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Emerging role of Psychosis in Parkinson's disease: from clinical relevance to molecular mechanisms

Novel insight into PD psychosis

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Abstract

Parkinson's disease (PD) is the second most common neurodegenerative diseases. Psychosis is one of common psychiatric presentations in the natural course of PD. PD psychosis is an important non-motor symptom which is strongly correlated with 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 identified from current clinical evidence. PD psychosis tended to have negative influence on patients' quality of life and increase the burden of family caregiving. Screening and identification in early stage of disease is crucial for establishing tailored therapeutic strategies and predicting the long-term outcome. Development of PD psychosis was thought to be a combination of exogenous and endogenous mechanisms, including involve dysfunctional imbalance of neurotransmitters, structural and network changes, genetic profiles, cognitive impairments 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. Undergo clinical trials will also provide new insights into tailoring therapy for PD psychosis. Emerging research on future based on new biomarkers and genetic factors may facilitate make a tailoring therapeutic strategy.

Key Words: psychosis; Parkinson's disease; hallucinations; delusions; antipsychotics

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Core Tip: PD psychosis encompasses a variety of misperception symptoms including illusions, passage hallucinations, and presence hallucinations, delusions as well as formed visual hallucinations. PD psychosis has been shown to be 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-HT2A receptor is a promising pharmacological intervention.

INTRODUCTION

With an ageing population, Parkinson's disease (PD) has become the second common neurodegenerative disease after Alzheimer's disease. A rising prevalence and incidence of PD with age without gender difference worldwide was showed[1]. The neuropathological hallmarks of PD are characterized by remarkably gradual degeneration and loss of dopaminergic neurons in the substantia nigra, pars compacta with the formation of Lewy bodies that project to the striatum and subsequent reduction of dopamine levels in striatum, resulting in disruption and imbalance of neurotransmitter homeostasis in the central nervous system. Although PD is traditionally recognized as a movement disorders with the notably motor symptoms (dyskinesia) including tremor, bradykinesia, rigidity, gait disturbance, instability posture and balance[2], which is leading cause of disability in PD patients, PD is thought to has a variable spectrum of complicated non-motor symptoms, such as cognitive and affective impairment, hyposmia, sleep disturbance, neuropsychiatric complications (depression, psychosis, apathy, dementia) and autonomic disorders, the onset of hyposmia is even 20 years earlier than the typical motor symptoms of PD [3], highlighting that PD is not only involved the dysfunction of the dopaminergic system, but also other neurotransmitter systems, such as cholinergic, noradrenergic and serotonergic systems related to above clinical entities[4].

Psychosis is one of common psychiatric presentations in the natural course of PD. Current studies indicated psychotic symptoms of PD is diverse but has not formed a unified standard, the spectrum of PD psychosis encompass a variety of misperception symptoms including illusions, passage hallucinations, and presence hallucinations, delusions, well-structured visual hallucinations and other perceptual disturbances. In general, visual illusions, passage and presence hallucinations were termed as minor

hallucinations, which is most common psychotic phenomena of psychosis in PD [5]. Minor hallucinations appeared to be accompanied with 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 even appear earlier than motor symptoms of PD [6]. Presence of the severe psychotic symptoms was an independent risk factor of the impaired health-related quality of life in PD[8].

PD psychosis tended to have negative influence on patients' quality of life and increase the burden of caregiver and family. A study including 80 patients with PD who were followed up for around 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 about 10 years follow-up including 12,077 PDP patients revealed an increased risk of falls and fractures in PD patients with psychosis[10]. A small case-control study involving 21 PD with mild cognitive impairment showed that patients with visual hallucinations appear to have a higher rate of dementia progression (50% with visual hallucinations compared with 25% without visual hallucinations)[11]. A long-term follow-up study showed that PD psychosis was an independent factor for predicting mortality[12] and likewise, increased occurrence of hallucinations contributed remarkably to mortality in PD patients[13].

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

2. 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* 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, at first year, and at second year was 3%, 5.3%, and 10%, respectively, increasing with duration of PD[20]. Yoritaka *et al* 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 twelfth 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 difference 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].

3. IDENTIFICATION AND SCREENING

3.1 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: 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 one month in the setting of a clear sensorium; 2) Diagnosis of PD is based on United Kingdom brain bank criteria and onset of characteristic phenomena follows the diagnosis of PD; 3) Exclusion of other disorders characterized by similar psychotic symptoms such as dementia with Lewy bodies (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 dementia with Lewy bodies (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* 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* 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 sloven[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].

3.2 SCREENING TOOLS

Explicitly screening for minor hallucinations in 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 underlines 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, 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 (NMSS) 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.

4. 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]. Study of the endogenous pathophysiological features of PD psychosis will facilitate the development of novel treatment strategies.

4.1 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-hydroxyltryptamine) receptor subtype, 5-hydroxytryptamine subtype 2A (5-HT2A) results in psychotic symptoms[41]. Ballanger *et al* 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* 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]. In 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].

4.2 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 the emergence 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 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 Aß1-42, decreased olfactory scores, increased depression scores, and increased symptoms of REM (rapid eye movement) 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].

4.3 STRUCTURAL AND NETWORK CHANGES

Recent studies have revealed that PD psychosis may also be provoked 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*, 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* studied 36 patients with PD by magnetic resonance spectroscopy, and found that the ratio of γ-aminobutyric acid/creatine 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* 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.

4.4 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.

4.5 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 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* (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.

4.6 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 8 categories of antiparkinsonian drugs in clinical use: 1) dopamine (DA) precursor (levodopa); 2) dopamine receptor (DR) agonists (ropinirole, pramipexole, rotigotine); 3) DA decarboxylase inhibitors (carbidopa, benserazide); 4) catechol-O-methyltransferase (COMT) inhibitors (entacapone, tolcapone); 5) monoamine oxidase (MAO) B inhibitors (rasagiline, selegiline, safinamide); 6) N-methyl-D-aspartate receptor antagonists (amantadine); 7) anticholinergics (trihexyphenidyl, benztropine); and 8) 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 follow-up and [60] 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 found more likely to develop PD psychosis during 2 years of follow-up[61]. In the PROPARK study, both DR agonists and DA precursors were identified as independent risk factors for hallucinations in patients with PD[62]. Barrett *et al* 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 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.

5. 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.

5.1 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 schizophrenia[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 serotonin type 2A (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 7 controlled trials revealed that the efficacy of quetiapine for treatment of psychosis in patients with PD, PD dementia, and DLB is not superior than 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.

5.2 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 Aug 2010 and Aug 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-week, 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* 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 4 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* 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].

5.3 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].

5.4 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 PD psychosis patients, 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 rispehdone, 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 (MPTP)-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.

5.5 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.

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