Management of Parkinson's disease psychosis—a European perspective

Walter Pirker,[a,b,*] Joaquim J. Ferreira,[c,d] Olivier Rascol,[e] and Werner Poewe[f]

[a]Department of Neurology, Klinik Ottakring, Vienna, Austria
[b]Sigmund Freud University, Vienna, Austria
[c]Laboratory of Clinical Pharmacology and Therapeutics, Faculdade de Medicina, Universidade de Lisboa, Portugal
[d]CNS Campus Neurológico, Torres Vedras, Portugal
[e]Departments of Clinical Pharmacology and Neurosciences, Clinical Investigation Center CIC1436 and NS-PARK/FCRIN Network, Toulouse University Hospital, University of Toulouse 3 and INSERM, Toulouse, France
[f]Department of Neurology, Medical University of Innsbruck, Austria

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Summary

Hallucinations and delusions are among the most disabling long-term complications of Parkinson's disease (PD). Their pathogenesis is based on a complex interaction of neurodegeneration in critical areas for visual and cognitive processing and PD medication effects. Management rests on the identification and treatment of acute triggers, simplification of PD medication and treatment with antipsychotics. Despite the high prevalence of psychosis in advanced PD there is still a lack of familiarity with its manifestations and therapeutic approaches. This gap is further enhanced by recent developments in drug availability and therapeutic monitoring. Pimavanserin is the only approved drug for the treatment of PD psychosis in the U.S., but currently not marketed elsewhere. The aim of this review is to provide an update on the management options for PD psychosis in other regions of the world with a focus on clinical practice in Europe. Quetiapine and clozapine remain cornerstones of treatment of PD psychosis in Europe. Despite limited evidence for efficacy, quetiapine is often used as first-line therapy, whereas severe PD psychosis usually requires treatment with clozapine, with clozapine demonstrating efficacy without worsening of motor symptoms in randomised, controlled trials. Other antipsychotics should be avoided in PD psychosis due to their ineffectiveness or high potential for worsening parkinsonian motor symptoms. Novel drugs with a better risk-benefit ratio in the treatment of PD psychosis are needed. Non-pharmacological treatments should be explored in relation to their potential to prevent or mitigate psychotic reactions in prospective studies.

Keywords: Parkinson's disease; Hallucinations; Delusions; Psychosis; Clozapine; Quetiapine

Introduction

Neurological disorders are the leading source of disability and second-leading cause of death worldwide,[1] and Parkinson's disease (PD) is the fastest growing of these disorders.[2] From 1990 to 2015, the number of people with PD increased from 2.6 to 6.3 million worldwide, with about a quarter of the global PD population living in Europe (around 1.4 million in 2015).[2] Owing to the increase in longevity, declining smoking rates, and rising industrialisation a further increase to over 17 million PD patients can be expected until 2040.[3] Although PD is best known for its cardinal motor features bradykinesia (slowness of movement), rigidity (muscle stiffness) and resting tremor, non-motor features are increasingly recognised as important contributors to disability throughout all stages of PD.[4] These include autonomic symptoms, cognitive impairment and psychiatric problems including depression, anxiety and psychosis.

PD psychosis represents one of the greatest therapeutic challenges in the course of PD. Hallucinations, delusions and paranoid ideation can necessitate dose reductions of dopaminergic medication below the threshold required for adequate control of motor symptoms. Psychotic symptoms have considerable impact on the quality of life of patients and their relatives,[5,6] and represent an important risk factor for nursing home placement and mortality in PD.[7] The appropriate and timely treatment of hallucinations and delusions in PD is critical in order to reduce the mental stress of patients and their carers and to avoid potentially serious disruptions of social relationships. At the same time, care must be taken to ensure that antipsychotic treatment does not lead to a critical worsening of mobility and everyday function.

Most antipsychotics can worsen PD motor symptoms due to their dopamine D2 receptor blocking activity. Quetiapine and clozapine act on multiple

*Corresponding author. Department of Neurology, Klinik Ottakring, Montleartstrasse 37, A-1160, Vienna, Austria.
E-mail address: walter.pirker@gesundheitsverbund.at (W. Pirker).

receptor types, have relatively low affinity for D2 receptors and at the low to moderate doses used in PD usually do not lead to clinically relevant worsening of motor symptoms.[8] Pimavanserin, a selective serotonin 5-HT2A receptor inverse agonist, is the first non-dopaminergic agent with proven efficacy in PD psychosis.[9] Since its introduction in 2016 pimavanserin remains the only approved drug for the treatment of PD psychosis in the United States (U.S.). Much of the currently published literature on the treatment of PD psychosis is focused on the use of pimavanserin.[10] Although pimavanserin is a substantial addition to the treatment armamentarium for PD psychosis, it is currently not marketed outside of the U.S. The aim of this narrative review is to provide an update on the management options for PD psychosis in other regions of the world with a focus on clinical practice in Europe.

Prevalence of PD psychosis

Hallucinations have only rarely been reported in PD patients in the pre-levodopa era.[11] After the introduction of levodopa, the lifetime prevalence of psychotic symptoms in PD rose to over 50%.[12,13] This is most likely due to the psychotogenic potential of dopamine replacement therapy in conjunction with an increase in life expectancy and disease duration and thus the proportion of patients developing cognitive decline and dementia. In a large outpatient cohort of PD patients, the prevalence of hallucinations was 40% after a mean disease duration of 9 years.[14] Mild hallucinatory phenomena like sense of presence hallucinations (feeling that a person is present in the room), passage hallucinations (fleeting visual perceptions in the peripheral visual field) or illusionary misperceptions were present in 25% of the patients. Formed visual hallucinations occurred in 22% of patients, and auditory hallucinations in 10%.[14] In a long-term observational study from Sydney, 74% of the patients with PD who were still alive 20 years after disease onset suffered from visual hallucinations requiring treatment.[15] A recent systematic metaanalysis of prevalence rates of psychotic phenomena in PD identified 32 relevant studies. The pooled frequencies of hallucinations and delusions were 21.6% and 6.1%, respectively.[16]

Phenomenology

The spectrum of psychotic symptoms in PD ranges from minor hallucinations or illusionary misperceptions with preserved insight to severe delusional and agitated paranoid states requiring institutional care. The latter may require dramatic reductions in dopaminergic medication, which in turn can lead to critical motor worsening ('akinetic crisis') and dopaminergic withdrawal symptoms.[17,18] Visual hallucinations are the most common manifestation of PD psychosis and entail simple or detailed, often vibrantly coloured images of people or animals, less frequently of objects. In many patients, visual hallucinations occur preferably in the evening, at night or under conditions of reduced lighting. The duration of the individual hallucinatory episodes is usually between a few seconds and half an hour. In addition to visual hallucinations, auditory, tactile, olfactory and gustatory perceptions can also occur, but are less common. Auditory hallucinations include voices, music or unstructured acoustic percepts.[14] Vocal auditory hallucinations are usually neutral in content but may also consist of negative comments on the affected person.[19,20] While auditory hallucinations may rarely be the sole manifestation of PD psychosis, the majority of patients experiencing auditory hallucinations also suffer from visual hallucinations.[14,19]

PD patients without dementia often have retained insight into the hallucinatory nature of their perceptions or are responsive when told by others that they are unreal but loss of insight into the unreal character of hallucinations may evolve over time.[13] Patients may also lose and regain insight or may be only partially insightful into the unreal nature of hallucinations. With the loss of insight into the unreal character of hallucinations, delusions often occur.[17] A delusional disorder is rarely observed in PD patients who have never suffered from hallucinations.[21] Typical of PD psychosis are severe delusions of persecution, in which the person feels fatally threatened or believes he or she is being robbed, or delusions of jealousy, which usually centre on the sexual infidelity of a partner.

Severe acute states of confusion in PD are often caused by external influences such as exsiccosis, an infection or anticholinergic medication, and therefore require a different treatment approach to classical PD psychosis.[22,23] In addition, some people with PD suffer from recurrent hallucinations or long-standing delusions, i.e. a classic PD psychosis, which may be superimposed by states of confusion and agitation with psychotic symptoms, e.g. during the night.

Progression

Psychotic symptoms in PD typically appear after ten or more years of disease duration.[22] Visual hallucinations in the first years of PD represent a significant risk factor for cognitive decline and for the early onset of Parkinson's disease dementia (PDD).[12] Hallucinations in PD, if untreated, usually remain a chronic problem with a low tendency to spontaneous remission. Patients with mild hallucinations usually develop hallucinations with loss of insight or delusions in the further course of disease.[13,17] Discontinuation of antipsychotic therapy often leads to recurrence of hallucinations or psychosis.[24]

Risk factors

The most important endogenous risk factor for the occurrence of psychosis is cognitive dysfunction and

dementia, which is closely linked to the spread of Lewy pathology from the brain stem to the limbic system and cortex as well as the degeneration of cholinergic projection systems.[25] Other independent risk factors include patient age, duration and severity of PD and depression.[17] Sleep-wake rhythm disorders, declining visual acuity and pre-existing neuropsychiatric conditions are additional risk factors.[13]

The most important external trigger is drug therapy for the motor symptoms of PD. In principle, any PD medication can cause psychotic symptoms in predisposed subjects. The risk of psychosis occurring under dopaminergic therapy is dose-dependent, although this dose-response relationship is complex and has not been found in all studies.[26,27] Randomised controlled studies showed that dopamine agonists have a higher potential to trigger PD psychosis than levodopa.[26] Anticholinergics and other medications with central anticholinergic activity (e.g. tricyclic antidepressants and drugs for overactive bladder such as oxybutinin) are considered to have high potential for inducing delirium and psychosis in PD.[22] However, there are no hard data from clinical trials to support this notion. Similarly, amantadine, in particular in patients with PDD, can induce delirium and psychosis, but the actual risk as compared to levodopa and dopamine agonists is unknown. Whereas monoamine oxidase B (MAO B) inhibitors such as selegiline and rasagiline may induce psychosis by interaction with central dopaminergic pathways, the peripherally acting catechol-O-methyltransferase (COMT) inhibitors entacapone and opicapone can trigger psychosis by increasing brain levodopa availability.[26]

Other external triggers of PD psychosis are intercurrent infections such as aspiration pneumonia or urinary tract infection, exsiccosis, metabolic or endocrine disorders, traumatic brain injury, cerebral hypoxia or acute cerebrovascular events. Endocrine triggers in particular, such as hyperthyroidism or hyperparathyroidism, can easily be overlooked if they are not accompanied by typical general medical symptoms.[22]

Diagnostic criteria

In 2007, a National Institute of Neurological Disorders and Stroke-National Institute of Mental Health (NINDS-NIMH) working group presented diagnostic criteria according to which recurrent presence hallucinations, illusions or hallucinations occurring over a period of one month or delusions persisting for at least one month in the presence of PD and absence of other causes including delirium are considered diagnostic criteria for PD psychosis.[17] This broad definition is justified for research purposes, but includes patients who do not require antipsychotic therapy (such as patients with isolated presence hallucinations). To assess the need for antipsychotic treatment, the Diagnostic and Statistical Manual of Mental Disorders version 5 (DSM-5) diagnostic criteria, according to which PD psychosis is characterised by prominent hallucinations or delusions that lead to significant impairment and do not only occur during a state of confusion, seem more relevant.[28]

Management of PD psychosis

Mild, intermittent hallucinatory phenomena typical of PD with preserved insight (e.g. presence hallucinations and illusions) are usually not very distressing, and with appropriate counselling antipsychotic therapy may not be required. Nonetheless, these symptoms should give rise to a search for possible triggers, a critical review of the current drug regimen and closer clinical follow-up.[22] The treatment of florid hallucinosis with lack of insight, delusions and acute states of confusion requires in-patient care with diagnostic work-up for external triggers, the revision of PD medications, starting with the discontinuation of adjuvant medication and the use of atypical antipsychotics (Figs. 1 and 2 and Panel 1).

Search for triggers and reduction of adjunct medication

In acute PD psychosis, an intensive search should be made for possible triggers (see above). If such a trigger is found (e.g. infection), the focus should be on combating the cause. In any case, attention should be paid to adequate fluid and electrolyte intake and regulation of the sleep-wake rhythm.[22] PD medication should be revised. Drugs with significant potential to induce or aggravate psychosis but limited effect on motor symptoms should be tapered off or stopped first (Fig. 2. Note that the recommendations therein reflect the authors' opinion). In particular, anticholinergic substances (PD medications such as biperiden, tricyclic antidepressants, paroxetine, muscle relaxants such as orphenadrine, and centrally active anticholinergic urological drugs) should be discontinued if possible. Even PD patients with dementia on cholinesterase inhibitors are often concurrently treated with mid- or high potency anticholinergic drugs, a situation regarded as frank prescribing error.[37] Anticholinergic burden scales can be helpful to identify potentially harmful drugs with anticholinergic activity.[38,39]

Subsequently, drugs with moderate motor benefit like amantadine or MAO-B inhibitors should be discontinued. Dopamine agonists should be tapered off before decreasing levodopa.[22] If this does not lead to a resolution of PD psychosis, discontinuing COMT inhibitors may be considered. In case of nocturnal psychotic symptoms, an attempt can be made to skip the last levodopa dose before sleep. In severe PD psychosis an overall reduction of the levodopa dose may be warranted. In the event of significant worsening of motor symptoms, we believe that a slight increase in levodopa dose is preferable to the additional administration of other PD medication.

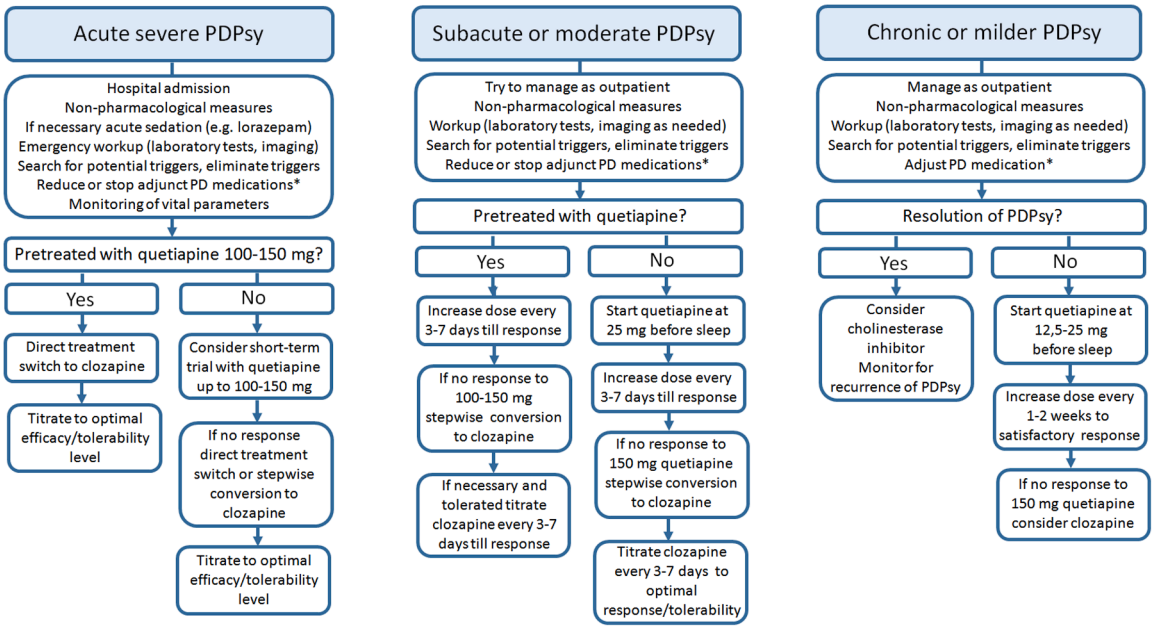

Fig. 1: Sequential treatment options in Parkinson's disease psychosis. *See Fig. 2 and text for details. Acute severe PD psychosis refers to patients with severe delusions or severely distressing hallucinations with loss of insight in need of in-patient care. Subacute or moderate PD psychosis refers to a group of patients with hallucinations with loss of insight and moderate delusions, in whom out-patient care is still possible. Chronic or milder PD psychosis refers to patients with formed visual hallucinations or mildly distressing hallucinations in other domains, usually with retained or intermittently retained insight or mild delusions, typically treated as out-patients. The figure reflects the authors' opinion. PD, Parkinson's disease; PDPsy, Parkinson's disease psychosis.

Antipsychotic treatment

If psychotic symptoms do not subside, antipsychotic treatment is indicated. In severe PD psychosis, antipsychotic therapy is initiated at the same time as reducing the PD medication, especially if symptoms are accompanied by a severe sleep-wake rhythm disorder, agitation or aggression (see Fig. 1. Note that the recommendations therein reflect the authors' opinion). In this situation, the additional administration of a benzodiazepine for sedation or as a hypnotic will often be necessary in the experience of the authors. Important accompanying non-pharmacological measures include providing a quiet environment, reassurance and education of the patient by doctors and nursing staff and reality training with the involvement of relatives.

Classical (first generation) antipsychotic drugs worsen PD motor symptoms due to their strong dopamine D2 receptor blocking activity. Atypical (second and third generation) antipsychotics that rarely trigger parkinsonism in schizophrenia patients, such as aripiprazole or olanzapine, can lead to significant worsening of motor symptoms in PD. This applies to an even greater extent to risperidone, which is nominally classified as atypical antipsychotic, but actually has strong D2 receptor blocking activity and frequently triggers drug-induced parkinsonism, especially in elderly subjects.

Table 1 provides an overview of published randomised-controlled studies on the treatment of PD psychosis. Four randomised, placebo-controlled trials found olanzapine to worsen parkinsonism without improving psychotic symptoms.[47–49] Moreover, a trial comparing olanzapine and clozapine in PD psychosis was terminated prematurely due to worsening of motor symptoms in the olanzapine group. Clozapine significantly improved hallucinations, whereas olanzapine had no effect.[54] A small trial comparing risperidone and clozapine showed an improvement of motor symptoms in the clozapine and a worsening of parkinsonism in the risperidone group.[40] In a randomised, placebo-controlled study the low affinity D2 receptor blocking drug melperone was well tolerated but proved ineffective against PD psychosis.[55] Contradictory results have been obtained for PD psychosis in small case series with ziprasidone with some patients showing benefit but lack of response and severe motor worsening in others.[56] Small short-term, open-label studies found the partial dopamine D2 receptor agonist aripiprazole to worsen motor symptoms in a substantial proportion of PD psychosis patients.[57,58] Marked worsening of parkinsonism was observed in a single case with PD psychosis following treatment with the partial dopamine receptor agonist brexpiprazole.[59] No data from prospective studies of brexpiprazole in PD are available. To summarise, most D2 receptor blocking drugs have

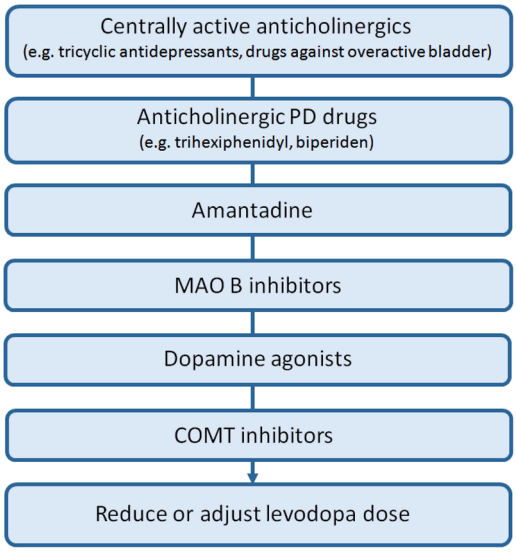

Fig. 2: Proposed sequence of reduction or withdrawal of adjunct medication in Parkinson's disease psychosis. PD psychosis should always prompt the withdrawal of centrally active anticholinergics. In acute or severe psychosis MAO B inhibitors and amantadine should be withdrawn immediately. Dopamine agonists should be reduced to a low dose and stopped within a few days if possible. In patients with persisting severe PD psychosis, this may be followed by stopping COMT inhibitors and, depending on the severity of the psychosis, a reduction in levodopa dose. Subacute or moderate PD psychosis may necessitate a stepwise-wise withdrawal of amantadine, MAO B inhibitors and reduction of dopamine agonists to a low dose within a week. Dopamine agonists may be stopped some days later and COMT inhibitors withdrawn later on in patients with ongoing psychosis. In patients with chronic or milder PD psychosis withdrawal of centrally active anticholinergics may be followed by a stepwise reduction of other adjuvant medication, starting with reduction of amantadine to a low dose and withdrawal of MAO B inhibitors, followed by withdrawal of amantadine and stepwise tapering of dopamine agonist dose. The figure reflects the authors' opinion. PD, Parkinson's disease; MAO B, monoamine oxidase B; COMT, catechol-O-methyltransferase.

been proven ineffective in the treatment of PD psychosis or harbour a high risk of worsening motor symptoms and are therefore not recommended for the treatment of PD psychosis. The exceptions to this rule are quetiapine and clozapine. Both drugs have relatively low affinity for D2 receptors and act on multiple receptor types.[8] Used at low to moderate doses they do not worsen the motor symptoms of PD and remain the cornerstones of treatment of PD psychosis in Europe.[29,60]

Clozapine

The efficacy of clozapine in the treatment of PD psychosis has been demonstrated by a number of open-label studies and two 4-week double-blind, randomised, controlled trials.[31,32,52,53] Clozapine leads to a significant improvement in psychosis in 85% of patients at low doses (6.25–50 mg/d) without worsening motor symptoms and cognitive performance.[31] The improvement in PD psychosis is evident after just one week of therapy, and the antipsychotic effect becomes stronger with increasing duration of therapy.[24,32] Hallucinations tend to respond earlier than delusions.[30] In one randomised and several open-label studies, an improvement in Parkinsonian tremor was observed with clozapine.[8,31] Other studies have described a favourable effect of clozapine on anxiety, depression, hypersexuality and sleep fragmentation in PD.[61] Clozapine also suppresses levodopa-induced dyskinesias.[62] Another possible benefit is the antisuicidal effect of clozapine documented in schizophrenia patients.[63] Clozapine has been labelled effective and clinically useful by an evidence-based review sponsored by the International Parkinson's Disease and Movement Disorder Society (MDS)[9] and is approved for psychotic disorders occurring during the course of PD, in cases where standard treatment has failed, by the European Medicines Agency (EMA).[64]

The initial clozapine dose should be 6.25 or 12.5 mg in the evening.[64] Under outpatient conditions, the dose should be increased slowly (e.g. by 12.5 mg per week). The maximum dose should generally be 50 mg, preferably as a single dose in the evening. In severe PD psychosis and under inpatient conditions, a relatively rapid increase in dosage (by about 12.5 mg per day) to maximum doses of about 100 mg per day may be required. In exceptional cases a further dose increase of up to 150 mg may be necessary.[8,30]

An important limiting factor for the use of clozapine is the known agranulocytosis risk of around 1%.[65] Possible causes are the formation of toxic nitrenium ions from clozapine metabolites in genetically predisposed individuals and immunological mechanisms.[65] Concerns about this side effect and the need for blood count monitoring result in a high underutilisation of clozapine in PD psychosis and schizophrenia.[33,66] The likelihood of occurrence of agranulocytosis increases in the first weeks, peaks between the 6th and 10th week of treatment and decreases after the 18th week.[65] As a result of regular blood count checks, mortality from clozapine-induced agranulocytosis is lower than that from other non-chemotherapy-induced agranulocytosis (approx. 3% compared to 7–10%). In case of agranulocytosis, the duration of the neutropenic phase can be shortened by administering filgrastim.[65] Late-onset mild neutropenia is more often due to other causes such as viral infections than to clozapine and does not always require discontinuation.[67] New safety data from Australia and New Zealand show that the risk of agranulocytosis occurring after 2 years of clozapine therapy may be negligible.[68] In response, the U.S. risk evaluation and mitigation strategies (REMS) program for clozapine was terminated by February 2025.[69] In September 2025, EMA followed with new recommendations limiting surveillance in clozapine-treated

Panel 1: **Key points**

- Treatment of PD psychosis is based on identifying and treating acute triggers, including a review of PD and other medication and reducing or simplifying PD medication and discontinuing other potentially psychosis-inducing drugs. If these measures prove insufficient, antipsychotics should be initiated.[8,22]
- Quetiapine and clozapine are the only antipsychotic drugs available and recommended for the treatment of PD psychosis in Europe.[22,29]
- Despite limited evidence, quetiapine remains first-line for the treatment of most patients with PD psychosis.[9]
- Quetiapine can be helpful in the treatment of PD-related hallucinations but its effect may wane over time. Quetiapine is less effective in severe psychosis and delusions.[30]
- The efficacy of clozapine in PD psychosis has been clearly demonstrated by randomised studies. Low doses lead to a significant improvement in psychosis in the majority of patients without worsening motor symptoms.[31,32]
- The side effects of clozapine must be taken seriously, but are generally manageable. In the past, the risk of clozapine-associated agranulocytosis has been overestimated whereas other risks (such as ileus, pneumonia and myocarditis) have received too little attention.[33–35]
- In the treatment of acute, severe PD psychosis, quetiapine should only be used if there are serious reasons against clozapine therapy. Also in other cases of PD psychosis, if troublesome psychotic symptoms remain unresponsive despite a daily dose increase of up to 150 mg quetiapine, a treatment change to clozapine should be considered.[8,30]
- In general, antipsychotics should be initiated at a low dose (at 12.5–25 mg for quetiapine and 6.25–12.5 mg for clozapine) and given preferentially at bedtime to avoid daytime sedation.[8,30]
- In general, antipsychotic dose should be increased slowly.[8] Severe acute PD psychosis may require a more rapid increase of antipsychotic dose and a direct treatment switch from quetiapine to clozapine.[30]
- Withdrawal of antipsychotic drugs is associated with a high risk of relapse of psychosis.[24] In general, patients should continue treatment as long as PD psychosis is well controlled and the drugs are well tolerated.
- Drug-treatment of PD psychosis should always be accompanied by non-pharmacological measures including optimising vision and hearing, patient and caregiver education and reality training.[36]

patients to weekly absolute neutrophil counts (ANC) during the first 18 weeks and monthly ANC for the following 34 weeks. In cases without preceding neutropenia, ANC should be collected every 12 weeks during the second year and once yearly thereafter.[70]

Physicians' overestimation of agranulocytosis risk contributes to under-monitoring of other adverse drug reactions with higher lethality such as pneumonia and ileus.[33,34] Since inflammation may lead to a reduction in clozapine biotransformation, halving its dose during acute infections was recommended to avoid hazardous increases in clozapine plasma levels.[34] Clozapine-associated myocarditis (CAM) and other inflammatory conditions have received more attention in recent years. CAM mainly occurs during the first 4 and up to 8 treatment weeks, with an average onset 21 days after clozapine initiation, and is linked to rapid up-titration of clozapine.[35] So far, only two cases of clozapine-associated myocarditis in subjects with PD, both with comorbid schizoaffective psychosis, have been reported. Clozapine daily doses in these cases were 50 and 300 mg, respectively.[71,72] In the context of treating drug-resistant schizophrenia, an international expert panel recently recommended weekly lab monitoring including c-reactive protein (CRP), full blood count and hs-troponin, 2-weekly electrocardiograms (ECG) and regular checks of vital parameters during the first 4 weeks of clozapine treatment as a safeguard against CAM.[35] ECG follow up is also recommended due to the QT-prolonging effect of clozapine.[73]

Drug reaction with eosinophilia and systemic symptoms (DRESS) is a very rare but potentially fatal hypersensitivity reaction with varying clinical manifestations including fever, skin rash, eosinophilia and lymphadenopathy. DRESS is most commonly associated with antiseizure medications but has been observed in a number of subjects on clozapine, particularly during the first weeks of treatment.[74] Monitoring of serum CRP in addition to full blood counts, as recommended for myocarditis screening, may assist in the early diagnosis of DRESS.

Another rare but serious side effect is venous thromboembolism, which can occur days to years after starting treatment, regardless of the clozapine dose.[75] The most common adverse effect, daytime sedation, often responds to a reduction of clozapine dose. Furthermore, single-dosing at bedtime can help to prevent this adverse event. Other relatively common side effects are hypersalivation and drooling, constipation, orthostatic hypotension and dizzines.[73] During long-term therapy, possible negative effects on lipid metabolism, an increased risk of diabetes and weight gain should be noted, although the latter is rarely observed in PD patients.[76] Electroencephalographic abnormalities and epileptic seizures are well known adverse events associated with clozapine.[73] Since

Study	Reference number	Region	Number of participants	Mean daily dose	Number of completers	Quality score (%)[a]	Improvement of psychosis	Worsening of motor symptoms
Clozapine vs. Placebo								
PSG 1999	31	U.S.	30/30	25 mg	27/27	93%	yes	no
FCPSG 1999	32	France	32/28	36 mg	27/19	58%	yes	in some patients
Risperidone vs. Clozapine								
Ellis 2000	40	U.S.	5/5	1.2/62.5 mg	5/4		yes/yes	yes/no
Quetiapine vs. Placebo								
Ondo 2005	41	U.S.	21/10	169 mg	17/8	68%	no	no
Rabey 2007	42	Israel	30/28	119 mg	15/17	74%	no	no
Shotbolt 2009	43	U.K.	11/13	73 mg	4/9	65%	no	no
Fernandez 2009	44	U.S.	8/8	58 mg	4/7	68%	yes	no
Quetiapine vs. Clozapine								
Morgante 2004[b]	45	Italy	22/23	91/26 mg	20/20	67%	yes/yes	no/no
Merims 2006[c]	46	Israel	14/13	91/13 mg	9/7	65%	yes/yes[d]	no/no
Olanzapine vs. Placebo								
Breier 2002 (EU)	47	EU	49/28	4.1 mg	37/24	63%	no	yes
Breier 2002 (US)	47	U.S.	41/42	4.2 mg	25/38	63%	no	yes
Ondo 2002	48	U.S.	19/11	4.6 mg	16/11	68%	no	yes
Nichols 2013	49	U.S.	6/8/9	2.5/5 mg	2/5/7	73.7%	no	yes
Melperone vs. Placebo								
Friedman 2012	55	U.S.	60/30	20/40/ 60 mg	75		no	no
Pimavanserin vs. Placebo								
Meltzer 2010	50	U.S.	29/31	44.8 mg	28/28	73.7%	yes (secondary outcomes)	no
Cummings 2014	51	U.S.	105/94	40 mg	89/87	90.5%	yes	no

Note: No quality score is presented for the studies by Ellis and Friedman,[40,55] since these studies were not included in the evidence-based reviews sponsored by the International Society for Parkinson's Disease and Movement Disorders. PSG, Parkinson Study Group; FCPSG, French Clozapine Parkinson Study Group; U.S., United States; U.K., United Kingdom; EU, European Union. [a]Data taken from evidence-based reviews sponsored by the International Society for Parkinson's Disease and Movement Disorders.[9,52,53] [b]Randomised, single blinded 12 week study; 12.5–50 mg Clozapine, 25–200 mg Quetiapine. [c]Randomised, single blinded 22 week study; 6.25–50 mg Clozapine, 25–150 mg Quetiapine. [d]Clozapine superior in controlling delusions.

Table 1: **Published randomised-controlled studies on the treatment of Parkinson's disease psychosis.**

seizures are associated with rapid dose titration and high daily doses of clozapine, the risk is probably very low in in PD psychosis. In rare instances, clozapine, especially at higher doses, can induce delirium, an adverse event most likely related to clozapine's intrinsic anticholinergic properties.[73,77]

Quetiapine

At low doses, quetiapine acts primarily as a strong antagonist at histamine H1 receptors and is therefore an excellent hypnotic. In moderate doses, it acts as a noradrenaline reuptake inhibitor via its metabolite norquetiapine and therefore has antidepressant properties. Due to its low dopamine D2 receptor affinity, only high doses have an antipsychotic effect in schizophrenia.[78]

There are positive data from open-label studies on the efficacy of quetiapine in the treatment of PD psychosis (for review see[22]). However, randomised, placebo-controlled quetiapine studies in PD psychosis have been negative,[41–43] with the exception of one small study that showed an improvement in sleep and visual hallucinations when quetiapine was given as a single dose before sleep.[44] Two small, single-blinded comparative studies of clozapine vs. quetiapine showed a positive effect of quetiapine on hallucinations,[45,46] with clozapine being more effective than quetiapine on delusions in one of the studies.[46] None of the studies showed a worsening of motor symptoms at average daily doses of up to 170 mg quetiapine. Despite limited evidence, quetiapine was classified as 'possibly useful' in an evidence-based MDS review.[9] Quetiapine continues to be the most commonly used antipsychotic in the treatment of PD psychosis in many countries, including the United States.[79]

The initial quetiapine dose should be 12.5–25 mg in the evening.[8] Under outpatient conditions, a slow increase in dosage is recommended. Daily doses of 150 mg (200 mg in exceptional cases) of quetiapine should not be exceeded in PD. Due to the strong sedative effect of quetiapine, based on our clinical experience, treatment with a single dose in the evening is preferable to multiple daily doses. Slow-release preparations may cause daytime sedation. Other side

effects include orthostatic hypotension, dizziness, dry mouth and constipation in addition to a possible worsening of motor symptoms under high doses. The metabolic side effects (lipid metabolism, reduced glucose tolerance, weight gain) are less severe than those of clozapine.[78] ECG follow up is recommended due to the QT-prolonging effect of quetiapine.

In our own experience, quetiapine can lead to satisfactory control of hallucinations in many PD patients. Delusions, on the other hand, are much less likely to respond to quetiapine. Quetiapine can therefore not be generally recommended as the drug of first choice for severe PD psychosis. If there is no response to 150 mg quetiapine daily at the latest, a treatment change to clozapine should be urgently considered.[8,30] A direct switch from quetiapine to clozapine in a dose ratio of 3:1 to 4:1 was suggested in the literature.[80] In a separate retrospective series, such a direct treatment switch was well tolerated by the majority of patients. Clozapine led to an improvement in PD psychosis in the vast majority of patients refractory to quetiapine.[30] However, the benefits of a direct treatment switch must always be weighed against the risks of rapid uptitration of clozapine (see above[35,74]).

Pimavanserin

The mechanisms underlying the specific action profile of atypical antipsychotics which provide an antipsychotic effect at a low risk of adverse motor symptoms are not fully understood. According to one hypothesis, their loose binding to D2 receptors with displaceability by the endogenous ligand dopamine is responsible for their atypical profile. According to another hypothesis, their high affinity for serotonin 5HT2A receptors underlies their antipsychotic efficacy and low propensity to cause neurological side effects.[78] Pimavanserin, a selective inverse agonist at 5HT2A receptors, has been shown to be effective in preclinical models of psychosis. Pimavanserin also acts as weak inverse agonist on 2HT2C receptors, but has no appreciable affinity to dopamine, adrenergic, histamine, or muscarinic acetylcholine receptors. In a randomised controlled trial in PD psychosis, the substance led to a significant improvement of hallucinations and delusions.[51] In exploratory analyses, pimavanserin also had positive effects on sleep and daytime wakefulness and reduced caregiver burden.[51] An effect on hallucinations and delusions was also noted in a smaller randomised controlled study comparing pimavanserin and placebo, although the primary outcome (the Scale for the Assessment of Positive Symptoms total domain score) was negative.[50] Moreover, in a subanalysis of a randomised pimavanserin washout trial in patients with dementia and psychosis responding to pimavanserin, a higher risk of psychosis relapse was observed in PD psychosis patients receiving placebo than in those staying on pimavanserin.[81] Pimavanserin confers no risk of motor worsening and is generally well tolerated.[8] Although no prospective comparative studies are available, there is indirect evidence for a somewhat weaker effect of pimavensarin versus clozapine.[82] Moreover, an uncontrolled study showed that patients with PD psychosis who initially responded to pimavanserin often require an additional antipsychotic drug in the further course[83] and may respond well to clozapine.[84] Although pimavanserin would certainly be a valuable addition to the treatment repertoire of PD psychosis in Europe and other regions, the drug is only marketed in the U.S., where it remains the only approved drug in this indication.

Cholinesterase inhibitors

The rationale for the use of cholinesterase inhibitors in the treatment of PD psychosis is based on the importance of the cholinergic deficit for the development of Parkinson's disease dementia and psychosis. The efficacy of the cholinesterase inhibitor rivastigmine in PDD has been proven by a randomised study.[85] Donepezil and galantamine were labelled as possibly useful for the treatment of PDD in the evidence based review by the MDS.[9] Rivastigmine not only led to cognitive improvement, but also had a significant effect on delusions and hallucinations.[85] The positive effect of cholinesterase inhibitors on psychotic symptoms was recently confirmed in a meta-analysis. However, the effect size of cholinesterase inhibitors in this indication is small.[86] In addition to their established role in the treatment of PDD, cholinesterase inhibitors are an option for patients with mild hallucinations and an important add-on therapy for manifest PD psychosis. In clinical practice, care has to be taken to ensure that the positive effect of cholinesterase inhibitors is not lost by the simultaneous prescription of avoidable centrally acting anticholinergics.[37]

Non-pharmacological measures

Antipsychotic drug treatment in PD psychosis should always be accompanied by non-pharmacological measures. There is no empirical evidence from clinical studies to guide in the right choice of non-pharmacological approaches in PD psychosis. However, some lessons can be drawn from the literature on the treatment of psychosis in schizophrenia and dementia and from non-pharmacological measures in the treatment of delirium.[23,36]

People with PD have a higher prevalence of ophthalmologic symptoms than controls including dry eyes, double vision, reduced contrast sensitivity, impaired colour vision, and visuospatial deficits.[87] If deficits in visual processing related to PD pathology or ophthalmological conditions contribute to visual misperceptions, correcting visual acuity may be helpful. The same accounts for hearing impairment which may contribute to auditory hallucinations and could be

ameliorated by provision of hearing aids.[23,36] In hallucinations with retained insight, reality training may help the patient to distinguish between misperceptions and actual perceptions. In fact, an observational study found that the majority of PD patients with visual hallucinations develop coping strategies to better deal with their hallucinations.[88] Patients who had developed this coping strategies found their hallucinations less troublesome than patients that did not.[36]

By nature, delusions are less responsive to non-pharmacological treatments. In more chronic delusions of persecution, theft, food poisoning or substitution of PD medications, empathetic reality training, depending on circumstances with or without the involvement of relatives, can be tried. Partner therapy can be an option in delusions of spousal infidelity. In acute PD psychosis with persecutory delusions providing a quiet and safe environment and reassurance of the patient by doctors and nursing staff are important in addition to immediate commencement of antipsychotics.

Cognitive behavioural therapy (CBT) is increasingly used in the treatment of depression and anxiety in PD.[89] Since relatively preserved cognition is a prerequisite for CBT and PD psychosis is related to cognitive decline, full-blown PD psychosis is probably not amenable to CBT. However, use of basic principles of CBT by the treating neurologist might be a helpful preventive measure in the early stages of the development of PD psychosis. In addition, family interventions including psychoeducation and emotional support for caregivers would be helpful to reduce the burden of PD psychosis for patients and families.[36]

Finally, electroconvulsive therapy (ECT) may be a treatment option for severe PD psychosis refractory to antipsychotic drug treatment. According to published literature ECT is safe, acts fast and may be overall more effective in elderly than in younger subjects.[90] Although a meta-analyis of ECT in PD described improvements in motor symptoms and psychosis, the actual efficacy of ECT in PD psychosis is unknown.[90]

For a summary of pharmacological and non-pharmacological measures in the management of PD psychosis see the Panel 1.

Future directions

The complex interaction of disease progression, cognitive decline and pharmacological triggers of PD psychosis are still incompletely understood. Further research is needed to unravel the different mechanisms and pathways by which dopaminergic, antiglutamatergic or anticholinergic PD medications can induce PD psychosis. Comparative pragmatic trials including available drugs and, if possible, pimavanserin may help to implement better standards of care. Novel drugs with a better risk-benefit ratio in the treatment of PD psychosis are needed. Drugs in development for the treatment of schizophrenia such as trace amine-associated receptor 1 agonists and novel cholingeric and serotonergic agents[91] may provide a better risk-benefit ratio and could hold promise also for PD psychosis.[92] Non-pharmacological treatments should be explored in relation to their potential to prevent or mitigate psychotic reactions in prospective studies. Finally, the development of comprehensive, specific care programmes for PD patients with cognitive decline and with psychosis might help to improve the quality of life of this severely disabled patient population and their caregivers.

Search strategy and selection criteria

References for this narrative review were identified through searches of PubMed for English-written articles and abstracts published between January 1st, 1980 and September 30th, 2025 using the keywords 'Parkinson's disease' AND 'psychosis' or 'hallucinations' or 'delusions' or AND 'treatment' or 'management' or 'randomised clinical trial', 'clinical trial', 'clozapine', 'quetiapine', 'pimavanserin', 'neuroleptic', 'atypical neuroleptic', 'antipsychotic', 'atypical antipsychotic', or 'non-pharmacological'. Previously published reviews on the treatment of PD psychosis and of non-motor symptoms were scanned for additional references. Randomised, placebo-controlled trials were included for further review. For drugs without evidence from randomised controlled studies, lower quality studies including open label trials and case reports, were also reviewed. The final reference list was based on originality and relevance to the European region.

A first draft including evidence from published studies and a proposal for the managment of PD psychosis was circulated between all authors several times until a consensus reflecting optimised management strategies of PD psychosis in three representative European countries was achieved. Recommendations on the choice of drugs and specific doses are based on published literature whenever available. Recommendations not supported by cited literature are based on the clinical experience of the authors.

Contributors

W. Pirker and W. Poewe conceptualised and planned the review. W. Pirker managed and coordinated the research activity planning and execution. W. Pirker screened the literature and prepared the first draft of the review, with important contributions from J.J. Ferreira, O. Rascol and W. Poewe. All authors critically reviewed and commented on the manuscript, and approved the final version. W. Poewe had supervisory and leadership responsibility for the research activity planning and execution. All authors had full access to all the materials of the study and had final responsibility for the decision to submit for publication.

Declaration of interests

W. Pirker attended advisory boards by Stada, AbbVie Pharma, Merz Pharma and Bial. He received travel grants and educational support from AOP Health, Stada, AbbVie Pharma and Bial as well as lecturing honoraria from Stada, AbbVie Pharma and Bial and Merz Pharma, all unrelated to the contents of this article.

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