, there have been no controlled therapeutic trials for anxiety disorders in PD.[39] Medications used to treat anxiety disorders in PD are similar to those utilized in non-PD populations, such as SSRIs, benzodiazepines, and in some, buspirone. Benzodiazepines should be given cautiously in elderly patients, those with cognitive impairment or psychosis, poor balance or falls, and daytime sleepiness. Surprisingly, anxiety treatments are underutilized even in movement disorder neurologist practices. PD anxiety was more likely to be treated when co-morbid depression or motor fluctuations occurred, and 53% of PD patients with anxiety disorders (n=38) were medically untreated.[50] For anxiety symptoms related to "off" periods, modification of the dopaminergic regimen may be effective, such as with longer acting dopaminergics, higher doses or adjunctive dopaminergic treatment, or more frequent and smaller doses. Non-pharmacological treatments such as counseling, psychotherapy, cognitive behavioral therapy, relaxation, stress reduction therapies, and exercise may reduce anxiety in PD but require further study in large, controlled trials.

Psychosis

Psychosis is frequent, affecting over one-third of PD patients treated with chronic dopaminergic therapy and over 50% in longitudinal studies of 10 years or more and contributes to increased mortality, nursing-home placement, and caregiver stress.[51] The clinical spectrum of PD psychosis ranges from illusions to hallucinations to delusions.[52] Most hallucinations in PD are visual, although they also can occur in auditory, tactile, olfactory, and gustatory modalities. Hallucinations in nonvisual modalities are frequently accompanied by visual hallucinations and occur in more advanced PD; once present in multiple sensory modalities, there is a high risk of multimodal hallucinations continuing.[53] Delusions occur less often than hallucinations, affecting about 5–10% of patients [51]. Common delusions include jealousy, spousal infidelity, paranoia, abandonment, or somatic illnesses, in contrast to grandiosity, reference, and bizarre beliefs seen in schizophrenia. Misidentification syndromes are specific types of delusions, frequently associated with PD dementia and commonly including Capgras syndrome (e.g., patient thinks that his recognizable spouse is an imposter) and Fregoli syndrome (e.g., patient believes that familiar people are disguised as strangers).

In the clinical setting, the diagnosis of PD psychosis is largely based on the report obtained from the patient, caregiver or other informant. PD psychosis, like many of the mood and behavioral symptoms, is frequently under-recognized and not always discussed between the patient and their family/caregiver or with their healthcare provider. It is important regularly ask about these symptoms at clinic visits and to do so in a non-judgmental way. Patients and caregivers may be reluctant to volunteer these symptoms due to stigma or their potentially bizarre nature. Unfortunately, in many cases, caregivers are often unaware of them until the psychosis becomes problematic.

The exact mechanisms of PD psychosis are not fully known but it is thought that psychosis may be caused by extrinsic (i.e., dopaminergic medications) and/or intrinsic (i.e., disease-related) factors. Intrinsic or PD-related factors include abnormalities in the visual, sleep, mood, and cognitive processes. Underlying sensory deficits (i.e. visual or hearing impairment) may contribute to psychosis. For example, in the Charles Bonnet syndrome, elderly people with low visual acuity may experience benign visual hallucinations as "release" phenomena.[54] Risk factors associated PD psychosis include older age, greater axial rigidity, advanced disease, and potentially genetic susceptibilities. Compared to nonhallucinating PD patients, PD hallucinators frequently exhibit greater cognitive deficits, particularly in attention, executive function, and visuospatial abilities. Neuroanatomically, the pathophysiology of PD psychosis incorporates dysfunction in or across three primary areas: the visual system, brainstem function and cortex. There also are accompanying neurochemical and neuropathological changes in these areas. PD psychosis may result from interactions between behavioral and cognitive phenomena and abnormalities in "top-down" and/or "bottom-up" processing as suggested by several neuroimaging and physiological studies.

Treating PD psychosis

Treatments for PD psychosis include pharmacological and nonpharmacological strategies.[34, 40, 55] Factors such as temporal course (acute versus chronic), psychosis severity, patient age, presence of dementia, mood or sleep disturbances, motor severity and motor function, along with the patient's support system may influence treatment decisions. Acute PD psychosis should prompt an evaluation for other medical and neurological conditions besides PD and a review of the patient's medication regimen and condition, similar to those discussed for acute cognitive changes. Acute management may require cautious, short-term use of low-dose benzodiazepines to reduce agitation, though one should be vigilant for paradoxical reactions, sedation, and confusion. Specific medical causes like infections should be treated. Non-PD medications with centrally acting properties (e.g., anticholinergics for bladder hyperactivity, TCAs for depression, benzodiazepines for anxiety or sleep, hypnotics for sleep, and opioids for pain) should be reduced or stopped. Dopaminergic medications for PD motor symptoms may need to be reduced or discontinued, in some cases while monitoring for worsened motor function. While there are a number of different proposed algorithms by which to decreased or stop PD medications and this depends on an individual patient's regimen and needs, one can consider this order for discontinuing those medications with the highest risk of psychosis symptoms: anticholinergics, amantadine, MAO-B inhibitors, dopamine agonists, COMT inhibitors, and lastly, levodopa.[56]

Antipsychotic medications may be required for acute and chronic PD psychosis, particularly if dopaminergic medications cannot be reduced without worsening parkinsonism. To date, there have been few randomized, double blind, placebo-controlled trials of atypical antipsychotics in PD.[39, 57] Clozapine is supported by double blind, placebo-controlled trials in PD demonstrating improvement in psychosis without worsening of motor function. However, its use requires blood-count monitoring given the rare, idiosyncratic risk of agranulocytosis as well as monitoring for side effects of sedation or hypotension. Quetiapine demonstrates comparable efficacy to clozapine in comparison studies, frequent and easy administration, and a relatively low-risk side effect profile but has not been successful in double-blind, placebo-controlled randomized trials. Doses for clozapine and quetiapine to treat PD psychosis typically are lower than those used for schizophrenia or other psychiatric disorders. In contrast to the serotonergic clozapine and quetiapine, medications with greater dopamine blockade, including olanzapine, should be avoided due to risk of increased parkinsonism. Antipsychotics also carry "black box" warning for antipsychotic use in elderly patients with dementia. A novel agent pimavanserin, a 5HT-2a receptor inverse agonist, recently demonstrated improvement on the primary outcome measure, the SAPS-PD scale, in a randomized, double-blind, placebo controlled 6 week trial of 199 patients with PD psychosis.[58] There was also a statistically significant improvement in the CGI scale, caregiver burden scale, and SCOPA-sleep scale. There was no significant worsening of motor function or major safety issues; an increase in QTc interval was noted in the drug group but without clinical effect. Pimavanserin was approved by the FDA in 2016 for the treatment of PD psychosis. Several reports suggest that cholinesterase inhibitors improve hallucinations associated with PDD. Subanalyses of the EXPRESS double-blind, placebo-controlled study in PDD [26] suggested that rivastigmine was mildly more effective in selected cognitive and behavioral measures in PD hallucinators compared to non-hallucinators.[59] Cholinesterase inhibitors may provide a treatment option for chronic psychosis in demented PD patients but are less likely useful in acute psychotic or emergency settings. At present, evidence for treating psychosis in non-demented PD is lacking and studies are currently underway to evaluate cholinesterase inhibitors for PD psychosis.

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