Emerging role of psychosis in Parkinson's disease: From clinical relevance to molecular mechanisms

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Abstract
Parkinson’s disease (PD) is the second most common neurodegenerative disease. Psychosis is one of the common psychiatric presentations in the natural course of PD. PD psychosis is an important non-motor symptom, which is strongly correlated with a poor prognosis. Increasing attention is being given to PD psychosis. In this opinion review, we summarized and analyzed the identification, screening, epidemiology, mechanisms, risk factors, and therapeutic approaches of PD psychosis based on the current clinical evidence. PD psychosis tends to have a negative effect on patients’ quality of life and increases the burden of family caregiving. Screening and identification in the early stage of disease is crucial for establishing tailored therapeutic strategies and predicting the long-term outcome. Development of PD psychosis is believed to involve a combination of exogenous and endogenous mechanisms including imbalance of neurotransmitters, structural and network changes, genetic profiles, cognitive impairment, and antiparkinsonian medications. The therapeutic strategy for PD psychosis includes reducing or ceasing the use of dopaminergic drug, antipsychotics, cholinesterase inhibitors, and non-pharmacological interventions. Ongoing clinical trials are expected to provide new insights for tailoring therapy for PD psychosis. Future research based on novel biomarkers and genetic factors may help inform individualized therapeutic strategies.

Key Words: Psychosis; Parkinson’s disease; Hallucinations; Delusions; Antipsychotics

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Core Tip: Parkinson’s disease (PD) psychosis encompasses a variety of misperception symptoms including illusions, passage hallucinations, presence hallucinations, and delusions as well as formed visual hallucinations. PD psychosis is an independent predictor of mortality. A variety of risk factors for development of PD psychosis have been identified. Side effects of anti-Parkinsonism medications and patient-specific characteristics are both involved in the onset and progression of PD psychosis. Targeting the 5-hydroxytryptamine subtype 2A receptor is a promising pharmacological intervention.

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INTRODUCTION

With progressive aging of the population, Parkinson’s disease (PD) has become the second most common neurodegenerative disease after Alzheimer’s disease. Studies have shown a global increase in the prevalence and incidence of PD with increasing age, with no predilection for a particular sex[1]. The neuropathological hallmarks of PD are gradual degeneration and loss of dopaminergic neurons in the pars compacta of the substantia nigra, along with the formation of Lewy bodies. Since these dopaminergic neurons project to the striatum, it causes reduction in dopamine levels in striatum, impairing neurotransmitter homeostasis in the central nervous system. PD is traditionally recognized as a movement disorder with prominent motor symptoms including tremor, bradykinesia, rigidity, gait disturbance, and unstable posture[2], which is the main cause of disability in these patients. However, PD is also believed to be associated with a variable spectrum of complex non-motor symptoms, such as cognitive and affective impairment, hypomnesia, sleep disturbance, neuropsychiatric complications (depression, psychosis, apathy, dementia), and autonomic disorders. Hyposmia may precede the onset of typical motor symptoms of PD by up to 20 years[3]. These findings highlight that PD not only involves the dysfunction of the dopaminergic system, but also other neurotransmitter systems, such as cholinergic, noradrenergic, and serotonergic systems related to the above clinical entities[4].

Psychosis is one of the common psychiatric presentations in the natural course of PD. Studies have indicated a diverse range of psychotic symptoms in patients with PD; however, there is no standardized classification of these symptoms. The spectrum of PD psychosis encompasses a variety of misperception symptoms including illusions, passage hallucinations, presence hallucinations, delusions, well-structured visual hallucinations, and other perceptual disturbances. In general, visual illusions, passage and presence hallucinations are termed minor hallucinations, which are the most common psychotic phenomena of psychosis in PD[5]. Minor hallucinations are accompanied by other non-motor symptoms (typically rapid eye movement sleep behavior disorder and cognitive impairment) in PD psychosis[6,7].

The onset of some psychotic manifestations may occur even earlier than motor symptoms of PD[6]. The presence of severe psychotic symptoms is an independent risk factor of impaired health-related quality of life in PD[8].

PD psychosis has a negative influence on patients’ quality of life and increases the burden of caregiver and family. A study including 80 patients with PD who were followed up for approximately four and a half years, found that visual hallucinations and visual illusions in PD patients heralded a higher risk in development of dementia[9]. A large-scale longitudinal study with approximately 10-year follow-up including 12077 PD patients revealed an increased risk of falls and fractures in PD patients with psychosis[10]. A small case-control study involving 21 PD patients with mild cognitive impairment suggested that patients with visual hallucinations may have a higher rate of dementia progression (50% vs 25% in patients without visual hallucinations)[11]. A long-term follow-up study showed that PD psychosis is an independent factor for predicting mortality[12] and likewise, increased occurrence of hallucinations contributed markedly to mortality in PD patients[13].

Furthermore, it is currently considered that minor hallucinations are important events during the natural history of PD; this is because patients with PD psychosis not only require increasing levels of assistance and care from their caregivers but also have increased likelihood of moving to a nursing home and being at potential risk of mortality[14,15].

EPIDEMIOLOGY

Almost all PD patients develop at least one of the neuropsychiatric manifestations in the late stage of the disease[16]. Nevertheless, the reported frequency of PD psychosis is slightly discrepant among studies due to the different assessment and screening methods used in epidemiological studies. In a
community-based cross-sectional study of 250 PD patients, the prevalence of any psychotic symptom was 26%; 47.7% of PD patients with psychosis had mild phenomena and 52.3% had hallucinations and/or delusions[17]. Similarly, Kulick et al[18] reported a 29% prevalence of any psychotic symptom in a cohort of 199 PD outpatients[18]. Longitudinal studies have suggested that the prevalence of psychosis in PD patients tends to increase over time. The incidence of PD psychosis gradually increases with the progression of PD[19]. Data from Parkinson’s Progression Markers Initiative showed that the incidence of PD psychosis at baseline, 1st year, and 2nd year was 3%, 5.3%, and 10%, respectively, increasing with duration of PD[20]. Yoritaka et al[21] conducted a retrospective study of 1,453 PD outpatients, and found that 53.9% of patients with late-onset PD and 22.1% of patients with early-onset PD finally developed psychosis by the 12th year[21]. In a recent cross-sectional study, 38% of PD patients were found to suffer minor hallucinations based on questionnaire analysis[22]. Moreover, it is noted that minor phenomena such as presence, passage hallucinations presented as a pre-motor symptom in approximately one-third of drug-naive PD patients; moreover, the minor phenomena preceded the onset of the first representative motor symptoms of PD by 7 mo to 8 years[6]. The variable rates of psychotic symptoms in PD patients may be attributable to different diagnostic criteria and study settings. However, more than 50% PD patients are expected to develop at least one psychotic symptom during the course of the disease[19].

IDENTIFICATION AND SCREENING

Diagnostic criteria

According to the consensus from working groups of National Institute of Neurology and Stroke (NINDS), and the National Institute of Mental Health (NIMH), the diagnostic criteria for psychosis spectrum related to PD is mainly defined as follows: (1) Hallucinations (passage and presence hallucinations, visual formed hallucinations), illusions, delusions, and a false perception of things or people that do not actually exist around them with preservation of insight. The psychotic and misperception symptoms appear periodically or continuously for more than 1 mo in the setting of a clearsensorium; (2) Diagnosis of PD is based on United Kingdom brain bank criteria and onset of characteristic phenomena follows the diagnosis of PD; and (3) Exclusion of other disorders characterized by similar psychotic symptoms such as dementia with Lewy bodies (DLB) (with accompanying visual hallucinations), primary psychiatric disorders, delirium, and extrapyramidal symptoms induced by drugs[23].

Notably, given the shared symptoms and overlapping crucial neuropathological characteristics, some clinicians considered that DLB and PD dementia are the two extremes or the different stages in the spectrum of a clinical entity[24,25]. Both PD and DLB are categorized as alpha synucleinopathies spectrum which commonly present with hallucination and delusions distress[26]. The relationship between DLB and PD dementia is still under debate; nevertheless, according to some experts, the treatment principles and the pathogenetic mechanisms of psychosis in DLB and PD share a certain commonality[27].

However, the diagnostic criteria formulated by NINDS-NIMH work group for PD psychosis was not completely concordant with the Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition (DSM-V) criteria for “psychosis due to a medical condition,” proposed by the American Psychiatric Association, which is generally acknowledged as the diagnostic reference standard for psychosis and psychotic disorders. It was highlighted that patients with PD psychosis who fulfilled the NINDS-NIMH criteria but not the formal DSM-V criteria for psychosis due to PD manifested only mild psychotic symptoms, suggesting that NINDS-NIMH diagnostic criteria would be useful for the surveillance and identification of early symptoms of emerging psychosis[28]. Gordon et al[29] proposed a modified score assessment for NINDS-NIMH criteria and showed that the scoring approach can improve the diagnostic performance for PD psychosis[29]. The NINDS-NIMH diagnostic criteria work group, DSM-V criteria, and modified NINDS criteria proposed by Gordon et al[29] are summarized in Table 1.

Patients who develop hallucinations can still retain their awareness about misperception in the early stage, a phenomenon previously referred to as “benign hallucinations.” However, with advancing disease, patients tend to lose insight into discerning hallucinations, a phenomenon referred to as “malignant hallucinations.” Malignant hallucinations are disabling, and are interspersed with paranoid thoughts of suspiciousness, accusations, and being slovenly[5]. In patients with PD psychosis, any form of hallucinations tend to persist intermittently once they occur. Minor hallucinations, such as illusions, are relatively easier to handle than visual hallucinations[30,31].

Screening tools

Explicitly screening for minor hallucinations in the early stage of disease might be crucial for establishing tailored therapeutic strategies and predicting the long-term outcome[30]. The high incidence and prevalence of PD psychosis in different stages and the associated mortality risk underlies the importance of routine screening for psychosis in all patients with PD. Optimal screening and identification of PD psychosis is vital for following treatment and management. Though some neuropsychiatric scales such as the Positive and Negative Syndrome Scale (SAPS), Brief Psychiatry Rating Scale,
### Table 1 Diagnostic criteria for Parkinson’s disease psychosis according to the National Institute of Neurology and Stroke-National Institute of Mental Health and Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition and Modified National Institute of Neurology and Stroke and score

| NINDS-NIMH diagnostic criteria | DSM-V criteria | Modified NINDS criteria score proposed by Gordon et al[29] |
|--------------------------------|----------------|----------------------------------------------------------|
| PD diagnosis                   | (1) United Kingdom Brain Banks criteria; and (2) The onset of PD must be preceded by the psychotic symptoms | Prominent hallucinations or delusions | Assigning scores to each psychotic symptom of NINDS-NIMH diagnostic criteria: (1) Delusions score with 2; (2) Other psychotic symptoms score with 1; and (3) Cut-off sum for PD psychosis equal to or higher than 2 |
| Psychotic symptoms: At least one of the following | (1) Hallucinations; (2) False perceptions; (3) Illusions; and (4) Delusions | There is evidence from the history, physical examination, or laboratory findings that the disturbance is the direct pathophysiological consequence of PD |
| The duration of psychotic symptoms | (1) Periodically or continuously; and (2) Last more than 1 mo | The disturbance is not better explained by another mental disorder |
| Exclusion of other probable disorders and conditions | (1) Dementia with Lewy bodies; (2) Primary psychiatric disorders; (3) Extrapyramidal symptoms induced by drugs; and (4) Delirium | (1) The disturbance does not occur exclusively during the course of a delirium; and (2) The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning |

**DSM-V:** Diagnostic and Statistical Manual of Mental Disorders-Fifth Edition; **PD:** Parkinson’s disease; **NINDS-NIMH:** National Institute of Neurology and Stroke and the National Institute of Mental Health.

Neuropsychiatric Inventory, Clinical Global Impression Scale, Schedule for Assessment of Positive Symptoms are recommended for assessment of psychotic symptoms, none of these scales has been tailor-made for PD psychosis[32]. In clinical practice, some tools need to be combined with other PD assessment scales such as Movement Disorder Society United PD Rating Scale (MDS-UPDRS) and Parkinson’s Psychosis Questionnaire. Currently, some abridged and clinically-designed versions such as perception/hallucinations domains of Non-Motor Symptom Assessment Scale for PD[33,34], SAPS for PD (SAPS-PD)[35], and modified version of SAPS-PD[18] with high reliability and sensitivity have been widely applied in clinical trials.

In summary, the NINDS-NIMH diagnostic criteria should be the basis for identifying PD psychosis in suspected patients. Since minor hallucinations may be missed in clinical practice, we recommend the use of scales such as SAPS-PD specifically for screening and assessment of abnormal perceptions in all patients with a diagnosis of PD.

### MECHANISMS AND RISK FACTORS

Although insights obtained from studies investigating the mechanisms of PD psychosis have opened new avenues for individualized treatment strategies for PD, the pathophysiology of PD psychosis is not fully elucidated owing to its complexity and multifactorial nature. Current evidence suggests the involvement of a combination of exogenous and endogenous mechanisms[36]. Studies of the endogenous pathophysiological features of PD psychosis will facilitate the development of novel treatment strategies.

**Neurotransmitters imbalance**

Some neurobiochemical studies have revealed the involvement of impaired homeostasis of some neurotransmitters (especially serotonin, dopamine, acetylcholine, and glutamate) in the endogenous development of PD psychosis. The imbalance between serotonergic and dopaminergic neurotransmission is one of the pivotal factors mediating the occurrence of PD psychosis[37]. Serotonin activators can elicit delirium and psychosis by inducing the release of dopamine from glutaminergic neurons in the ventral tegmental area and nucleus accumbens, while reducing the activity of serotonin can alleviate psychiatric symptoms[38,39]. Additionally, PD patients have been considered to have cholinergic deficiency in the nucleus basalis of Meynert; this phenomenon is more likely to occur in patients with PD who have cognitive impairment and psychotic symptoms[40].

Abnormal activation of the special serotonin (5-hydroxytryptamine) receptor subtype, 5-hydroxytryptamine subtype 2A (5-HT2A) results in psychotic symptoms[41]. Ballanger et al[42] first performed a serotonergic imaging study using the 5-HT2A receptor ligand setoperone-F18 positron emission tomography. They found remarkable enhancement of 5-HT2A receptor binding in PD patients with visual hallucinations. The regions with excessive binding were located in the cortex and were involved...
in ventral visual pathway, medial orbitofrontal cortex, and bilateral dorsolateral prefrontal cortex[42]. Additionally, Huot et al[43] performed an autoradiographic study using [(3)H]-ketanserin and spiperone binding 5-HT2A receptor, and revealed increased 5-HT2A receptor binding in inferolateral temporal cortex, which is also involved in visual processing[43]. By contrast, another study using a similar imaging technique found no relationship between 5-HT1A receptor-binding and psychosis, though high expression of 5-HT1A binding was universally observed in all patients with PD, regardless of visual hallucination status[44].

**Clinical biomarkers**

A variety of risk factors related to the underlying mechanisms of the development of PD psychosis have been identified[45]. Studies have focused on clinical presentations and laboratory indices as clinical markers of PD psychosis. In a case-control study including 111 PD patients, elevated level of plasma C-reactive protein was found to be an independent predictor of the occurrence of hallucinations or illusions[46]. A cross-sectional study conducted in Japan showed a significant correlation of minor hallucinations with cognitive impairment and rapid eye movement (REM) sleep behavior disorders[22]. In a study of 423 subjects (mean follow-up: More than 4 years), patients with PD early-onset psychosis had lower cerebrospinal fluid amyloid Aβ1-42, decreased olfactory scores, increased depression scores, and increased symptoms of REM sleep behavior disorders compared with those without early-onset psychosis. A pathological study revealed a close association of visual hallucination with amyloid deposition, the density of neurofibrillary tangles, and α-synuclein in the brain of PD patients[47].

**Structural and network changes**

Recent studies have revealed that PD psychosis may also be triggered by altered brain structural connectivity that disturbs the normal attention and perception, resulting in high-amplitude activity of the default mode network.

In a study by Ffytche et al[48], patients with early-onset formed hallucinations showed low-level visual function, thinning of right cortex (frontal, occipital, parieto-temporal, and insular lobes), and reduced volumes of bilateral basal ganglia and bilateral hippocampus at baseline[48]. Firbank et al[49] studied 36 patients with PD by magnetic resonance spectroscopy, and found that the ratio of γ-aminobutyric acid/creatinine in occipital lobe of PD patients with visual hallucinations was lower than that in PD patients without any psychotic symptom; in addition, there were signs of gray matter loss in V4 region of anterior temporal lobe and visual cortex[49]. Patients with PD with minor hallucinations showed reduced gray matter atrophy in visuoperceptive regions[50,51]. Zarkali et al[52] used fixel-based analysis to assess neural network and structure; they found that left inferior fronto-occipital white matter tracts connected with posterior thalamic projections were degenerated and decreased in PD patients with hallucinations[52], suggesting that splenium and posterior thalamus may play a major role in maintaining the network balance and regulating the default mode network.

**Genetic profiles**

Genetic susceptibility to PD psychosis is a subject of ongoing research. Studies have largely focused on the polymorphism of related genes such as apolipoprotein (Apo) E genes, cholecystokinin system-related genes, dopamine system-related genes, serotonergic system-related genes, and tau protein-related genes. However, with the exception of polymorphisms of cholecystokinin system-related genes, the conclusions pertaining to most of the other studies were inconsistent with respect to predicting the development of any psychotic profile in PD[53]. This suggests that Mendelian genetic inheritance may not play a predominant role in the development of PD psychosis. Additionally, a longitudinal cohort study of 215 PD patients and 126 controls with up to 12 years of follow-up identified mutations in the glucocerebrosidase gene as a susceptibility factor for early-onset PD psychosis[54]. This highlights that standardized long-term follow-up studies may help unravel the predisposing genes of PD psychosis.

**Motor and cognitive impairment**

Motor symptoms of PD are also inextricably linked with psychosis. In a cross-sectional study of 500 subjects, PD psychosis was related to freezing of gait (as evaluated by UPDRS Part II score), age, and disease duration, rather than genetic polymorphisms of ApoE, α-synuclein promoter, and microtubule-associated protein tau[55]. In a retrospective cohort study of PD patients (n = 331) conducted by Sawada et al[56] (duration of follow-up: 2 years), longer duration and high severity of PD (modified Hoehn-Yahr stage ≥ 4) was identified as a risk factor for PD psychosis[56]. Cognitive impairment (Mini-Mental State Examination scores ≤ 24) increases the risk of PD psychosis[56]. In addition, PD clinical subtypes are also believed to be closely related to PD psychosis. A prospective study categorized 206 PD patients into four subgroups based on motor symptoms. Compared with the tremor subtype, patients with rigid-kinetic subtype showed a tendency for development of visual hallucinations[57]. Moreover, the prevalence of visual hallucinations in patients with late-onset PD was found to be higher than that in patients with early-onset PD[58]. However, research on the pathophysiology of PD psychosis is still in the exploratory stage, and there is no robust evidence of the pathophysiology and risk factors for PD psychosis. Neither biomarkers nor
genetic mutations play a dominant role as endogenous factors in the pathophysiology of PD psychosis. Multivariate analysis of data from large-scale clinical trials with long-term follow-up may help characterize the pathogenesis of PD psychosis.

**Antiparkinsonian medications**

Both environmental susceptibility factors and patient-specific characteristics are involved in the initiation and progression of PD psychosis. The side effects of some antiparkinsonian medications are well recognized as exogenous factors triggering PD psychosis. Currently, the treatment strategy for motor symptoms of PD involves targeting several molecular targets. Based on these targets, there are eight categories of antiparkinsonian drugs in clinical use: Dopamine (DA) precursor (levodopa), dopamine receptor (DR) agonists (ropinirole, pramipexole, rotigotine), DA decarboxylase inhibitors (carbidopa, benzerazide), catechol-O-methyltransferase (COMT) inhibitors (entacapone, tolcapone), monoamine oxidase (MAO)-B inhibitors (rasagiline, selegiline, safinamide), N-methyl-D-aspartate receptor antagonists (amantadine), anticholinergics (trihexyphenidyl, benztropine), and adenosine A2A antagonist (istradefylline)[59]. Long-term use of almost all types of antiparkinsonian medications may lead to psychotic symptoms in patients with PD.

A decade earlier, treating with higher levodopa equivalent daily dose at baseline was found to be a predictor of developing PD psychosis in a large-scale prospective study during 12 years of follow-up[60] and in a small retrospective study[22].

Compared with levodopa, the risk of psychosis may be higher with DR agonists. DR agonists are widely prescribed to patients with early-onset PD and PD patients in whom levodopa does not effectively control the motor symptoms. In a prospective multicenter study, patients with early-onset PD receiving DR agonist treatment at baseline were more likely to develop PD psychosis during the 2 years of follow-up[61]. In the PRO-PARK study, both DR agonists and DA precursors were identified as independent risk factors for hallucinations in patients with PD[62]. Barrett et al[63] showed a significant relationship between the occurrence of psychosis and the use of dopamine agonists in PD patients without dementia[63]. Similarly, in a cross-sectional study involving 805 PD patients, use of DR agonists was associated with impulse control disorders (mainly pathological gambling and hypersexuality)[64].

A comprehensive retrospective analysis of serious adverse drug events reported by the United States Food and Drug Administration (FDA) over a 10-year period also revealed an association of DR agonists with impulse control disorders; of these, pramipexole and ropinirole showed the strongest correlation due to their strong affinity for dopamine D3 receptors[65]. Moreover, a cross-sectional study of 805 PD patients also found an association between DR agonists and delusional jealousy[66].

PD psychosis also occurred during long-term treatment with amantadine, especially in elderly patients. A report showed that excessive reduction or sudden withdrawal of amantadine can cause delirium, which may be due to the rapid shortage of functional dopamine in the cerebral cortex and limbic system[67]. In addition, other anti-PD drugs, such as anticholinergics[56] and COMT inhibitors [68] may also increase the risk of PD psychosis.

The underlying mechanism of the relationship between antiparkinsonian medications and PD psychosis has not been fully elucidated, and relevant clinical studies have yielded contradictory results [69]. PD psychosis induced by dopaminergic drugs may be associated with abnormal upregulation of serotonin receptors in the cerebral cortex and the ventral striatum that presumably are the results of shift from dorsal to ventral in midbrain dopaminergic projections and increased thalamic/raphe serotonergic function[70]. Slow and sustained stimulation of DA receptors by dopaminergic drugs in the nigra-striatal pathway can also enhance the sensitivity of dopamine receptor and dysfunction of cerebral limbic system. PD psychosis is also believed to be due to dyshomeostasis of serotonin-dopamine balance [37].

It is worth noting that not all PD patients receiving dopamine replacement therapy present psychotic symptoms. A high prevalence of minor symptoms was shown in drug-naïve PD patients[6], and in some prospective studies, L-dopa dose equivalence was not found to increase the risk of psychosis[71]. We believe that psychosis and other neuropsychiatric complications are potential side effects of DA replacement therapy. That is, in the pathophysiology of PD psychosis, antiparkinsonian medications may act as an external factor that triggers the development of psychosis in genetically-predisposed individuals.

**TREATMENT AND MANAGEMENT**

Development of psychosis in PD patients should prompt careful evaluation of the potential causes by neurologists and psychiatrists. If psychotic symptoms are regarded to be related to antiparkinsonian medications, PD medications should be gradually withdrawn, and discontinued in the following sequence: Firstly, reduce the dosage or discontinue anticholinergic drugs, followed by MAO-B inhibitors, amantadine, DR agonists, COMT inhibitors, and finally DA precursors[72]. If psychotic symptoms persist after withdrawal of antiparkinsonian medications, antipsychotic drugs should be initiated early. Although reducing or even stopping the use of DA precursor and DA agonists may...
minimize psychological distress, it may lead to worsening of motor symptoms of PD. Otherwise, if PD psychosis is less relevant with deterioration of motor symptoms, use of antipsychotics should be considered.

**Serotonin 5-HT2A receptors antagonists**

Antipsychotics can be divided into two categories. First-generation antipsychotics are not recommended for the treatment of PD psychosis due to extrapyramidal side effects (EPS). EPS caused by the use of antipsychotics can cause deterioration of motor function, including acute dystonia, akathisia, parkinsonism, and tardive dyskinesia[73]. Second-generation antipsychotics, also known as atypical antipsychotics (including clozapine, quetiapine, olanzapine, risperidone, and amisulpride) mainly mitigate or antagonize the activity of DA on receptors of DA2 and 5-HT2A. Two network meta-analyses and systematic reviews revealed that most antipsychotic medications may potentially cause EPS in schizophrenial[74] and worsening of motor function in PD psychosis[75]. EPS occurs less frequently during treatment with second-generation antipsychotics compared to the first-generation antipsychotics, which were widely used as the standard treatment for PD psychosis. The development of EPS is believed to be related to the non-specific blocking of DA2 receptors signaling in the nigrostriatal dopaminergic system by antipsychotics. Targeting only the 5-HT2A receptor is an ideal pharmacological intervention which can relieve PD psychosis without worsening PD motor function[38].

Prior to the approval of pimavanserin for the treatment of PD psychosis by the United States FDA, most guidelines for pharmacological treatment relied mainly on clinical evidence pertaining to second-generation antipsychotics. Among the antipsychotics, clozapine and quetiapine were the most commonly prescribed for PD psychosis[76].

Clozapine is a benzodiazepine antipsychotic that can regulate DA receptors (binding affinity DR1 > DR4 > DR2). It also targets multiple types of receptors, and is a potent antagonist at the 5-HT2A receptor. The therapeutic efficacy of clozapine is believed to be mediated through antagonism of the dopamine type 2 and 5-HT2A receptors. In addition, it acts as an antagonist at alpha-adrenergic, histamine H1, cholinergic, and other dopaminergic and serotonergic receptors. Clozapine was the first atypical antipsychotic drug to be proven effective in the treatment of PD psychosis with relatively low impact on PD motor symptoms[75]. Two randomized, controlled, double-blind trials conducted more than 10 years ago demonstrated the effectiveness of low-dose clozapine for the treatment of PD psychosis without significantly worsening the motor symptoms[77,78]; however, poor patient tolerance of the adverse effects of clozapine (granulocytopenia, excessive sedation, orthostatic hypotension, salivation, and metabolic syndrome) limits its clinical utility. A recent network meta-analysis suggested a notable therapeutic performance of clozapine without marked exacerbation of motor symptoms in patients with PD psychosis[79].

Quetiapine, an atypical antipsychotic medication with a similar molecular structure to clozapine, is a selective antagonist of 5-TH2 and DA2 in the limbic system of the midbrain, and it also has a high affinity for histamine and adrenergic α1 receptors in the brain. In a double-blind, placebo-controlled study of quetiapine for treatment of PD psychosis, none of the PD patients withdrew from the clinical trial due to adverse reactions, indicating favorable safety profile of quetiapine in PD patients[80]. In comparative studies for PD psychosis, the efficacy of quetiapine was similar to that of clozapine, but the results were not consistent between quetiapine and placebo[80-83]. A meta-analysis of data from six studies indicated that the efficacy of quetiapine for alleviating psychotic symptoms in PD is not higher than that of clozapine[84]. A recent systematic review of seven controlled trials revealed that the efficacy of quetiapine for treatment of psychosis in patients with PD, PD dementia, and DLB is not superior to that of placebo or clozapine; however, quetiapine showed less adverse reactions, EPS, and greater safety than clozapine[85]. Although the therapeutic benefit of quetiapine does not fully meet the need in the treatment of PD psychosis, quetiapine was one of the predominant first-line antipsychotic drugs due to its high tolerability and safety.

**Pimavanserin**

Pimavanserin has a unique mechanism of action in the treatment of PD psychosis. It is a highly-selective inverse agonist of the serotonin 5-HT2A receptors (Ki value: 0.087 nmol/L) rather than a DR antagonist. Different with other atypical antipsychotics with 5-HT2A receptor antagonism, pimavanserin is an inverse agonist which not only predominantly mediates 5-HT2A receptor antagonism but also mitigates the intrinsic activity of the receptors. It also has a certain affinity for 5-HT2C (Ki value: 0.44 nmol/L) [86]. In the neocortex of PD patients, with the increase in 5-HT2A receptor affinity in the visual regions, PD patients are more likely to experience visual hallucinations. Pimavanserin regulates 5-HT2A activity by targeting and controlling the excitatory impulses in the central nervous system, reducing the risk of hallucinations and delusions. In addition, pimavanserin has minimal effect on 5-HT2B, dopaminergic, adrenergic, histaminergic and muscarinic receptors, and calcium channels. Therefore, theoretically, unlike other antipsychotics, it is not expected to have adverse effects, such as worsening of motor symptoms, excessive sedation, or orthostatic hypotension[87].
The efficacy and safety of pimavanserin were evaluated in a randomized, double-blind, placebo-controlled multicenter phase III clinical trial. The trial was conducted at 52 medical centers in the United States and Canada and included 199 patients with PD psychosis recruited from August 2010 and August 2012. Compared to placebo, patients receiving pimavanserin showed 37% improvement in SAPS-PD scores without any noteworthy safety concerns or deterioration of PD motor function as assessed by the UPDRS. The results of this trial indicated a clinically significant therapeutic effect of pimavanserin for psychotic symptoms related to PD[88]. In another 6-wk, randomized, double-blind, placebo-controlled phase III clinical trial enrolling 298 PD patients with psychotic symptoms, pimavanserin arm showed a significant improvement in nighttime sleep score without affecting daytime sleepiness[89]. Ballard et al[90] reported the largest clinical trial to date evaluating the long-term tolerability and safety of pimavanserin in the treatment of PD psychosis with a median follow-up of approximately 15 mo (mean follow-up: Approximately 2 years; maximum: Approximately 9 years).

The phase III open-label extension study was performed in 14 countries spanning three continents and included 459 PD patients with psychotic symptoms who had completed previous randomized, placebo-controlled studies. The results indicated a favorable benefit/risk profile of long-term treatment with 34 mg daily of pimavanserin without increasing caregiver burden or mortality risk related to long-term use of pimavanserin. Pimavanserin had some moderate and mild adverse reactions, the most common of which were falls, urinary tract infection, mental, and psychological abnormalities[90].

Overall, there is conclusive evidence of the favorable therapeutic effect, safety, and tolerability of pimavanserin for PD psychosis[91]. Ten-week treatment with pimavanserin showed persistent efficacy in improving psychotic symptoms, as evaluated by SAPS-PD, and improved the quality of life of caregivers[92]. A meta-analysis of four randomized controlled trials (n = 680) in patients with PD psychosis showed that pimavanserin significantly recovered psychotic symptoms, as assessed by SAPS score[93].

A recent systematic review and Bayesian network meta-analysis of four antipsychotics showed that both pimavanserin and clozapine are effective antipsychotics that may improve the symptoms of PD psychosis compared to a placebo; however, the adverse effects of clozapine were a cause for concern[79, 94].

Compared with quetiapine, pimavanserin exhibited lower discontinuation rate with in early duration and higher discontinuation rate with in late duration for treating DLB and PD psychosis[95] Moreno et al[96] retrospectively analyzed medical records of 676 PD patients treated with atypical psychotics, and found that patients receiving pimavanserin monotherapy showed a lower risk of mortality than patients receiving quetiapine or a combination of pimavanserin and quetiapine[96]. Coincidentally, in a multicenter, open-label extension safety study assessing the long-term impact of antipsychotics compared with pimavanserin, subjects treated with pimavanserin with an add-on antipsychotic drug showed higher mortality rate in comparison with pimavanserin monotherapy group[97].

The therapeutic responsiveness of pimavanserin may be enhanced or facilitated by other PD-related drugs or interventions, such as cholinesterase inhibitors and deep brain stimulation[98]. Currently, there is limited understanding of the discrepancy between pimavanserin and other antipsychotics with respect to efficacy, safety, and tolerability and further large-scale multicenter studies are required to confirm the clinical utility of pimavanserin in other clinical settings[84].

**Cholinesterase inhibitors**

An increasing body of evidence from experimental and clinical research has indicated a pivotal role of dysfunction of cholinergic system in addition to dysfunction of serotonergic and dopaminergic systems in the causation of PD psychosis. These findings indicate that the cholinergic system is a viable therapeutic target in the context of PD psychosis[99,100]. In a randomized controlled study, pimavanserin significantly improved PD psychotic symptoms (assessed by SAPS-PD score) either with or without accompanying cognitive dysfunction; the study also demonstrated that cholinesterase inhibitors as cognitive-enhancing medications may augment the efficacy of pimavanserin[101]. Long-term use of anticholinergic drugs (benzhexol) was strongly associated with high risk of developing PD psychosis, while cholinesterase inhibitors (donepezil) reduced the risk[56]. The cholinesterase inhibitor rivastigmine has been recommended as first-line drug for the treatment of PD dementia by the collaborators of the Parkinson’s Disease Update on Non-Motor Symptoms Study Group[102]. Cholinesterase inhibitors may also ameliorate the gait disturbance and risk of falls in PD patients[103]. Furthermore, compared with PD dementia without psychosis, PD patients with concomitant dementia and psychosis were more likely to benefit from rivastigmine[104,105]. In a randomized, double-blind, placebo-controlled phase II single-center trial, donepezil showed a significant protective effect against the development of psychotic symptoms in PD patients with apolipoprotein E ε4 non-carriers, suggesting that ApoE ε4 allele status may contribute to the resistance of cholinesterase inhibitors[106].

Most Parkinson’s hallucinations are accompanied by a decline in cognitive function, ranging from mild cognitive impairment to severe dementia. In addition to improving cognitive performance, cholinesterase inhibitors may significantly alleviate hallucinations in patients with PD. Because the reported incidence of adverse effects of cholinesterase inhibitors is much lower than that of atypical antipsychotics, cholinesterase inhibitors may be an alternative treatment for improving “benign or minor” hallucinations, especially in PD dementia with psychosis[104].
Other antipsychotics and N-methyl-D-aspartate receptors agonists

Ondansetron is a selective 5-HT3 receptor antagonist which can theoretically attenuate PD psychosis. Compared with other 5-HT receptors, the 5-HT3 receptor is the only ligand-gated 5-HT receptor which has a particular mechanism to mediate the release of neurotransmitters. Although a series of clinical studies on ondansetron in the treatment of PD psychosis were carried out in the 1990s, there are three open-label trials on the efficacy of ondansetron with contradictory results, to our knowledge. In two open-label trials enrolling 40 patients, ondansetron moderately improved the symptoms of hallucination and paranoid delusion with favorable tolerability, and without severe adverse effects; furthermore, ondansetron did not deteriorate motor functions of PD or attenuate the efficacy of levodopa. However, in another study of 5 patients with PD psychosis, a similar dose of ondansetron failed to show long-term benefit. Due to the high cost of ondansetron, no further clinical trials have been reported in the subsequent two decades[107]. Investigations of other antipsychotic drugs including risperidone, ziprasidone, aripiprazole, however, have been confined to small open-label trials.

Dysfunction of N-methyl-D-aspartate receptors (NMDAR)-mediated neurotransmission is believed to contribute to neuropsychiatric symptoms of PD. Enhancing glutamatergic transmission through blocking of glycine re-uptake was found to ameliorate the psychosis-like behaviors in a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced PD marmoset model[108]. NMDAR stimulation, accomplished through allosteric modulation via the glycine modulatory site, may be a potential therapeutic target for PD psychosis. As a glycine re-uptake inhibitor, sarcosine was found to increase synaptic glycine concentration to activate NMDAR glycine site, thereby enhancing NMDAR function. A small-scale randomized controlled study suggested that sarcosine may relieve the neuropsychiatric symptoms of PD with dementia[109].

Further high-quality randomized controlled trials examining the efficacy and tolerability of other antipsychotics and NMDAR agonists are required to confirm these findings.

Non-pharmacological interventions

A recent cross-sectional study showed that caregivers and partners of PD patients were more inclined to use non-pharmacological treatment strategies to cope with the occurrence of psychosis compared to the use of medications[110]. Nevertheless, there is inadequate clinical evidence supporting the use of non-pharmacological interventions for PD psychosis. The role of psychological therapies such as cognitive behavioral therapy, reasoning and rehabilitation is less certain than pharmacological interventions in the therapeutic strategy for PD psychosis. Physical activity can not only improve motor symptoms, but may also play a role in relieving non-motor symptoms of PD.

CONCLUSION

The current review suggests that PD psychosis is an important non-motor symptom that predicts poor outcome. Development of PD psychosis may involve dyshomeostasis of neurotransmitters, structural and network changes, genetic profiles, and cognitive impairment. The side effects of anti-Parkinsonism medications and patient-specific characteristics are both involved in the onset and progression of psychosis during the course of PD. Unfortunately, most of the studies included in this review were observational studies which did not distinguish between treated and non-treated PD patients, since treatment with antiparkinsonian medications (e.g., DA agonists) is considered as a potential cause of PD psychosis. A follow-up prospective study investigating whether antiparkinsonian medications have a significant impact on the development and progression of PD psychosis in a cohort of patients receiving different kinds and doses of antiparkinsonian medications should be conducted in future. The therapeutic approaches for PD psychosis include reducing or ceasing the use of dopaminergic drugs, and use of antipsychotics, cholinesterase inhibitors, NMDAR agonist, and non-pharmacological interventions. Pharmacological interventions for PD psychosis remain an outstanding need in clinical practice. Emerging research on future targeted therapies based on new biomarkers and genetic factors may help inform tailored therapeutic strategies.

FOOTNOTES

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REFERENCES

1. Ascherio A, Schwarzschild MA. The epidemiology of Parkinson's disease: risk factors and prevention. *Lancet Neurol* 2016; 15: 1257-1272 [PMID: 27751556 DOI: 10.1016/S1474-4422(16)30320-7]
2. Yates D. Taking a closer look at PD pathology. *Nat Rev Neurosci* 2019; 20: 511 [PMID: 31388186 DOI: 10.1038/s41583-018-0207-4]
3. Fereshtehnejad SM, Yao C, Pelletier A, Montplaisir JY, Gagnon JF, Postuma RB. Evolution of prodromal Parkinson's disease and dementia with Lewy bodies: a prospective study. *Brain* 2019; 142: 2051-2067 [PMID: 31111143 DOI: 10.1093/brain/awz111]
4. Powell A, Ireland C, Lewis SJG. Visual Hallucinations and the Role of Medications in Parkinson's Disease: Triggers, Pathophysiology, and Management. *J Neuropsychiatry Clin Neurosci* 2020; 32: 334-343 [PMID: 32574649 DOI: 10.1176/appi.neuropsych.19110316]
5. Ffytche DH, Creebe B, Politis M, Chaudhuri KR, Weintraub D, Ballard C, Aarsland D. The psychosis spectrum in Parkinson disease. *Nat Rev Neurol* 2017; 13: 81-95 [PMID: 28106066 DOI: 10.1038/nnuro.2016.200]
6. Pagonabarraga J, Martinez-Horta S, Fernandez de Bobadilla R, Perez J, Ribosa-Nogué R, Marin J, Pascual-Sedano B, Garcia C, Gironell A, Kuliseskav J. Minor hallucinations occur in drug-naive Parkinson's disease patients, even from the premotor phase. *Mov Disord* 2016; 31: 45-52 [PMID: 26408291 DOI: 10.1002/mds.26432]
7. Pacchetti C, Manni R, Zangaglia R, Mancini F, Marchioni E, Tassorelli C, Terzaghi M, Ossola M, Martignoni E, Moglia A, Nappi G. Relationship between hallucinations, delusions, and rapid eye movement sleep behavior disorder in Parkinson's disease. *Mov Disord* 2005; 20: 1439-1448 [PMID: 16028215 DOI: 10.1002/mds.20582]
8. Balestrino R, Martinez-Martín P. Neuropsychiatric symptoms, behavioural disorders, and quality of life in Parkinson's disease. *J Neurol Sci* 2017; 373: 173-178 [PMID: 28131182 DOI: 10.1016/j.jns.2016.12.060]
9. Anang JB, Gagnon JF, Bertrand JA, Romenets SR, Lateille V, Panisset M, Montplaisir J, Postuma RB. Predictors of delirium in Parkinson's disease: a prospective cohort study. *Neurology* 2014; 83: 1253-1260 [PMID: 25171928 DOI: 10.1212/WNL.0000000000000842]
10. Formis J, Layton JB, Bartsch J, Turner ME, Dempsey C, Anthony M, Ritchey ME, Demos G. Increased risk of falls and fractures in patients with psychosis and Parkinson disease. *Plos One* 2021; 16: e0246121 [PMID: 35303061 DOI: 10.1371/journal.pone.0246121]
11. Gasca-Salas C, Claverio P, García-García D, Obeso JA, Rodríguez-Oroz MC. Significance of visual hallucinations and cerebral hypometabolism in the risk of dementia in Parkinson's disease patients with mild cognitive impairment. *Hum Brain Mapp* 2016; 37: 968-977 [PMID: 26663702 DOI: 10.1002/hbm.23080]
12. Forsaa EB, Larsen JP, Wentzel-Larsen T, Alves G. What predicts mortality in Parkinson disease? *Neurology* 2010; 75: 1270-1276 [PMID: 20921512 DOI: 10.1212/WNL.0b013e3181f1311]
13. Bugalho P, Ladeira F, Barbosa R, Marto JP, Borbinha C, Salavisa M, da Conceição L, Saraiva M, Fernandes M, Meira B. Motor and non-motor function predictors of mortality in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2019; 126: 1409-1415 [PMID: 31385098 DOI: 10.1007/s00702-019-02055-3]
14. Aarsland D, Larsen JP, Tandberg E, Laake K. Predictors of nursing home placement in Parkinson's disease: a population-based, prospective study. *J Am Geriatr Soc* 2000; 48: 938-942 [PMID: 10968298 DOI: 10.1111/j.1532-5415.2000.tb08913.x]
15. Kang GA, Bronstein JM. Psychosis in nursing home patients with Parkinson's disease. *J Am Med Dir Assoc* 2004; 5: 167-173 [PMID: 15115577 DOI: 10.1016/j.jamda.2003.10.006]
16. Hommel ALAJ, Meinders MJ, Lorenz S, Dodel R, Coelho M, Ferreira JJ, Laurens B, Spannata D, Meissner W, Rosqvist K, Timpka J, Odin P, Wittenborg M, Bloem PH, Booms, MC, Wuchtz A, Care of Late-Stage Parkinsonism Consortium. The Prevalence and Determinants of Neuropsychiatric Symptoms in Late-Stage Parkinsonism. *Mov Disord Clin Pract* 2020; 7: 531-543 [PMID: 32626798 DOI: 10.1002/mdc3.12965]
17. Mack J, Rabins P, Anderson K, Goldstein S, Grill S, Hirsch ES, Lehmann S, Little JT, Margolis RL, Palanci J, Pontone G, Weiss H, Williams JR, Marsh L. Prevalence of psychotic symptoms in an community-based Parkinson disease sample. *Am J Geriatr Psychiatry* 2012; 20: 123-132 [PMID: 21617521 DOI: 10.1097/JGP.0b013e3182f1b4f1]
18. Kulick CV, Montgomery KM, Nirenberg MJ. Comprehensive identification of delusions and olfactory, tactile, gustatory, and minor hallucinations in Parkinson's disease psychosis. *Parkinsonism Relat Disord* 2018; 54: 40-45 [PMID: 29653909 DOI: 10.1016/j.parkreldis.2018.04.008]
19. Weintraub D. Progress Regarding Parkinson's Disease Psychosis: It's No Illusion. *Mov Disord Clin Pract* 2016; 3: 431-
434 [PMID: 30365321 DOI: 10.1002/mdc3.12377]

20 de la Riva P, Smith K, Xie SX, Weimtraub D. Course of psychiatric symptoms and global cognition in early Parkinson's disease. *Neurology* 2014; 83: 1096-1103 [PMID: 25128183 DOI: 10.1212/WNL.0000000000000801]

Yoritaka A, Shimo Y, Takanashi M, Fukae J, Hatano T, Nakahara T, Miyamoto N, Urabe T, Mori H, Hattori N. Motor and non-motor symptoms of 1453 patients with Parkinson's disease: prevalence and risks. *Parkinsonism Relat Disord* 2013; 19: 725-731 [PMID: 23699756 DOI: 10.1016/j.parkreldis.2013.04.001]

21 Omoto S, Murakami H, Shiraiishi T, Bono K, Uenohara T, Iguchi Y. Risk factors for minor hallucinations in Parkinson's disease. *Acta Neurol Scand* 2021; 143: 538-546 [PMID: 33222166 DOI: 10.1111/an.13380]

22 Ravina B, Marder K, Fernandez HH, Friedman JH, McDonald W, Murphy D, Aarsland D, Babcock D, Cummings J, Endicott J, Factor S, Galpern W, Lees A, Marsh L, Stacy M, Gwinn-Hardy K, Voon V, Goetz C. Diagnostic criteria for psychosis in Parkinson's disease: report of an NINDS, NIMH work group. *Mov Disord* 2007; 22: 1061-1068 [PMID: 17266092 DOI: 10.1002/mds.21382]

23 Jellinger KA, Korczyn AD. Are dementia with Lewy bodies and Parkinson's disease dementia the same disease? *BMC Med* 2018; 16: 34 [PMID: 29510692 DOI: 10.1186/s12916-018-1016-8]

24 Friedman JH. Dementia with Lewy Bodies and Parkinson Disease Dementia: It is the Same Disease? *Parkinsonism Relat Disord* 2016; 48 Suppl 1: S6-S9 [PMID: 28756177 DOI: 10.1016/j.parkreldis.2017.07.013]

25 Russo M, Carrarini C, Dono F, Rispoli MG, Di Pietro M, Di Stefano V, Ferri L, Bonannì L, Sensi SL, Onofri M. The Pharmacology of Visual Hallucinations in Synucleinopathies. *Front Pharmacol* 2019; 10: 1379 [PMID: 31920635 DOI: 10.3389/fphar.2019.01379]

26 Kyle K, Bronstein JM. Treatment of psychosis in Parkinson's disease and Lewy Bodies: A review. *Parkinsonism Relat Disord* 2020; 75: 55-62 [PMID: 32480308 DOI: 10.1016/j.parkreldis.2020.05.026]

27 Gordon PC, Kauark RB, Costa CD, de Oliveira MO, Godinho FL, Rocha MS. Clinical Implications of the National Institute of Neurological Disorders and Stroke Criteria for Diagnosing Psychosis in Parkinson's Disease. *J Neuropsychiatry Clin Neurosci* 2016; 28: 26-31 [PMID: 26449268 DOI: 10.1176/appi.neuropsych.15050119]

28 Gordon PC, Rocha MS, Kauark RG, Costa CD, de Oliveira MO, Godinho F, Borges V. Validation of the National Institute of Neurological Disorders and Stroke Criteria for Psychosis in Parkinson Disease. *Am J Geriatr Psychiatry* 2017; 25: 73-80 [PMID: 27704252 DOI: 10.1016/j.jagp.2016.08.011]

29 Lenka A, Pagobanabraga J, Pal PK, Beji-Kasem H, Kulysvsky J. Minor hallucinations in Parkinson disease: A subtle symptom with major clinical implications. *Neurology* 2019; 93: 259-266 [PMID: 31289146 DOI: 10.1212/01.wnl.000000000007913]

30 Goetz CG, Fan W, Leurgans S. Antipsychotic medication treatment for mild hallucinations in Parkinson's disease: Positive impact on long-term worsening. *Mov Disord* 2008; 23: 1541-1545 [PMID: 18567004 DOI: 10.1002/mds.22132]

31 Goetz CG. Scales to evaluate psychosis in Parkinson's disease. *Parkinsonism Relat Disord* 2009; 15 Suppl 3: S38-S41 [PMID: 20083004 DOI: 10.1016/S1383-8200(09)70777-1]

32 Martinez-Martin P, Ray Chaudhuri K. Comprehensive grading of Parkinson's disease using the motor and non-motor assessments: addressing a key unmet need. *Expert Rev Neurother* 2018; 18: 41-50 [PMID: 29090594 DOI: 10.1080/14744422.2018.1400383]

33 Storch A, Schneider CB, Klingelhofter L, Odin P, Fuchs G, Jost WH, Martinez-Martin P, Koch R, Reichmann H, Chaudhuri KR, NoMoFlu-PD study group, Ebersbach G. Quantitative assessment of non-motor fluctuations in Parkinson's disease using the Non-Motor Symptoms Scale (NMSS). *J Neural Transm (Vienna)* 2015; 122: 1673-1684 [PMID: 26264174 DOI: 10.1007/s00702-015-1347-z]

34 Voss T, Baehr D, Cummings J, Mills R, Ravina B, Williams H. Performance of a shortened Scale for Assessment of Positive Symptoms for Parkinson disease psychosis. *Parkinsonism Relat Disord* 2013; 19: 295-299 [PMID: 23211417 DOI: 10.1016/j.parkreldis.2012.10.022]

35 Schneider RB, Jourinets J, Richard H. Parkinson's disease psychosis: presentation, diagnosis and management. *Neurodegener Dis Manag* 2017; 7: 365-376 [PMID: 29160144 DOI: 10.2217/nmt-2017-0028]

36 Stahl SM. Parkinson's disease psychosis as a serotonin-dopamine imbalance syndrome. *CNS Spectr* 2016; 21: 355-359 [PMID: 26868027 DOI: 10.1071/S1092852916000602]

37 Huot P. 5-HT_{2A} receptors and Parkinson's disease psychosis: a pharmacological discussion. *Neurodegener Dis Manag* 2018; 8: 363-365 [PMID: 30451579 DOI: 10.2217/nmt-2018-0039]

38 Meltzer HY, Massey BW, Horiguchi M. Serotonin receptors as targets for drugs useful to treat psychosis and cognitive impairment in schizophrenia. *Curr Pharm Biotechnol* 2012; 13: 1572-1586 [PMID: 22283753 DOI: 10.2174/138920112800784880]

39 Bosboom JL, Stoffers D, Wolters ECh. The role of acetylcholine and dopamine in dementia and psychosis in Parkinson's disease. *J Neural Transm Suppl* 2003; 185-195 [PMID: 12946056 DOI: 10.1007/978-3-7091-0643-3_11]

40 Lieberman JA, First MB. Psychotic Disorders. *N Engl J Med* 2018; 379: 270-280 [PMID: 30021088 DOI: 10.1056/NEJMra1801490]

41 Ballanger B, Stralletta AP, van Eimeren T, Zuroski M, Rusjan PM, Houle S, Fox SH. Serotonin 2A receptors and visual hallucinations in Parkinson disease. *Arch Neurol* 2010; 67: 416-421 [PMID: 20385906 DOI: 10.1001/archneurol.2010.35]

42 Huot P, Johnston TH, Darr T, Hazrati LN, Visanji NP, Pires D, Brochije JM, Fox SH. Increased 5-HT2A receptors in the temporal cortex of parkinsonian patients with visual hallucinations. *Mov Disord* 2010; 25: 1399-1408 [PMID: 20629135 DOI: 10.1002/mds.23083]

43 Huot P, Johnston TH, Visanji NP, Darr T, Pires D, Hazrati LN, Brochije JM, Fox SH. Increased levels of 5-HT1A receptor binding in ventral visual pathways in Parkinson's disease. *Mov Disord* 2012; 27: 735-742 [PMID: 22419526 DOI: 10.1002/mds.24964]

44 Marinus J, Zhu K, Marras C, Aarsland D, van Hulten JJ. Risk factors for non-motor symptoms in Parkinson's disease. *Lancet Neurol* 2018; 17: 559-568 [PMID: 29699914 DOI: 10.1016/S1474-4422(18)30127-3]

45 Sawada H, Oeda T, Umemura A, Tomita S, Hayashi R, Koshaka M, Yamamoto K, Sudo H, Sugiyama H. Subclinical elevation of plasma C-reactive protein and illusions/hallucinations in subjects with Parkinson's disease: case-control study.
Zhang S et al. Novel insight into PD psychosis.

PLoS One 2014; 9: e85886 [PMID: 24497930 DOI: 10.1371/journal.pone.0085886]

Jacobsen SA, Moreshed T, Dugger BN, Beach TG, Hentz JG, Adler CH, Shill HA, Sabbagh MN, Belden CM, Sue LI, Cavness JN, Hu C; Arizona Parkinson's Disease Consortium. Plaques and tangles as well as Lewy-type alpha synucleinopathy are associated with formed visual hallucinations. Parkinsonism Relat Disord 2014; 20: 1009-1014 [PMID: 25027359 DOI: 10.1016/j.parkreldis.2014.06.018]

Fytyche DH, Pereira JB, Ballard C, Chaudhuri KR, Weintraub D, Aarsland D. Risk factors for early psychosis in PD: insights from the Parkinson's Progression Markers Initiative. J Neurol Neurosurg Psychiatry 2017; 88: 325-331 [PMID: 28315816 DOI: 10.1136/jnnp-2016-314832]

Firbank MJ, Parikh J, Murphy N, Killen A, Allan CL, Collettion D, Blamire AM, Taylor JP. Reduced occipital GABA in Parkinson disease with visual hallucinations. Neurology 2018; 91: e675-e685 [PMID: 30021920 DOI: 10.1212/WNL.0000000000006607]

Bejr-Kasem H, Sampeedo F, Marin-Lahoz J, Martinez-Horta S, Pagonabarraga J, Kulishevsky J. Minor hallucinations reflect early gray matter loss and predict subjective cognitive decline in Parkinson's disease. Eur J Neurol 2021; 28: 438-447 [PMID: 33032389 DOI: 10.1111/ejn.14576]

Goldman JG, Stebbins GT, Dinh V, Bernard B, Merkitch D, deToledo-Morrell L, Goetz CG. Visuoperceptve region atrophy indpendent of cognitive status in patients with Parkinson disease's with hallucinations. Brain 2014; 137: 849-859 [PMID: 24480486 DOI: 10.1093/brain/awt360]

Zarkali A, McCollan P, Leyland LA, Lees AJ, Rees G, Weil RS. Fiber-specific white matter reductions in Parkinson hallucinations and visual dysfunction. Neurology 2020; 94: e1525-e1538 [PMID: 32094242 DOI: 10.1212/WNL.000000000009914]

Lenka A, Arumugham SS, Christopher R, Pal PK. Genetic substrates of psychosis in patients with Parkinson's disease: A critical review. J Neurol Sci 2016; 364: 33-41 [PMID: 27084212 DOI: 10.1016/j.jns.2016.03.005]

Oeda T, Umemura A, Mori Y, Tomita S, Kohsaka M, Park K, Inoue K, Fujimura H, Hasegawa H, Sugiyama H, Sawada H. Impact of glucocerebrosidase mutations on motor and nonmotor complications in Parkinson's disease. Neurobiol Aging 2015; 36: 3106-3113 [PMID: 26722560 DOI: 10.1016/j.neurobiolaging.2015.08.027]

Factor SA, Steenland NK, Higgins DS, Molho ES, Kay DM, Montimurro J, Rosen AR, Zabetian CP, Payami H. Disease-related and genetic correlates of psychotic symptoms in Parkinson's disease. Mov Disord 2011; 26: 2190-2195 [PMID: 21714002 DOI: 10.1002/mds.23806]

Sawada H, Oeda T, Yamamoto K, Umemura A, Tomita S, Hayashi R, Kohsaka M, Kawamura H. Trigger medications and patient-related risk factors for Parkinson disease psychosis requiring anti-psychotic drugs: a retrospective cohort study. BMC Neuro 2013; 13: 145 [PMID: 24119306 DOI: 10.1186/1471-2377-13-145]

Baumann CR, Held U, Valko PO, Wiencke M, Waldvogel D. Body side and predominant motor features at the onset of Parkinson's disease are linked to motor and nonmotor progression. Mov Disord 2014; 29: 207-213 [PMID: 24105646 DOI: 10.1002/mds.25650]

Spica V, Pekmezovic T, Svetel M, Kostić VS. Prevalence of non-motor symptoms in young-onset vs late-onset Parkinson's disease. J Neurol 2013; 260: 131-137 [PMID: 22820720 DOI: 10.1007/s00415-012-6600-9]

Oertel W, Schulz JB. Current and experimental treatments of Parkinson disease: A guide for neuroscientists. J Neurochem 2016; 139 Suppl 1: 325-337 [PMID: 27577098 DOI: 10.1111/jnc.13570]

Forsaa EB, Larsen JP, Wentzel-Larsen T, Goetz CG, Stebbins GT, Aarsland D, Alves G. A 12-year population-based study of psychosis in Parkinson disease. Arch Neurol 2010; 67: 996-1001 [PMID: 20669701 DOI: 10.1001/archneur.2010.166]

Morgante L, Colosimo C, Antonini A, Marconi R, Meco G, Pederzoli M, Pontieri FE, Cicarelli G, Abbruzzese G, Zappulla S, Ramat S, Manfredi M, Bottoncchi E, Abrignani M, Berardelli A, Cozzolino A, Paradiso C, De Gaspari D, Morgante F, Barone P. PRIAMO Study Group. Psychosis associated to Parkinson's disease in the early stages: relevance of cognitive decline and depression. J Neurol Neurosurg Psychiatry 2012; 83: 76-82 [PMID: 21836035 DOI: 10.1136/jnnp-2011-300043]

Zhu K, van Hulten JJ, Putter H, Marinus J. Risk factors for hallucinations in Parkinson's disease: results from a large prospective cohort study. Mov Disord 2013; 28: 755-762 [PMID: 23520046 DOI: 10.1002/mds.25389]

Barrett MJ, Smolikin ME, Flanigan JL, Shah BB, Harrison MB, Sperling SA. Characteristics, correlates, and assessment of psychosis in Parkinson disease without dementia. Parkinsonism Relat Disord 2017; 43: 56-60 [PMID: 28735797 DOI: 10.1016/j.parkreldis.2017.07.011]

Poletti M, Logi C, Lucetti C, Del Dotto P, Baldacci F, Vergallo A, Ulivi M, Del Santo S, Rossi G, Ceravolo U. A single-center, cross-sectional prevalence study of impulse control disorders in Parkinson disease: association with dopaminergic drugs. J Clin Psychopharmacol 2013; 33: 691-694 [PMID: 23857310 DOI: 10.1097/CPJ.0b013e3182979830]

Moore TJ, Glenmullen J, Mattison DR. Reports of pathological gambling, hypersexuality, and compulsive shopping associated with dopamine receptor agonist drugs. JAMA Intern Med 2014; 174: 1930-1933 [PMID: 25329919 DOI: 10.1001/jamainternmed.2014.5262]

Poletti M, Perugi G, Logi C, Romano A, Del Dotto P, Ceravolo R, Rossi G, Pepe P, Dell'OssO L, Bonuccelli U. Dopaminergic agonists and delusional jealousy in Parkinson's disease: a cross-sectional prevalence study. Mov Disord 2012; 27: 1679-1682 [PMID: 23150469 DOI: 10.1002/mds.25129]

Fryni LD, Williams KR, Pelic CG, Fox J, Sahlem G, Robert S, Revuelta GJ, Short EB. The Role of Amantadine Withdrawal in 3 Cases of Treatment-Refractory Altered Mental Status. J Psychiatr Pract 2017; 23: 191-199 [PMID: 28492457 DOI: 10.1097/PRA.0000000000000237]

Munhoz RP, Teive HA, Eleftherohorinou H, Coin LJ, Lees AJ, Silveira-Moriyama L. Demographic and motor features associated with the occurrence of neuropsychiatric and sleep complications in Parkinson disease. J Neurol Neurosurg Psychiatry 2013; 84: 883-887 [PMID: 23463867 DOI: 10.1136/jnnp-2012-304440]

Meriñs D, Shabtai H, Korczyn AD, Perez C, Weizman N, Giladi N. Antiparkinsonian medication is not a risk factor for the development of hallucinations in Parkinson's disease. J Neural Transm (Vienna) 2004; 111: 1447-1453 [PMID: 15541473]
Zhang S et al. Novel insight into PD psychosis

15408045 DOI: 10.1007/s00702-004-0209-9

Joutsa J, Johansson J, Seppänen M, Noponen T, Kaasinen V. Dorsal-to-Ventral Shift in Midbrain Dopaminergic Projections and Increased Thalamic/Raphe Serotonergic Function in Early Parkinson Disease. J Neurol Med 2015; 56: 1036-1041 [PMID: 25952735 DOI: 10.2967/jnumed.115.153734]

Gibson G, Mottram PG, Burn DJ, Hindle JV, Landau S, Samuel M, Hurt CS, Brown RG, M Wilson KC. Frequency, prevalence, incidence and risk factors associated with visual hallucinations in a sample of patients with Parkinson's disease: a longitudinal 4-year study. Int J Geriatr Psychiatry 2013; 28: 626-631 [PMID: 22972175 DOI: 10.1002/gps.3669]

Weintraub D, Mamikonyan E. The Neuropsychiatry of Parkinson Disease: A Perfect Storm. Am J Geriatr Psychiatry 2019: 27: 998-1018 [PMID: 31006550 DOI: 10.1161/j.g.j.p.19.03.002]

Misrahi D, Tessier A, Daubigney A, Meissner WG, Schurhoff F, Boyer L, Godin O, Bulzacka E, Aouizerate B, Andrianarisoa M, Berna F, Capdevielle D, Chereau-Boudet I, D’Amato T, Dubertret C, Dubreucq J, Fagnat-Aguis C, Langon C, Mallet J, Passieux C, Rey R, Schandrau A, Urbach M, Vidalail P, Llorea FM, Fond G; FACE-SZ (FondaMental Academic Centers of Expertise for Schizophrenia) Group. Prevalence of and Risk Factors for Extrapyramidal Side Effects of Antipsychotics: Results From the National FACE-SZ Cohort. J Clin Psychiatry 2019; 80: 30695288 DOI: 10.4088/JCP.18m12246

Krause M, Zhu Y, Huhn M, Schneider-Thoma J, Bighelli I, Chainani A, Leucht S. Efficacy, acceptability, and tolerability of antipsychotics in children and adolescents with schizophrenia: A network meta-analysis. Eur Neuropsychopharmacol 2018; 28: 659-674 [PMID: 29802039 DOI: 10.1016/j.euro.2018.03.008]

Iketani R, Kawasaki Y, Yamada H. Comparative Utility of Atypical Antipsychotics for the Treatment of Psychosis in Parkinson's Disease: A Systematic Review and Bayesian Network Meta-analysis. Biol Pharm Bull 2017; 40: 1976-1982 [PMID: 29693347 DOI: 10.1248/bpb.b17-00602]

Kitten AK, Hallowell SA, Saklad SR, Eovy KE. Pimavanserin: A Novel Drug Approved to Treat Parkinson's Disease Psychosis. Innov Clin Neurosci 2018; 15: 16-22 [PMID: 29497575]

Faruk P, Tison F, Rascal O, Destée A, Pérez JJ, Senard JM, Durif F, Bourdeix I. Clozapine in drug induced psychosis in Parkinson's disease: a randomised, placebo controlled study with an open follow up. J Neurol Neurosurg Psychiatry 2004; 75: 689-695 [PMID: 15090561 DOI: 10.1136/jnnp.2003.029866]

Parkinson Study Group. Low-dose clozapine for the treatment of drug-induced psychosis in Parkinson's disease. N Engl J Med 1999; 340: 757-763 [PMID: 10072410 DOI: 10.1056/NEJM199903313401003]

Iketani R, Furushima D, Imai S, Yamada H. Efficacy and safety of atypical antipsychotics for psychosis in Parkinson's disease: A systematic review and Bayesian network meta-analysis. Parkinsonism Relat Disord 2020; 78: 82-90 [PMID: 32755800 DOI: 10.1016/j.parkreldis.2020.07.021]

Ono YG, Tintner R, Young KD, Lai D, Ringholz G. Double-blind, placebo-controlled, unfenced titration parallel trial of quetiapine for dopamnergic-hallucinations in Parkinson's disease. Mov Disord 2005; 20: 958-963 [PMID: 15800373 DOI: 10.1002/mds.200474]

Fernandez HH, Okun MS, Rodriguez RL, Malaty IA, Romrell J, Sun A, Wu SS, Pillarisetty S, Nyathappa A, Eisenschenk S. Quetiapine improves visual hallucinations in Parkinson disease: A systematic review and Bayesian network meta-analysis. J Neuropsychiatry Clin Neurosci 2019; 31: 188-195 [PMID: 30848989 DOI: 10.1176/appi.neuropsych.18080180]

Shoftlop P, Samuel M, Fox C, David AS. A randomized controlled trial of quetiapine for psychosis in Parkinson's disease. Neuropsychiatr Dis Treat 2009; 5: 327-332 [PMID: 19557142 DOI: 10.2147/nmd.s3335]

Rabey JM, Prokhorov T, Minioptiz A, Dobronevsky E, Klein C. Effect of quetiapine in psychotic Parkinson's disease patients: a double-blind labelled study of 3 mo' duration. Mov Disord 2007; 22: 313-318 [PMID: 17034006 DOI: 10.1002/mds.21116]

Wilby KJ, Johnson EG, Johnson HE, Ensom MHH. Evidence-Based Review of Pharmacotherapy Used for Parkinson's Disease Psychosis. Am Pharmacother 2007; 51: 682-695 [PMID: 28385039 DOI: 10.1016/j.amphar.2007.01.008]

Chen JJ, Tanaka Y, Sato H, Massahi L, Portillo I, Alipour A, Ono Y, Dastipour K. Systematic Literature Review of Quetiapine for the Treatment of Psychosis in Patients With Parkinsonism. J Neuropsychiatry Clin Neurosci 2019; 31: 188-195 [PMID: 30848989 DOI: 10.1176/appi.neuropsych.18080180]

Stahl SM. Mechanism of action of pimavanserin in Parkinson's disease: targeting serotonin 5HT2A and 5HT2C receptors. CNS Spectr 2016; 21: 271-275 [PMID: 27503570 DOI: 10.1017/S1092852916004047]

Kianirad Y, Simmon T. Pimavanserin, a novel antipsychotic for management of Parkinson's disease psychosis. Expert Rev Clin Pharmacol 2017; 10: 1161-1166 [PMID: 28817967 DOI: 10.1080/17512433.2017.1369405]

Cummings J, Isaacson S, Mills R, Williams H, Chi-Burrus K, Corbet A, Dhall R, Ballard C. Pimavanserin for patients with Parkinson's disease psychosis: a randomised, placebo-controlled phase 3 trial. Lancet 2014; 383: 533-540 [PMID: 24183563 DOI: 10.1016/S0140-6736(13)62106-6]

Sahli ZT, Tarazi FI. Pimavanserin: novel pharmacotherapy for Parkinson's disease psychosis. Expert Opin Drug Discov 2018; 13: 103-110 [PMID: 29047301 DOI: 10.1080/17460441.2018.1394838]

Ballard CG, Kreitzman DL, Isaacson S, Liu Y, Norton JC, Demos G, Fernandez HH, Illic TV, Azulay JP, Ferreira JJ, Ahler V, Stankovic S, 035 Study Group. Long-term evaluation of open-label pimavanserin safety and tolerability in Parkinson's disease psychosis. Parkinsonism Relat Disord 2020; 77: 100-106 [PMID: 32712560 DOI: 10.1016/j.parkreldis.2020.06.026]

Tampi RR, Tampi DJ, Young JJ, Balachandran S, Hoq RA, Manikka G. Evidence for using pimavanserin for the treatment of Parkinson's disease psychosis. J Alzheimers Dis 2019; 10: 47-54 [PMID: 31211112 DOI: 10.5198/wjp.v9.4.47]

Isaacson SH, Coate B, Norton J, Stankovic S. Blinded SAPS-PD Assessment After 10 Weeks of Pimavanserin Treatment for Parkinson's Disease Psychosis. J Parkinsons Dis 2020; 10: 1389-1396 [PMID: 32716320 DOI: 10.3233/JPD-200247]

Yasu I, Matsumura S, Kishi T, Fujita K, Iwata N. Serotonin 2A Receptor Inverse Agonist as a Treatment for Parkinson's Disease Psychosis: A Systematic Review and Meta-analysis of Serotonin 2A Receptor Negative Modulators. J Alzheimers Dis 2019; 31: 1365-1375 [PMID: 31672516 DOI: 10.3233/JAD-190061]
Zhang et al. Novel insight into PD psychosis

Dis 2016; 59: 733-740 [PMID: 26757194 DOI: 10.3233/JAD-150818]

94 Zhang H, Wang L, Fan Y, Yang L, Wen X, Liu Y, Liu Z. Atypical antipsychotics for Parkinson's disease psychosis: a systematic review and meta-analysis. Neuropsychiatr Dis Treat 2019; 15: 2137-2149 [PMID: 31551655 DOI: 10.2147/NDT.S201029]

95 Horn S, Richardson H, Xie SX, Weintraub D, Dahodwala N. Pimavanserin vs quetiapine for the treatment of psychosis in Parkinson's disease and dementia with Lewy bodies. Parkinsonism Relat Disord 2019; 69: 119-124 [PMID: 31751863 DOI: 10.1016/j.parkreldis.2019.11.009]

96 Moreno GM, Gandhi R, Lessig SL, Wright B, Litván I, Nahab FB. Mortality in patients with Parkinson disease psychosis receiving pimavanserin and quetiapine. Neurology 2018; 91: 797-799 [PMID: 30258020 DOI: 10.1212/WNL.0000000000004396]

97 Ballard C, Isaacson S, Mills R, Williams H, Corbett A, Coate B, Pahwa R, Rascol O, Burn DJ. Impact of Current Antipsychotic Medications on Comparative Mortality and Adverse Events in People With Parkinson Disease Psychosis. J Am Med Dir Assoc 2015; 16: 898-898.e7 [PMID: 26239690 DOI: 10.1016/j.jamda.2015.06.021]

98 DashtiPour K, Gupta F, Hauser RA, Karunapuzha CA, Morgan JC. Pimavanserin Treatment for Parkinson's Disease Psychosis in Clinical Practice. Parkinsons Dis 2021; 2021: 2603641 [PMID: 33489083 DOI: 10.1155/2021/2603641]

99 Tanimura A, Du Y, Kondapalli J, Wokosin DL, Surmeier DJ. Cholinergic Interneurons Amplify Thalamostriatal Excitation of Striatal Indirect Pathway Neurons in Parkinson's Disease Models. Neuron 2019; 101: 444-458.e6 [PMID: 30658860 DOI: 10.1016/j.neuron.2018.12.004]

100 Hagino Y, Kasi S, Fujita M, Setogawa S, Yamaura H, Yanagihara D, Hashimoto M, Kobayashi K, Meltzer HY, Ikeda K. Involvement of cholinergic system in hyperactivity in dopamine-deficient mice. Neuropsychopharmacology 2015; 40: 1141-1150 [PMID: 25367503 DOI: 10.1038/npp.2014.297]

101 Espay AJ, Guskey MT, Norton JC, Coate B, Vizcarra JA, Ballard C, Factor SA, Friedman JH, Lang AE, Larsen NJ, Andersson C, Fredericks D, Weintraub D. Pimavanserin for Parkinson's Disease psychosis: Effects stratified by baseline cognition and use of cognitive-enhancing medications. Mov Disord 2018; 33: 1769-1776 [PMID: 30387904 DOI: 10.1002/mds.27485]

102 Seppi K, Ray Chaudhuri K, Coelho M, Fox SH, Katzenschlager R, Perez Lloret S, Weintraub D, Sampaio C; the collaborators of the Parkinson's Disease Update on Non-Motor Symptoms Study Group on behalf of the Movement Disorders Society Evidence-Based Medicine Committee. Update on treatments for nonmotor symptoms of Parkinson's disease—an evidence-based medicine review. Mov Disord 2019; 34: 180-198 [PMID: 30653247 DOI: 10.1002/mds.27602]

103 Morris R, Martini DN, Madhyastha T, Kelly VE, Grabowski TJ, Nutt J, Horak F. Overview of the cholinergic contribution to gait, balance and falls in Parkinson's disease. Parkinsonism Relat Disord 2019; 63: 20-30 [PMID: 30796007 DOI: 10.1016/j.parkreldis.2019.02.017]

104 Weil RS, Reeves S. Hallucinations in Parkinson's disease: new insights into mechanisms and treatments. Adv Clin Neurosci Rehabil 2020; 19: ONNSS189 [PMID: 33102741 DOI: 10.47795/ONNSS189]

105 Burn D, Emre M, McKeith I, De Deyn PP, Aarsland D, Hsu C, Lane R. Effects of rivastigmine in patients with and without visual hallucinations in dementia associated with Parkinson's disease. Mov Disord 2006; 21: 1899-1907 [PMID: 16960863 DOI: 10.1002/mds.21077]

106 Sawada H, Oeda T, Kohsaka M, Umemura A, Tomita S, Park K, Mizuguchi K, Matsuo H, Hasegawa K, Fujimura H, Sugiyama H, Nakamura M, Kikuchi S, Yamamoto K, Fukuda T, Ito S, Goto M, Kiyohara K, Kawamura T. Early use of donepezil against psychosis and cognitive decline in Parkinson's disease: a randomised controlled trial for 2 years. J Neurol Neurosurg Psychiatry 2018; 89: 1332-1340 [PMID: 30076270 DOI: 10.1136/jnnp-2018-318107]

107 Kwan C, Huot P. 5-HT3 receptors in Parkinson's disease psychosis: a forgotten target? Neuropsychologica Dis Manag 2019; 9: 251-253 [PMID: 31580227 DOI: 10.2217/nmd-2019-0014]

108 Frouni I, Belfield S, Maddaford S, Nuara SG, Gourdon JC, Huot P. Effect of the glycine transporter 1 inhibitor ALX-5407 on dyskinesia, psychosis-like behaviours and parkinsonism in the MPTP-lesioned marmoset. Eur J Pharmacol 2021; 1010: 174452 [PMID: 34480885 DOI: 10.1016/j.ejphar.2021.174452]

109 Tsai CH, Huang HC, Liu BL, Li CI, Lu MK, Chen X, Tsai MC, Yang YW, Lane HY. Activation of N-methyl-D-aspartate receptor glycine site temporally ameliorates neuropsychiatric symptoms of Parkinson's disease with dementia. Psychiatry Clin Neurosci 2014; 68: 692-700 [PMID: 24612097 DOI: 10.1111/pcn.12175]

110 Mantri S, Edison B, Alzyoud L, Albert SM, Daeschler M, Kopil C, Marras C, Chahine LM. Knowledge, Responsibilities, and Peer Advice From Care Partners of Patients With Parkinson Disease Psychosis. Front Neurol 2021; 12: 636345 [PMID: 33597918 DOI: 10.3389/fneur.2021.636345]
