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Therapies under investigation for treating Parkinson's disease psychosis

Parkinson's disease (PD) psychosis is a distressing condition that affects up to 60% of patients at the advanced stages of the disease. It significantly impairs patients' and caregiver's quality of life. Current therapeutic options are limited, and only clozapine and, more recently, pimavanserin were demonstrated to be effective in Phase III clinical trials. Phase II studies, open-label trials, case series and case reports have suggested an anti-psychotic efficacy of donepezil, melperone, mianserin, mirtazapine, ondansetron, quetiapine, rivastigmine and sarcosine. In contrast, aripiprazole, galantamine and memantine do not appear effective to alleviate PD psychosis. This review article discusses some of the available therapies to treat PD psychosis and surveys drugs that have recently undergone investigation, or that are presently being studied to address this condition.

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The most recognizable manifestations of Parkinson's disease (PD), bradykinesia, resting tremor and rigidity [1–3], affect the motor system. With disease progression, a breadth of nonmotor symptoms becomes increasingly important and significantly impairs patient's quality of life. Psychiatric manifestations, including anxiety, depression and psychosis, are amongst the most frequent and disturbing nonmotor manifestations of advanced PD [4].

The phenomenology of PD psychosis is complex. Visual hallucinations are the most common psychotic manifestation and affect up to 60% of patients with advanced PD [5–7]. Visual hallucinations may consist of shadows at the periphery of the visual field, but may also consist of well-formed hallucinations such as familiar faces [8]. Less commonly, patients experience hallucinations involving other sensory modalities, such as auditory, olfactory or tactile hallucinations [9–14]. With disease progression, up to 60% of patients with hallucinations experience multimodal hallucinations, where visual hallucinations coexist with other types of hallucina-

tions [15,16]. Some patients develop feelings of presence [17] or paranoid delusions [18]. The occurrence of visual hallucinations precedes death by approximately 5 years [19].

The first step in the management of PD psychosis often entails a reduction of anti-parkinsonian medication, but this approach is frequently marred by an increase of parkinsonian disability, which limits its clinical usefulness [20]. Moreover, a simple reduction of anti-parkinsonian medication may not fully address psychotic manifestations, as these are not necessarily triggered by administration of dopaminergic agents [21]. For instance, intravenous administration of high dose L-3,4-dihydroxyphenylalanine (L-DOPA) does not necessarily trigger visual hallucinations in PD patients who have previously experienced hallucinations [22]. Adding to the challenge of managing PD psychosis is that several anti-psychotics are dopamine-receptor blockers, which interfere with L-DOPA anti-parkinsonian benefit and deteriorate motor function [23–25]. PD psychosis is therefore more complex than a mere pharmacological phe-

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nomenon. Indeed, it is associated with greater Lewy bodies burden within the amygdala [26,27], as well as reduction of gray matter volume in several brain areas involved in visual processing, such as the left lingual gyrus, hippocampal head, parietal lobe and thalamus [28–31]. Reduction of cholinergic neurons from the pedunculopontine nucleus [32,33] is also regarded as a culprit in the pathophysiology of visual hallucinations. *In vivo* imaging studies performed in PD patients with visual hallucinations have shown altered metabolism in brain areas involved in visual processing, such as the temporal and frontal lobes [31,34–37]. Anomalies in serotonergic (5-HT) transmission mediated by 5-HT type 1A (5-HT_{1A}) [38] and 2A (5-HT_{2A}) receptors are also involved in visual hallucinations in PD [39,40]. Abnormal visual perception is also likely to play an etiological role in visual hallucinations [41].

As mentioned above, several anti-psychotics are dopamine-receptor blockers and the use of dopamine-receptor antagonists is counterproductive in PD. The current therapeutic strategies for PD psychosis are therefore centered on the modulation of other neurotransmitter systems, that is, the 5-HT and cholinergic systems. Very few therapies acting by mechanisms unrelated to 5-HT or acetylcholine are currently undergoing investigation.

This qualitative systematic review article discusses the current therapeutic options for treatment of PD psychosis and surveys new promising therapies. As will be seen, there is a paucity of effective treatments for PD psychosis and drugs presently under investigation are also scant. The review of literature and of active clinical trials was performed through PubMed [42], The Michael J Fox Foundation for Parkinson's Research [43], ClinicalTrials.gov [44], the International Clinical Trials Registry Platform [45], the Current Controlled Trials website [46] and the Parkinson Pipeline Project [47]. Therapies for psychosis in Lewy body disease are not discussed.

The main points presented in the article are summarized in Tables 1–3. Table 1 lists the drugs discussed in the article along with their effectiveness in the treatment of PD psychosis. Table 2 lists the active clinical trials, or lack thereof, for each drug. Table 3 shows the pharmacological affinity of each molecule presented in this review.

Drugs to treat PD psychosis
Aripiprazole
Aripiprazole (Abilify®, Aripiprex®) is a relatively new atypical anti-psychotic with a unique pharmacological profile. Aripiprazole acts as an antagonist at 5-HT_{2A} receptors, and as a partial agonist at 5-HT_{1A} [48,49], and dopamine D_2 and D_3 receptors [50]. Aripiprazole also exhibits high affinity for the 5-HT transporter, 5-HT_{2C} and 5-HT_7 receptors [51]. In an open-label 6-week study with a 20-week extension phase conducted in 14 patients, aripiprazole (1–5 mg orally daily) generally improved PD psychosis, but was poorly tolerated by a majority of patients, and eight subjects discontinued the study [52]. Aripiprazole (15 mg orally daily) also reduced PD psychosis, while being well tolerated, in a case series of three patients [53] and in a case report [54]. Aripiprazole (10 mg orally thrice daily) did not improve PD psychosis and worsened parkinsonism in one case report [55], and was ineffective (7.5–22.5 mg orally daily) in six out of eight PD patients in a case series [56]. Based on these studies, aripiprazole does not appear as a promising agent to treat PD psychosis. No randomized, double-blind, placebo-controlled clinical trial for PD psychosis with aripiprazole has been published so far and, given the limited efficacy of aripiprazole and its propensity to worsen parkinsonism, it is unlikely that the drug will be further studied in PD psychosis.

Clozapine
Clozapine (Clozaril®) is an atypical anti-psychotic that exhibits affinity for many receptors, including 5-HT_{2A}, 5-HT_{2C}, 5-HT_3, 5-HT_6, 5-HT_7, D_4, muscarinic $(M)_{1-5}$ and alpha (α)-adrenoceptors [57–60]. Despite its nonselectivity, *in vivo* imaging and pharmacokinetic studies have suggested that clozapine, at doses administered to PD patients, which are lower than those usually administered in schizophrenia, interacts primarily with 5-HT_{2A} receptors [61,62]. In an evidence-based medicine (EBM) review article published in 2011, the International Parkinson and Movement Disorder Society (IPMDS) stated that clozapine was efficacious to treat PD psychosis [63]. Indeed, low-dose clozapine (6.25–50 mg daily, mean daily dose of 24.7 mg at the end of the study) effectively alleviated psychosis in 60 PD patients in a 14-month randomized, double-blind, placebo-controlled Phase III clinical trial [64]. In this study, clozapine improved score at each of the Brief Psychiatric Rating Scale (BPRS), the Clinical Global Impression Scale (CGIS), as well as the Scale for Assessment of Positive Symptoms (SAPS). Low-dose clozapine (6.25–50 mg daily, mean daily dose of 36 mg at the end of the study) effectively improved the CGIS and the Positive And Negative Syndrome Scale in 60 patients over a 4-week administration period in another randomized, double-blind, placebo-controlled, Phase III clinical trial [65]. Clozapine (6.25–50 mg daily, average daily dose of 35.8 mg at the end of the study) had beneficial effects on the CGIS and Positive And Negative Syndrome Scale in another 4-week, randomized, double-blind, placebo-controlled trial

Table 1. Summary of the drugs discussed in this review article.

Drug	Methodology	Efficacy in PD psychosis
Aripiprazole (7-{4-[4-(2,3-Dichlorophenyl)piperazin-1-yl]butoxy}-3,4-dihydroquinolin-2(1H)-one; Abilify®, Aripiprex®)	No randomized, double-blind, placebo-controlled trials; administered up to 22.5 mg daily	Unclear efficacy, potential worsening of parkinsonism
Clozapine (8-Chloro-11-(4-methylpiperazin-1-yl)-5H-dibenzo [b,e] [1, 4] diazepine; Clozaril®)	Two Phase III clinical trials; administered up to 50 mg daily	Efficacious, no worsening of parkinsonism
Donepezil ((RS)-2-[(1-benzyl-4-piperidyl)methyl]-5,6-dimethoxy-2,3-dihydroinden-1-one; Aricept®)	No randomized, double-blind, placebo-controlled trials; administered up to 12 mg daily	Possibly efficacious, potential worsening of tremor
Galantamine ((4aS,6R,8aS)-5,6,9,10,11,12-hexahydro-3-methoxy-11-methyl-4aH-[1] benzofuro[3a,3,2-ef] [2] benzazepin-6-ol; Lycoremine®, Nivalin®, Razadyne®, Reminyl®)	One randomized, double-blind, placebo-controlled trial; administered up to 24 mg daily	Possibly not efficacious, potential worsening of tremor
Melperone (1-(4-fluorophenyl)-4-(4-methyl-1-piperidyl)butan-1-one; Bunil®, Buronil®, Eunerpan®)	No randomized, double-blind, placebo-controlled trials; administered up to 75 mg daily	Possibly efficacious, no worsening of parkinsonism
Memantine (3,5-dimethyltricyclo[3.3.1.13,7]decan-1amine, 3,5-dimethyladamantan-1-amine; Abixa®, Akatinol®, Axura®, Ebixa®, Memox®, Namenda®)	Two Phase II and one Phase IV trials (not primary end point); administered up to 30 mg daily	Possibly not efficacious, no worsening of parkinsonism
Mianserin ((±)-2-methyl-1,2,3,4,10,14b-hexahydrodibenzo[c,f]pyrazino[1,2-a]azepine; Depnon®, Lantanon®, Lerivon®, Lumin®, Norval®, Tolmin®, Tolvon®)	No randomized, double-blind, placebo-controlled trials; administered up to 30 mg daily	Possibly efficacious, no worsening of parkinsonism
Mirtazapine ((±)-2-methyl-1,2,3,4,10,14b-hexahydropyrazino[2,1-a]pyrido[2,3-c][2] benzazepine; Avanza®, Axit®, Mirtaz®, Mirtazon®, Remeron®, Zispin®)	No randomized, double-blind, placebo-controlled trials; administered up to 30 mg daily	Possibly efficacious, no worsening of parkinsonism
Ondansetron ((RS)-9-methyl-3-[(2-methyl-1H-imidazol-1-yl)methyl]-2,3-dihydro-1H-carbazol-4(9H)-one; Zofran®)	No randomized, double-blind, placebo-controlled trials; administered up to 24 mg daily	Possibly efficacious, no worsening of parkinsonism
Pimavanserin (N-(4-fluorophenylmethyl)-N-(1-methylpiperidin-4-yl)-N'-(4-(2-methylpropyloxy)phenylmethyl)carbamide; ACP-103)	One Phase III clinical trial; administered up to 60 mg daily	Efficacious, no worsening of parkinsonism
Quetiapine (2-(2-(4-dibenzo [b,f] [1, 4] thiazepine-11-yl-1-piperazinyl)ethoxy)ethanol; Ketipinor®, Seroquel®, Xeroquel®)	Efficacy not demonstrated in Phase III clinical trials; often used as first-line therapy; administered up to 800 mg daily	Possibly efficacious, rare worsening of parkinsonism
Rivastigmine ((S)-3-[1-(dimethylamino)ethyl]phenyl N-ethyl-N-methylcarbamate; Exelon®)	One randomized, double-blind, placebo-controlled trial; administered up to 12 mg daily	Probably efficacious, potential worsening of tremor
Sarcosine (2-(methylamino)acetic acid; N-methyl-glycine, sarcosinic acid)	One randomized, double-blind, placebo-controlled trial; administered up to 2 g daily	Possible transient anti-psychotic effect

The left column provides the generic name of each drug discussed in the article (emboldened), along with its chemical and commercial names. The central column details the type of studies that were performed and maximal doses that were administered to PD patients. The right column details the effectiveness of each drug.
PD: Parkinson's disease.

Drug	Clinical trials
Aripiprazole	No active clinical trial
Clozapine	No active clinical trial
Donepezil	One active study assessing the efficacy of donepezil to prevent PD psychosis development (UMIN000005403)
	One active study assessing the efficacy of donepezil at improving cognitive function and neuro-psychiatric burden in PD patients with early dementia (NCT01014858)
Galantamine	One active study assessing neuro-psychiatric symptoms and brain perfusion in PD patients with dementia receiving galantamine (NCT01944436)
Melperone	No active clinical trial
Memantine	No active clinical trial
Mianserin	No active clinical trial
Mirtazapine	No active clinical trial
Ondansetron	No active clinical trial
Pimavanserin	One active study assessing the safety and efficacy of pimavanserin in the treatment of PD psychosis (NCT00550238)
Quetiapine	No active clinical trial
Rivastigmine	One active study assessing the efficacy of rivastigmine to prevent the progression of minor visual hallucinations to major visual hallucinations (NCT01856738)
Sarcosine	No active clinical trial

†This table provides a list of the active clinical trials, or lack thereof, for each molecule discussed in the article.
PD: Parkinson's disease.

followed by open-label and wash-out phases performed in 60 PD patients [66]. Interestingly, some patients experienced relapses of their psychotic symptomatology during the wash-out period [66]. In all of these clinical trials, clozapine improved the severity of psychosis by 25–40%, did not worsen motor condition and was well tolerated by patients. Despite its efficacy demonstrated in Phase III clinical trials and the fact that it is well tolerated by the PD population, clozapine is seldom prescribed as a first-line therapy for PD psychosis, because its use is associated with a 1% risk of agranulocytosis, which may be fatal and requires regular hematological monitoring [67,68]. There are currently no active clinical trials assessing the efficacy of clozapine for PD psychosis.

Cholinesterase inhibitors

Donepezil (Aricept®) is an acetylcholinesterase (AChE) inhibitor that is used to treat cognitive dysfunction in people suffering from Alzheimer's disease [69]. Rivastigmine (Exelon®) is a dual butyrylcholinesterase and AChE inhibitor [70]. Galantamine (Lycoremine®, Nivalin®, Razadyne®, Reminyl®) is an AChE inhibitor with positive allosteric effect on nicotinic receptors [71]. Donepezil and rivastigmine are currently employed to treat PD dementia. In the 2011 EBM review published by the IPMDS, donepezil was considered as 'investigational', whereas rivastigmine was considered 'efficacious' to treat PD dementia [63]. In contrast, there was 'insufficient evidence' to recommend the use of galantamine to treat PD dementia [63]. In the United States, the US FDA has approved the use of rivastigmine to treat PD dementia in 2006 [72]. Evidence suggests that both donepezil and rivastigmine may effectively reduce PD psychosis. Thus, in a case series, rivastigmine (up to 12 mg orally daily) improved visual hallucinations in four PD patients, three of whom had cognitive impairment [73]. In a randomized, double-blind, placebo-controlled 24-week study, an arm of which was conducted on 188 PD patients with visual hallucinations, rivastigmine (average dose of ≈8 mg orally daily at week 24) significantly improved the ten-item Neuropsychiatric Inventory (NPI) [74].

In an open-label study conducted in eight PD patients, donepezil (5 mg orally at bedtime for 2 months) significantly improved the Psychosis Rating Scale for PD [75]. Other uncontrolled studies have also found a reduction of PD psychosis with donepezil (10 mg orally daily) administration [75–78].

Open-label trials and case-report studies suggested that galantamine (up to 24 mg orally daily) improved the NPI in PD patients with dementia [79–82]. However, galantamine (up to 24 mg orally daily) had no effect on the NPI score in a randomized, double-blind,

Table 3. Pharmacological profile of the drugs used to treat Parkinson's disease psychosis.	
Enzyme/receptor/transporter	**Drugs**
5-HT system	
5-HT$_{1A}$ receptors	Aripiprazole, mirtazapine
5-HT$_{2A}$ receptors	Aripiprazole, clozapine, melperone, mianserin, mirtazapine, pimavanserin, quetiapine
5-HT$_{2C}$ receptors	Aripiprazole, clozapine, mianserin, mirtazapine, pimavanserin
5-HT$_3$ receptors	Clozapine, mirtazapine, ondansetron
5-HT$_6$ receptors	Clozapine
5-HT$_7$ receptors	Aripiprazole, clozapine
SERT	Aripiprazole
Adrenergic system	
α-adrenoceptors	Clozapine, mianserin, mirtazapine, quetiapine
β-adrenoceptors	Memantine
Dopaminergic system	
D$_2$ receptors	Aripiprazole, melperone, quetiapine
D$_3$ receptors	Aripiprazole
D$_4$ receptors	Clozapine, melperone
Cholinergic system	
Acetylcholinesterase	Donepezil, galantamine, rivastigmine
Butyrylcholinesterase	Rivastigmine
Muscarinic receptors	Clozapine (M$_{1-5}$), memantine, quetiapine
Nicotinic receptors	Galantamine
Glutamatergic system	
NMDA receptors	Memantine
Glycinergic system	
Glycine transporter I	Sarcosine
Histaminergic system	
H receptors	Memantine (H$_1$), mianserin, mirtazapine (H$_1$), quetiapine (H$_1$)
This table summarizes pharmacological profile of the drugs discussed in the article. It is noteworthy that the extent to which some of the targets listed here contribute to an anti-psychotic action remains to be elucidated. H: xxx; HT: xxx; NDMA: *N*-methyl-ᴅ-aspartate; SERT: xxx.	

placebo-controlled trial conducted in nondemented PD patients [83], which is possibly why galantamine is not used to treat PD psychosis.

In the studies cited above, motor function was sometimes impaired by cholinesterase inhibitors, and this potential adverse effect has to be taken into consideration when implementing treatment with either donepezil or rivastigmine. In particular, AChE inhibitors may have a deleterious effect on PD tremor [84–89].

Four studies assessing the efficacy of cholinesterase inhibition for PD psychosis are currently active. The 'Efficacy of Donepezil against Psychosis in Parkinson's Disease' (EDAP; UMIN000005403) study assesses the effect of donepezil to prevent the development of PD psychosis. In that study, PD psychosis is assessed

at a 4-week interval for 96 weeks using the Parkinson Psychosis Questionnaire part B, which assesses hallucinations/illusions, and part C, which assesses delusions. Patients are randomized into two groups, one receives donepezil (up to 5 mg orally daily), while the other is administered placebo. Eighty-four patients will be included in each group. The hypothesis of the study is that donepezil treatment will prevent the development of PD psychosis; secondary outcome measures include changes in Parkinson Psychosis Questionnaire and Unified Parkinson's Disease Rating Scale scores [90]. As of 31 March 2014, the EDAP study was no longer recruiting. The 'Multi-Centre UK Study of the Acetylcholinesterase Inhibitor Donepezil in Early Dementia Associated With Parkinson's Disease', a 24-month

randomized, double-blind, placebo-controlled Phase III trial to demonstrate the efficacy of donepezil (5 or 10 mg orally daily) at improving cognitive function and neuro-psychiatric burden, is currently on-going. Secondary outcome measures include assessment of patients' and caregivers' quality of life and determination of donepezil cost–effectiveness (NCT01014858). Another trial, the 'Cholinesterase Inhibitors to Slow Progression of Visual Hallucinations in Parkinson's Disease' study, will assess the effect of rivastigmine to prevent the progression of minor visual hallucinations to major hallucinations, without insight or frank psychosis. This randomized, double-blind, placebo-controlled Phase IV study will include 168 subjects, who will be administered rivastigmine 6 mg orally twice daily or placebo over 24 months. Secondary outcome measures will include effects of rivastigmine on motor and cognitive functions, as well as on daytime sleepiness, to name a few (NCT01856738). The fourth trial, 'A Genetic and Perfusion Study of Response to Cognitive Enhancers in Lewy Body Disease', encompasses a group of demented PD patients who will receive galantamine. Neuro-psychiatric evaluations will be performed and brain perfusion will be assessed (NCT01944436).

Despite some trials conducted in PD (none of which had psychosis as primary end point) [91,92], the dual AChE and butyrylcholinesterase inhibitor tacrine (Cognex®) is not discussed in this article, because it was withdrawn from the market in the United States due to hepatic toxicity [93].

Melperone

Melperone (Bunil®, Buronil®, Eunerpan®) is an atypical anti-psychotic that exhibits high affinity for dopamine D_2, D_4 and 5-HT_{2A} receptors [94]. An open-label 2-year study performed in 30 PD patients suggested that melperone (average daily dose of 37.5 mg, ranging from 12.5 to 75 mg) might effectively reduce PD psychosis, assessed with the BPRS [95]. Despite these positive results, melperone (20–60 mg orally daily) did not alleviate PD psychosis when assessed with the SAPS scale in an 8-week randomized, double-blind, placebo-controlled Phase II study performed on 90 patients [96]. Although melperone did not worsen motor function and was well tolerated in the two studies, it is unlikely that further studies will be conducted with melperone as an anti-psychotic agent in PD, given the negative results of the Phase II trial.

Memantine

Memantine (Abixa®, Akatinol®, Axura®, Ebixa®, Memox®, Namenda®) is an uncompetitive [97] N-methyl-D-aspartate antagonist that exhibits affinity for histamine (H) type 1 and M receptors, as well as beta (β)-adrenoceptors [98,99]. Memantine is currently, albeit rarely, employed to treat PD dementia, although there is insufficient evidence to support its use, according to the 2011 EBM review by the IPMDS [63]. Most of the studies performed with memantine in PD were addressing its potential to reduce cognitive symptoms; however, some of these had psychosis as a secondary end point.

In a randomized, double-blind, placebo-controlled Phase IV trial, 62 demented PD patients were administered memantine (20 mg orally daily), while 58 were administered placebo for 24 weeks. In that study, memantine had no effect on PD psychosis, assessed by the NPI [100]. In a 22-week randomized, double-blind, placebo-controlled study conducted in 25 PD patients with dementia, memantine (20 mg orally daily) did not improve the NPI score [101]. Similar results were obtained in a 24-week randomized, double-blind, placebo-controlled Phase II trial performed in 72 patients with PD dementia or Lewy body disease, in which memantine (20 mg orally daily) failed to improve the NPI [102]. Memantine was generally well tolerated in these studies. However, given its lack of efficacy in the trials cited above, it does not appear as a promising strategy for PD psychosis and it is unlikely that memantine anti-psychotic potential will be the primary end point of upcoming studies. In agreement with a lack of anti-psychotic effect of memantine in PD, an article published in 1991 reported that memantine (10–30 mg orally daily for up to 6 weeks) triggered psychotic symptoms when administered to PD patients [103].

Mianserin

Mianserin (Depnon®, Lantanon®, Lerivon®, Lumin®, Norval®, Tolmin®, Tolvon®) is a nonselective antidepressant that exhibits high affinity for 5-HT_{2A}, 5-HT_{2C} and H receptors, as well as to α-adrenoceptors [104]. In an open-label study conducted in 12 PD patients, administration of mianserin daily for 8 weeks (average dose 36.7 mg orally) abolished psychotic features in eight patients and moderately improved psychosis in two, while decreasing parkinsonian disability in eight patients [105]. In another open-label trial, mianserin (5–30 mg orally daily) abolished hallucinations in 17 patients and suppressed delusions in five out of eight patients [106]. In these studies, mianserin was well tolerated by PD patients. However, albeit promising, these studies are open-label trials, and the efficacy of mianserin needs to be established in the context of randomized, controlled trials. No such trial is currently active.

Mirtazapine

Mirtazapine (Avanza®, Axit®, Mirtaz®, Mirtazon®, Remeron®, Zispin®) is a structural analog of mianserin [104]. As for mianserin, mirtazapine is a

nonselective antidepressant that exhibits high affinity for α-adrenoceptors, 5-HT$_{2A}$, 5-HT$_{2C}$, 5-HT$_3$ and H$_1$ receptors, as well as moderate affinity for 5-HT$_{1A}$ receptors [107,108]. One case report [109] and one case series of four patients [110] mention the emergence of psychotic manifestations in PD patients treated with mirtazapine (15–30 mg orally daily). In contrast, mirtazapine (7.5–30 mg orally daily) was reported to be beneficial against PD psychosis in three case reports that have been published since 2012 [111–114]. The efficacy of mirtazapine against PD psychosis has never been assessed in randomized, double-blind, placebo-controlled trials. Thus, the therapeutic potential of mirtazapine for PD psychosis is uncertain and its efficacy is, at most, anecdotal. Nevertheless, in light of the results of the three recent case reports, the anti-psychotic potential of mirtazapine might be worth assessing in the context of randomized, controlled clinical trials.

Ondansetron

Ondansetron (Zofran®) is a potent and selective 5-HT$_3$ receptor antagonist [115,116]. The efficacy of ondansetron for treating PD psychosis was tested in several early clinical trials [117–124]. Ondansetron was well tolerated and demonstrated a certain efficacy. For instance, in an open-label trial, ondansetron (12–24 mg orally daily over 4–8 weeks) significantly improved visual hallucinations, paranoid delusions and the BPRS in 16 PD patients [119]. In another open-label trial conducted in seven PD patients with psychosis, ondansetron (12–20 mg orally daily for 1–2 months) abolished visual hallucinations in three and reduced hallucinations in four patients. In all patients, discontinuation of ondansetron led to the resurgence of psychotic manifestations within a week, and re-introduction of ondansetron again attenuated psychosis [117]. Despite these encouraging results, 5-HT$_3$ blockade as a therapeutic approach to alleviate PD psychosis has not been further studied, perhaps because another open-label trial suggested a limited efficacy and a possible tachyphylaxis to the anti-psychotic effect [120]. Nevertheless, the anti-psychotic potential of ondansetron and other 5-HT$_3$ antagonists in PD might be worth re-exploring, as several agents with this mechanism of action are used in clinic and as clozapine, which alleviated psychosis in Phase III studies, exhibits significant affinity for 5-HT$_3$ receptors.

Pimavanserin

Pimavanserin (ACP-103) is a 5-HT$_{2A}$ inverse agonist with approximately fourfold selectivity over 5-HT$_{2C}$ receptors [125,126]. Pimavanserin (20, 40 or 60 mg orally daily) effectively reduced the severity of PD psychosis, especially hallucinations, persecutory delusions and delusions of reference, in a randomized, double-blind placebo-controlled, 4-week Phase II study in which 60 patients were enrolled [127]. More recently, pimavanserin was administered to PD patients in the context of a Phase III study encompassing 199 subjects [128]. In that study, pimavanserin (40 mg orally daily) reduced the severity of PD psychosis by 37%, as assessed by the Scale for Assessment of Positive Symptoms adapted for PD (SAPS-PD). As this was the first trial conducted in PD using this scale, it is impossible to compare the efficacy of pimavanserin and clozapine or quetiapine, and this should be addressed in future clinical studies. Pimavanserin was well tolerated by patients and improved night-time sleep. Pimavanserin increased duration of the QTc interval by 7.3 ms, and a baseline electrocardiogram may have to be obtained prior to prescribing the drug. An open-label Phase II extension study assessing the long-term safety and tolerability of pimavanserin was completed last year (NCT01518309), but results have not been published.

One clinical trial with pimavanserin in PD is currently on-going (NCT00550238). This multicenter, open-label, Phase III study assesses the safety and tolerability of pimavanserin in the treatment of PD psychosis. 500 patients older than 40 years old are expected to be enrolled in the study. The estimated primary completion date is December 2015.

Quetiapine

Quetiapine (Ketipinor®, Seroquel®, Xeroquel®) is an atypical anti-psychotic that displays high affinity for 5-HT$_{2A}$, H$_1$ and M receptors, α-adrenoceptors, and moderate affinity for D$_2$ receptors [60,129]. Several studies have been performed with quetiapine in PD psychosis, and doses as high as 800 mg daily were administered to patients [130]. However, in its 2011 EBM review, the IPMDS concluded that there was insufficient evidence to conclude on the anti-psychotic efficacy of quetiapine in PD, because of conflicting data and small size of the published studies [63]. Although no study assessing the effectiveness of quetiapine for PD psychosis is currently on-going, it is important to include quetiapine here, as it is often prescribed as a first-line anti-psychotic therapy. This may be attributed to quetiapine being well tolerated by PD patients and because of the risk of agranulocytosis associated with the use of clozapine and the required hematological monitoring [131,132].

Sarcosine

Sarcosine, also known as *N*-methyl-glycine or sarcosinic acid, is an inhibitor of the glycine transporter I that increases synaptic levels of glycine and potentiates the action of the *N*-methyl-D-aspartate glutamatergic receptor [133]. Previous studies performed in

schizophrenia have suggested that sarcosine may potentiate the effect of anti-psychotics, but not of clozapine [133,134]. Sarcosine (1 g orally twice daily) was tested in an 8-week randomized, double-blind, placebo-controlled clinical trial in which 30 PD patients were enrolled. Sarcosine significantly improved results of the NPI after 2 and 4 weeks, but not after 8 weeks, suggesting a possible tachyphylaxis to its anti-psychotic effect [135]. The results of this study are interesting, as sarcosine acts by a mechanism shared by no other drug currently used or being tested for PD psychosis, although the potential tachyphylaxis mitigates the drug clinical potential. Its unique action mechanism raises the possibility that sarcosine might be combined with other anti-psychotics, and possibly synergize with them to alleviate psychosis. However, further studies are required with sarcosine in PD psychosis before it can be offered as a treatment.

Other anti-psychotics

Olanzapine (Lanzek®, Zypadhera®, Zyprexa®) is an atypical anti-psychotic that exhibits high affinity for 5-HT_{2A} and D_2 receptors [136]. In the 2011 IPMDS EBM review, the efficacy of olanzapine for PD psychosis was stated as unclear and its use was not recommended, as it is associated with an unacceptable risk of worsening parkinsonism [63]. No study assessing the anti-psychotic effect of olanzapine in PD is currently on-going. Similarly, the anti-psychotics risperidone (Risperdal®) and ziprasidone (Geodon®, Zeldox®) have shown questionable efficacy in clinical trials, in addition to exerting a deleterious effect on parkinsonian disability [130,137–139]; no recommendation was made about these two drugs in the last IPMDS EBM review and no trial with these two anti-psychotics is currently active.

Conclusion & future perspective

PD psychosis is increasingly recognized as an important determinant of patients' and families' quality of life in advanced PD [4]. Optimal treatment of PD psychosis requires a delicate balance between, on one hand, maintaining an optimal anti-parkinsonian benefit and, on the other hand, reducing psychiatric symptoms. This delicate balance is difficult to achieve with most of the anti-psychotic agents available and, for that reason, in practice, the anti-psychotics employed with the PD population are usually limited to clozapine and quetiapine. However, the anti-psychotic efficacy of quetiapine is not well established, and the use of clozapine requires continuous hematological monitoring, which limits its use as a first-line agent. Moreover, it is noteworthy that clozapine attenuates PD psychosis severity by 25–40%, without abolishing the manifestation. Although such a reduction of psychosis severity is an important step forward, the problem of PD psychosis still remains unsolved. Pimavanserin recently reduced PD psychosis severity by ≈40% in a Phase III clinical trial. However, the scale used in the study to assess psychosis severity, the SAPS-PD, differs to those employed in the clozapine trials, and whether pimavanserin is as effective as clozapine remains uncertain. Unlike most of the drugs cited here, however, pimavanserin has a selective mechanism of action, that is, $5\text{-HT}_{2A/2C}$ receptor inverse agonism. Pimavanserin was well tolerated by the PD population, but further studies are needed with pimavanserin in PD psychosis, notably to establish its efficacy compared with clozapine. An open-label trial to determine the long-term safety of pimavanserin in the PD population is currently active and will provide important data.

The cholinesterase inhibitors donepezil and rivastigmine are currently being studied to address PD psychosis. The two drugs are presently used to treat cognitive deficits in PD, although only rivastigmine appears efficacious. Unlike clozapine and pimavanserin, they target the cholinergic system, and these different mechanisms of action might open the way to combination therapies. Hence, perhaps the combination of a cholinesterase inhibitor and clozapine or pimavanserin will lead to a synergistic effect. This may provide potentially greater relief to PD psychosis than what is currently achieved with clozapine/pimavanserin, which essentially modulate 5-HT transmission. Although this is highly speculative, perhaps the most efficacious therapy for PD psychosis will be a synergistic approach, where two (or more) systems are targeted, either with multiple drugs, or with a single drug displaying affinity for several neurotransmitter systems shown to be involved in psychosis etiology. In agreement with such a hypothesis, mianserin and its analog mirtazapine, two nonselective drugs, have both demonstrated anti-psychotic efficacy in case reports and case series; their anti-psychotic benefit now needs to be demonstrated in the context of controlled trials. Should an anti-psychotic effect be demonstrated with mianserin/mirtazapine in controlled trials, perhaps studies where one of these antidepressants is combined with an anti-psychotic agent such as clozapine or a cholinesterase inhibitor such as rivastigmine could be undertaken, to investigate whether a greater anti-psychotic benefit can be achieved.

Thus, the optimal management of PD psychosis remains difficult and the agents that can be used are limited. Moreover, the therapeutic targets are also limited, as the agents undergoing investigation display affinity for either the 5-HT or the cholinergic system, an exception being sarcosine, which modulates glutamatergic transmission and temporarily alleviated PD psychosis in an early clinical trial. However, all of these targets

have shown limited efficacy and other targets have to be sought actively. Modulation of down-stream signalling mechanisms might represent new therapeutic avenues, as it might enable the modulation of several systems at the same time, by interacting with intra-cellular effectors common to several pathways. No clinical study with such agents is currently registered, but drugs with such a mechanism might represent an exciting, potentially very effective, new generation of anti-psychotic agents to address the debilitating condition of PD psychosis.

Executive summary

- Parkinson's disease (PD) psychosis is a common and distressing condition.
- Clozapine effectively reduces PD psychosis, but is rarely used as a first-line therapy because of the risk of agranulocytosis.
- Open-label clinical trials have suggested that ondansetron might be beneficial for PD psychosis.
- Quetiapine is often used as a first-line therapy for PD psychosis, but its efficacy was not demonstrated in Phase III clinical trials.
- Pimavanserin recently alleviated PD psychosis in a Phase III clinical trial.
- The cholinesterase inhibitors donepezil and rivastigmine are currently being studied to alleviate PD psychosis.

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