Curr Psychiatry Rep (2016) 18: 97
DOI 10.1007/s11920-016-0730-1

Current Understanding of Psychosis in Parkinson's Disease

Oluwadamilola O. Ojo[1,2] · **Hubert H. Fernandez**[2,3,4]

Published online: 14 September 2016

Abstract Psychosis in Parkinson's disease (PD) is one of the greatest determinants of nursing home placement and caregiver stress. Traditionally associated with medications with dopaminergic effect, it has now been linked to other medications and other stressors e.g. systemic illnesses. The development of hallucinations in a PD patient can herald the onset of dementia and usually predicts increased mortality risk. Medication reduction in PD psychosis usually reduces the symptoms; however, this comes at the cost of worsening motor function. If gradually decreasing the patient's medications does not resolve the psychosis, the treatment of choice is an atypical antipychotic. Though only clozapine has level A recommendation for this indication, other atypicals like quetiapine continue to get used for this purpose on account of the logistics involved with clozapine use. Cholinesterase inhibitors are also increasingly being used for PD psychosis on account of the association with dementia. The treatment of PD psychosis is an unmet need in PD management and search for suitable agents constitutes an active area of research in PD.

This article is part of the Topical Collection on *Geriatric Disorders*

✉ Hubert H. Fernandez
fernanh@ccf.org

Oluwadamilola O. Ojo
drlaraoyatoye@yahoo.com; oluojo@unilag.edu.ng

[1] Neurology Unit, Department of Medicine, College of Medicine, University of Lagos, Lagos, Nigeria

[2] Center for Neurological Restoration, Cleveland Clinic, Cleveland, OH, USA

[3] Cleveland Clinic Lerner College of Medicine, Cleveland, OH, USA

[4] Department of Medicine, College of Medicine University of Lagos, P.M.B. 12003, Idi-araba, Lagos, Nigeria

Keywords Parkinson's disease · Psychosis · Hallucinations · Atypical antipsychotics

Introduction

Parkinson's disease (PD) is now recognized as a multifaceted disorder manifesting with the well-elucidated motor features and the more recently recognized non-motor features which include cognitive, behavioural, psychiatric and autonomic complications. These cognitive and behavioural features are often deemed more disabling and distressing to both patients and their caregivers than the cardinal motor features that define the disorder [1, 2].

The behavioural features of PD are now recognized as the greatest determinants of caregiver stress [3•, 4, 5], poor quality of life [6, 7] and risk for nursing home placement [8, 9].

Psychosis is one of the most clinically significant behavioural/neuropsychiatric problems in PD because of its relation to poor outcomes. In particular, the presence of psychosis predicts institutionalization or nursing home placement [8, 10], increased caregiver burden [11] and increased mortality [8, 10].

The recognition and treatment of PD psychosis is important in the optimal management of the PD patient and its definitive treatment has been consistently described as one of the greatest unmet needs in management of PD [3•].

Initial reports of PD psychosis claimed that it was uncommon in the non-demented PD population and occurred mainly in relation to PD medication use [12]. Very early reports of hallucinations and/or psychosis in PD dating back to the late nineteenth/early twentieth century were also confusing because of the lumping together of cases of post-encephalitic parkinsonism (PEP) with idiopathic PD cases. Behavioural abnormalities and hallucinations were common in cases of PEP.

It is now known that antiparkinsonian medications (in addition to other medications) are but one of the factors involved in the development of PD psychosis. This review article intends to define PD psychosis, describe its features, explore the current pathophysiology and discuss current trends in the management.

PD Psychosis: Phenomenology and Definitions

PD psychosis is characterized by a constellation of clinical features that are different from those seen in other primary psychotic conditions e.g. schizophrenia. The characteristic features are hallucinations, illusions and delusions occurring usually in the context of a clear sensorium and, often but not always, retained insight [13, 14]. Hallucinations are defined as sensory phenomena not induced by physical stimuli and which can occur in any of the sensory modalities; visual, auditory, tactile, olfactory or gustatory; in the context of PD psychosis, they are mainly visual. Illusions are altered perceptions of actual physical stimuli while delusions are fixed false beliefs despite evidence to the contrary.

The hallucinations in PD psychosis are usually visual [15] (although hallucinations in other modalities also occur), stereotyped and have recently been classified into *minor* and *non-minor* categories.

Minor hallucinations [16] are *passage hallucinations* [15] (typically characterized by fleeting shadows in the visual periphery), *presence hallucinations* [15] (i.e. "sense of presence" hallucinations, which is somewhat of a misnomer considering it is the perception that another person is in the same room with the patient or behind the patient) and *illusions*. Visual hallucinations tend to be well formed, complex, recurrent [15, 17–19] and are the most common form of hallucinations in PD. They tend to occur with low levels of visual stimulation e.g. in dim lighting, in the evenings and when patient is alone. Delusions typically manifest as phantom boarder phenomenon or with paranoid delusions of spousal infidelity and abandonment, which often co-occur with hallucinations [20].

In the last decade, new criteria for the diagnosis of PD psychosis have been provided by the National Institute of Neurologic Disorders and Stroke and National Institute of Mental Health (NINDS/NIMH) working group [15]. The revised criteria require the occurrence of at least one of the following after the onset of PD: hallucinations, illusions, sense of presence or delusions; occurring continuously for 1 month or recurrently; with symptoms not being better accounted for by other causes of parkinsonism (e.g. dementia with Lewy bodies [DLB]) or a psychiatric disorder. The criteria also indicate specifying if symptoms of psychosis occur in the presence or absence of the following: retained insight, medication to treat PD and dementia.

Epidemiology

The estimated prevalence of PD psychosis varies considerably due to differences in the methodology employed across studies, specifically the definition of the study sample as well as the symptomatology studied. In a recent review of epidemiologic studies on PD psychosis, Fenelon and Alves [21••] estimated the lifetime prevalence of a PD patient developing visual hallucinations at 50 %. In a 2010 study of 116 PD patients followed at a movement disorders clinic employing the new criteria, prevalence of PD psychosis was 43 % when the usual definition of hallucinations +/− delusions was used, and this increased to 60 % when the NINDS/NIMH definition was used [22••]. In a community-based sample of 250 PD patients but with MMSE greater than 23, Mack et al. [23] studied the prevalence of psychotic symptoms and retrospectively applied the more recent NINDS/NIMH criteria to those with psychotic symptoms. Of this sample, 26 % were experiencing psychotic symptoms at the time of study, and 90.8 % of the cohort fulfilled the new criteria. Employing a modified psychosis rating scale, Lee and Weintrub [24] studied 191 non-demented PD patients as part of a larger study of frequency and correlates of psychiatric and cognitive disorders in PD. In their cohort, 21.5 % had psychotic symptoms.

While the use of dopaminergic medications was the first factor associated with the development of PD psychosis, other factors had been associated with this condition in the last two decades, namely increasing age, disease duration and severity, presence of other non-motor symptoms especially depression, cognitive impairment and dementia and sleep disturbances [14, 15].

Pathophysiology

Initially PD psychosis was thought to arise solely as a side effect of medications, especially dopaminergic medications. That view was brought into question with the finding that PD psychosis also occurs in patients with PD who have never been [12, 25•] exposed to dopaminergic medications. The current view in the scientific community is that PD psychosis occurs from a complex interaction of many factors—some of which are inherent to the disease process and others that are extrinsic/iatrogenic [20, 26].

Medications—Initial concepts regarding the pathophysiology of PD psychosis were centred solely on the relationship of dopaminergic medications, especially the dopamine agonists, with the development of psychosis [27, 28]. However, this concept has been challenged as there is no relationship to dose or duration of dopaminergic medication to psychosis [29, 30] and other drugs such as anticholinergics [31] and amantadine [32] have been implicated in causing/triggering PD psychosis. There are also reports of psychotic symptoms, specifically hallucinations, occurring in patients with PD who are levodopa-naïve [25•] and prior to the levodopa era [12]. It is well

known that dopamine receptor agonists such as cocaine can induce psychotic symptoms [33, 34]. Chronic stimulation of the dopamine receptors in the nigrostriatal pathway leading to hypersensitization of the receptors and dysfunction of limbic structures has been theorized to be the mechanism by which antiparkinsonian medications increase susceptibility to development of psychosis [34, 35]. The resulting dysfunction causes internal stimuli to be attributed to coming from the external environment [34, 35].

Factors involved in the pathogenesis of PD psychosis that are intrinsic to the disease process include deficits in visual processing, neurochemical abnormalities and sleep dysfunction.

Visual processing deficits—Impairment in visual processing in addition to ocular pathology have been implicated in the development of hallucinations in PD patients [36, 37•, 38, 39]. Deficits such as reduced visual acuity [17], deficits in colour and contrast recognition [40] and ocular pathology such as cataracts, glaucoma and retinal disease [15] have been associated with visual hallucinations in PD.

Sleep disorders—PD psychosis has been linked to sleep disturbances and it has even been suggested that visual hallucinations are actually a partial syndrome of REM sleep behaviour disorder [3•, 41]. It is well known that sleep disturbances, such as insomnia and daytime somnolence, are common in PD; it has been postulated that these sleep disturbances result in altered dreams which subsequently lead to daytime hallucinations and delusions [34].

Neurochemical abnormalities—Apart from the well-known effects of dopamine in causing psychosis, other neurotransmitters have also been implicated in the emergence of psychotic symptoms especially serotonin and acetylcholine [42]. It is recognized that the use of anticholinergic medications to treat motor symptoms of PD can precipitate psychotic symptoms. The occurrence of a cholinergic deficit in PD has been known for quite some time, especially in the nucleus basalis of Meynert [43] and this deficit occurs more in PD with cognitive impairment and dementia [44]. Furthermore, a cholinergic deficit has been linked to psychosis in DLB [45]. The implication of serotonin in the pathogenesis of PD psychosis comes from observations that serotonergic agonists induce delirium and psychosis [46] while medications known to reduce serotonergic activity alleviate psychotic symptoms [47]. Generally, it will seem that the dysregulation of a combination of neurotransmitter systems results in PD psychosis.

Structural abnormalities—The deposition of Lewy bodies has been identified as a risk factor of for PD psychosis [48].

Management

The principles of management of PD psychosis include general management and specific treatment of the psychotic symptoms. The development of psychosis in the early stages of a PD diagnosis or within a short period of starting levodopa therapy could be due to the prior existence of a psychiatric disorder or an alternate parkinsonian syndrome such as DLB. A study by Goetz et al. showed that patients who had hallucinations within 3 months of initiating levodopa therapy were eventually found to carry a diagnosis other than, or in addition to PD, that would account for their psychotic symptoms [49].

General management involves evaluating and treating underlying medical conditions that can precipitate symptoms of psychosis; e.g. infections, especially urinary and pulmonary infections, which in elderly people could be occult; presence of metabolic and endocrine derangements; and cerebral hypoperfusion states [50]. Psychosocial stressors should also be explored [50]. A review of the patient's medications should be undertaken as polypharmacy has been found to be an independent risk factor for development of PD psychosis [14, 51]. Medications including sedative hypnotics, anxiolytics, anticholinergics (which may be given for control of bladder symptoms) and antidepressants may need to be reduced or eliminated where possible.

After ruling out any underlying or contributing somatic illness, or the effect of non-dopaminergic medications, one of the most effective strategies in the treatment of PD psychosis is a systematic reduction in antiparkinsonian medications. Researchers agree on the strategy of gradually decreasing anti-PD medications in the following order: anticholinergics, amantadine, monoamine oxidase B (MAO-B) inhibitors, dopamine agonists, catechol-O-methyltransferase (COMT) inhibitors and, if still needed, levodopa [52]. The short-acting formulation of levodopa is typically favoured over the long-acting or sustained-release formulations because of the lower risk of accumulation of adverse effects with the former [34]. If the reduction of antiparkinsonian medications to the lowest bearable dose without worsening of motor symptoms does not improve the psychosis, the addition of an antipsychotic agent should be considered [34].

Antipsychotic Agents for Treatment of PD Psychosis

The atypical antipsychotic agents have been the treatment of choice for managing PD psychosis for some years; this is despite a US Food and Drug Administration (FDA) mandate on black box labelling stating that these medications are associated with higher risk of mortality when used in elderly patients with dementia [53]. However, despite the well-described risk of motor deterioration with the use of many of the atypical antipsychotics other than clozapine and quetiapine, and all of the first-generation or typical antipsychotics, a recent review by Weintraub et al. [54••] on drug utilization of a large cohort of PD among US veterans revealed that clinicians rarely prescribed clozapine—currently the most efficacious treatment for PD-Psych. Moreover, clinicians were frequently prescribing other atypical antipsychotics that could cause motor worsening such as olanzapine and risperidone and even occasionally prescribed first-generation or typical

antipsychotic agents which carry the highest probability of extrapyramidal effects.

The Quality Standards Subcommittee of the American Academy of Neurology (AAN) released that clozapine improves psychosis (level B recommendation) and results in improved motor function in some cases while quetiapine possibly improves PD psychosis (level C recommendation), while olanzapine does not improve psychosis and is likely to worsen motor function [55]. The Movement Disorder Society (MDS) review committee on evidence-based medicine [56] published that as of 2011 only clozapine was efficacious in the treatment of PD psychosis and had convincing beneficial evidence (level A recommendation).

Clozapine

Although the first reports of clozapine use in PD psychosis were published as early as 1978 [57, 58], it did not become the standard agent for treatment until 1991 [27, 58]. Clozapine is a dibenzodiazepine derivative and, according to a meta-analysis, is the only antipsychotic unequivocally recommended for the treatment of drug-induced psychosis in PD [59] although not approved by the FDA for this indication. Clozapine selectively binds D1 mesolimbic receptors, sparing striatal dopamine D2 receptors and also has a greater affinity for serotonin 5HT-2A/2C receptors resulting in little to no effect on motor symptoms in PD.

The efficacy and tolerability of clozapine in PD has been repeatedly demonstrated in both double-blind and open-label studies. Two landmark studies published almost simultaneously in the USA [60] and Europe [61] in 1999 demonstrated significant improvement in symptoms of psychosis while reporting no significant decline in motor function. There was also an additional improvement in tremor noted.

Effective doses for PD psychosis are much lower than that used in the treatment of schizophrenia; therapeutic benefit was observed in doses as low as 6.25 mg/day [61] while the mean dose in the US study was 25 mg/day [60]. Noteworthy is the fact that the first double-blind controlled trial on use of clozapine in PD-Psych was a negative study and had to be aborted [62]. A retrospective explanation given for the lack of a benefit in this study was the fact that the investigators employed doses and titration used in the treatment of refractory schizophrenia which resulted in excessive sedation, which could not be tolerated by elderly frail subjects [58] that typify the PD-Psych cohort.

A retrospective analysis reported that clozapine continues to be effective and safe in the long term [63] while a 5-year follow-up study revealed that 28 % (9 of 32) of PD discontinued treatment on account of resolution of the psychotic symptoms while 9 % (3 of 32) discontinued use of clozapine because of somnolence [64]. Despite the unequivocal demonstration of clozapine's efficacy, clinicians still avoid using it because of its potential for causing agranulocytosis which is idiosyncratic in nature. Because of this, product labelling states clozapine use should be accompanied by weekly white cell count (WCC) monitoring for the first 6 months, then bi-weekly for the next 6 months and monthly monitoring thereafter. Other adverse effects of clozapine include orthostatic hypotension, sedation and sialorrhea [65], all of which can worsen the clinical state of the PD patient. Associations of clozapine with the metabolic syndrome which have been previously documented in schizophrenia have not been reported in PD.

Quetiapine

Quetiapine is a dibenzothiazepine which is structurally similar to clozapine [66]. It has greater affinity for serotonergic 5HT2 receptors than to D2 receptors which confers a favourable motor profile in PD but not as favourable as that of clozapine. Recent clinical trials on use of quetiapine in PD psychosis have given conflicting data—two double-blind trials of quetiapine in PD reported no significant improvement in psychosis [67, 68], a third double-blind trial showed quetiapine's efficacy versus placebo in controlling visual hallucinations in PD [69] while a fourth double-blind trial that compared quetiapine and clozapine showed a significant improvement in psychosis in both groups with no difference in mean improvement between the two groups [70]. Currently, there is insufficient evidence on the efficacy of quetiapine for the treatment of PD psychosis although strong evidence exists that it did not significantly worsen motor function. Despite its level C evidence label, quetiapine has become the de facto first line treatment in PD psychosis instead of clozapine on account of its more favourable side effect profile, ease of use and lack of need for blood monitoring. However, it commonly causes sedation (and therefore has been used also as a treatment for insomnia) and worsen orthostatic hypotension.

Pimavanserin

Pimavanserin is an emerging agent in the treatment of PD psychosis. It is a 5-HT2A *inverse agonist* (which acts as a serotonin antagonist) with negligible action at dopamine D2 receptors [71]. It has been reported to relieve PD psychosis without deterioration in motor symptoms [72]. In a randomized, double-blind, placebo-controlled trial over a 6-week period, pimavanserin at a dose of 40 mg/day was compared to placebo. Pimavanserin met the primary endpoints of improvement in the modified Scale for Assessment of Positive Symptoms PD (SAPS-PD) and also met secondary endpoints of improvements in sleep, daytime somnolence and caregiver burden [73••]. On August 13, 2014, pimavanserin was granted the status of breakthrough therapy by the US Food and Drug Administration (USFDA) [74] while on April 29, 2016 it was approved by the FDA to treat hallucinations and delusions experienced by patients living with PD psychosis [75].

Other Atypical/Second-Generation Antipsychotics

Due to dopamine blockade most of the other members of this class of drugs should be avoided in the treatment of PD psychosis. Although aripiprazole is a partial dopamine agonist/antagonist, available data suggests a variable efficacy and tolerability in PD, with a higher risk of adverse events especially motor worsening [76, 77]. Olanzapine also causes significant decline in motor symptoms with, at best, inconsistent improvement in PD psychosis [78, 79].

Most trials with risperidone in PD are open-label and the only double-blind study of risperidone versus clozapine did not reveal a difference in mean improvement between the two groups [80]. A review of the open-label studies with atypical antipsychotics found significant improvement in PD-Psych overall; however, reports of adverse events regarding motor function vary across studies [14].

Cholinesterase Inhibitors for the Treatment of PD Psychosis

Cholinesterase inhibitors have been studied in the treatment of chronic PD psychosis symptoms. There are no large double blind placebo-controlled studies examining their efficacy in PD psychosis, although there are several case reports, open-label studies, and post hoc investigation on their utility in alleviating hallucinations in the context of PD dementia or DLB [20, 81–86].

Rivastigmine which in addition to inhibiting acetylcholinesterase also inhibits butyrylcholinesterase is the promising agent in this group. A post hoc analysis of a large double-blind placebo-controlled trial with over 500 subjects compared the effect of rivastigmine on visual hallucinations in PD dementia [86]. The group with hallucinations experienced greater benefit than the non-hallucinating group.

However, most of the open-label studies have shown no significant improvement in the symptoms of psychosis, but with little or no motor worsening—if motor worsening did occur it usually was a transient increase in the tremor.

Other Treatment Modalities

Case reports have suggested that certain antidepressants such as clomipramine and citalopram may improve psychotic symptoms especially among patients with concurrent depression [87].

Electroconvulsive therapy (ECT) used in medication-refractory cases of depression and schizophrenia may also be useful in reducing symptoms of PD psychosis especially if there is coexisting depression and when oral pharmacologic approaches have been unsuccessful [88]. The disadvantage is the need for hospitalization and the potential for confusion and possible memory loss.

Conclusion

PD psychosis is more prevalent than realized, and it usually, but not exclusively, occurs in the context of a PD patient taking dopaminergic therapy to improve motor symptoms. It is regarded as one of the greatest unmet needs in the management of PD. It is a source of great distress for both the patient and the caregiver and is one of the most common reasons for long-term placement in the developed world. The development of psychosis especially hallucinations are a harbinger of dementia and increased mortality and its management involves a search for precipitating somatic illnesses such infections and electrolyte imbalance, a thorough review of psychotropic medication, a reduction in antiparkinsonian medications hopefully without sacrificing motor function and often the addition of specific antipsychotic therapy. Although clozapine remains the gold standard in the treatment of this condition, the need for regular serum blood counts has made clinicians shy away from its use. Therefore, the search for promising agents to treat PD psychosis continues. Pimavanserin is the first agent with a non-dopaminergic mechanism of action that is seeking an official indication for the treatment of PD psychosis.

Compliance with Ethical Standards

Conflict of Interest Oluwadamilola O. Ojo declares no conflict of interest.

Hubert H. Fernandez has received grants from Abbvie, Acadia, Auspex, Biotie Therapeutics, Civitas, KYOWA/Prostrakan, the Michael J. Fox Foundation, Movement Disorders Society, NIH/NINDS, the Parkinson Study Group, Rhythm, Synosia and Teva. Dr. Fernandez has also received personal fees from Demos Publishing, Prime Education, Ohio State University, the International Parkinson & Movement Disorders Society, Carling Communications, Medscape, Biogen, GE Healthcare, Lundbeck, Merz Pharmaceuticals, and Pfizer Pharmaceuticals as well as non-financial support from Abbvie, Merz and IPSEN Pharmaceuticals. Dr. Fernandez also receives a stipend for serving as the Medical Editor of the MDS website.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Witjas T et al. Nonmotor fluctuations in Parkinson's disease: frequent and disabling. Neurology. 2002;59(3):408–13.

2. Global Parkinson's disease Survey Steering Committee. Factors impacting on quality of life in Parkinson's disease: results from an international survey. Mov Disord. 2002;17(1):60–7.
3.• Friedman JH. Parkinson's disease psychosis: update. Behav Neurol. 2013;27(4):469–77. **Updated review article highlighting the epidemiology, clinical features, diagnosis, differential diagnoses, pathophysiology and management of psychosis in Parkinson's disease**.
4. Schrag A et al. Caregiver-burden in Parkinson's disease is closely associated with psychiatric symptoms, falls, and disability. Parkinsonism Relat Disord. 2006;12(1):35–41.
5. Lee DR et al. Examining carer stress in dementia: the role of subtype diagnosis and neuropsychiatric symptoms. Int J Geriatr Psychiatry. 2012;28(2):135–41.
6. Gallagher DA, Lees AJ, Schrag A. What are the most important non-motor symptoms in patients with Parkinson's disease and are we missing them? Mov Disord. 2010;25(15):2493–500.
7. Qin Z et al. Health-related quality of life in early Parkinson's disease: impact of motor and non-motor symptoms: results from Chinese levodopa exposed cohort. Park Rel Disord. 2009;15(10): 767–71.
8. Goetz CG, Stebbins GT. Risk factors for nursing home placement in advanced Parkinson's disease. Neurology. 1993;43(11):2227–9.
9. Aarsland D et al. Predictors for nursing home placement in Parkinson's disease: a population-based, prospective study. J Am Geriatr Soc. 2000;48(8):938–42.
10. Goetz CG, Stebbins GT. Mortality and hallucinations in nursing home patients with advanced Parkinson's disease. Neurology. 1995;45:669–71.
11. Marsh L et al. Psychiatric comorbidities in patients with Parkinson's disease and psychosis. Neurology. 2004;63:293–300.
12. Fénelon G, Goetz CG, Karenberg A. Hallucinations in Parkinson disease in the pre-levodopa era. Neurology. 2006;66(1):93–8.
13. Wolters EC, Berendse HW. Management of psychosis in Parkinson's disease. Curr Opin Neurol. 2001;14(4):499–504.
14. Zahodne LB, Fernandez HH. Course, prognosis, and management of psychosis in Parkinson's disease: are current treatments really effective? CNS Spectr. 2008;13(3Suppl 4):26–33.
15. Fenelon G et al. Hallucinations in Parkinson's disease: prevalence, phenomenology and risk factors. Brain. 2000;123(Pt 4):733–45.
16. Ravina B et al. Diagnostic criteria for psychosis in Parkinson's disease: report of an NIND, NIMH work group. Mov Disord. 2007;22:1061–8.
17. Holroyd S, Currie L, Wooten GF. Prospective study of hallucinations and delusions in Parkinson's disease. J Neurol Neurosurg Psychiatry. 2001;70:734–8.
18. Mosimann UP et al. Characteristics of visual hallucinations in Parkinson's disease dementia and dementia with Lewy bodies. Am J Geriatr Psychiatry. 2006;14:153–60.
19. Aarsland D et al. A comparative study of psychiatric symptoms in dementia with Lewy bodies and Parkinson's disease with and without dementia. Int J Geriatr Psychiatry. 2001;16:528–36.
20. Goldman JG, Holden S. Treatment of psychosis and dementia in Parkinson's disease. Curr Treat Options Neurol. 2014;16(3):281. doi:10.1007/S11.940-013-0281-2.
21.•• Fenelon G, Alves G. Epidemiology of psychosis in Parkinson's disease. J Neurol Sci. 2010;289:12–7. **Review focusing on the epidemiology of psychosis in Parkinson's disease; highlighting methodological issues contributing to variability in prevalence estimates and also identifies areas where data is lacking and more research/longitudinal studies required—incidence and associated risk factors**.
22.•• Fenelon G et al. The changing face of Parkinson's disease associated psychosis: a cross-sectional study based on the new NINDS-NIMH criteria. Mov Disord. 2010;25(6):763–6. **Cross-sectional outpatient study that evaluated the prevalence of Parkinson's disease psychosis using new criteria established by NINDS-NIMH. Study confirmed an increase in prevalence with application of the new criteria**.
23. Mack J et al. Prevalence of psychotic symptoms in a community-based Parkinson disease sample. Am J Geriatr Psychiatry. 2012;20(2):123–32.
24. Lee AH, Weintraub D. Psychosis in Parkinson's disease without dementia: common and comorbid with other non-motor symptoms. Mov Disord. 2012;27(7):858–63.
25.• Dotchin CL, Jusabani A, Walker RW. Non-motor symptoms in a prevalent population with Parkinson's disease in Tanzania. Parkinsonism Relat Disord. 2009;15(6):457–60. **Community-based study that revealed the presence of non-motor symptoms at varying stages of Parkinson's disease in an African community. Study added to the body of evidence highlighting the presence of symptomatology of Parkinson's disease psychosis in treatment-naïve and non-demented Parkinson's disease patients**.
26. Goldman JG. New thoughts on thought disorders in Parkinson's disease: review of current research strategies and challenges. Parkinsons Dis. 2011;2011:675630.
27. Friedman JH. The management of the levodopa psychoses. Clin Neuropharmacol. 1991;14:283–95.
28. Factor SA et al. Parkinson's disease: drug-induced psychiatric states. Adv Neurol. 1995;65:115–38.
29. Aarsland D et al. Prevalence and clinical correlates of psychotic symptoms in Parkinson's disease: a community-based study. Arch Neurol. 1999;56(5):595–601.
30. Merims D et al. Antiparkinsonian medication is not a risk factor for the development of hallucinations in Parkinson's disease. J Neural Transm. 2004;111(10 – 11):1447–53.
31. Tanner CM et al. Hallucinations in Parkinson's disease: a population study. Ann Neurol. 1983;12:136.
32. Postuma JU, Van Tilburg W. Visual hallucinations and delirium during treatment with amantadine (Symmetrel). J Am Geriatr Soc. 1975;23:212–5.
33. Glenthoj BY, Hemmigsen R. Dopaminergic sensitization: implications for the pathogenesis of schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry. 1997;21:23–46.
34. Zahodne LB, Fernandez HH. Pathophysiology and treatment of psychosis in Parkinson's disease: a review. Drugs Aging. 2008;25(8):665–82.
35. Wolters EC. Intrinsic and extrinsic psychosis in Parkinson's disease. J Neurol. 2001;Suppl 3:III/22–7.
36. Friedman JH. Parkinson's disease psychosis 2010: a review article. Parkinsonism Relat Disord. 2010;16(9):553–60.
37.• Kurita A et al. Visual hallucinations and altered visual information processing in Parkinson disease and dementia with Lewy bodies. Mov Disord. 2010;25(2):167–71. **Neurophysiology study of the pathophysiology of visual hallucinations in dementia with Lewy Bodies and Parkinson's disease dementia**.
38. Ibarretze-Bilbao N, et al. Differential progression of brain atrophy in Parkinson's disease with and without visual hallucinations. J Neurol Neurosurg Psychiatry. 2010;81(6):650–7.
39. Meppelink AM et al. Impaired visual processing preceding image recognition in Parkinson's disease patient with visual hallucinations. Brain. 2009;132:2980–93.
40. Diedrich NJ et al. Poor visual discrimination and visual hallucinations in Parkinson's disease. Clin Neuropharmacol. 1998;21:289–95.
41. Arnulf I et al. Hallucination, REMsleep, and Parkinson's disease: a medical hypothesis. Neurology. 2000;55(2):281.
42. Fenelon G. Psychosis in Parkinson's disease: phenomenology, frequency, risk factors and current understanding of pathophysiologic mechanisms. CNS Spectr. 2008;13:18–25.

43. Whitehouse PJ. Clinical and neurochemical consequences of neuronal loss in the nucleus basalis of Meynert in Parkinson's disease and Alzheimer's disease. Adv neurol. 1987;45:393–7.
44. Kuhl DE et al. In vivo mapping of cholinergic terminals in normal aging, Alzheimer's disease and Parkinson's disease. Ann Neurol. 1996;40:399–410.
45. Perry E et al. Acetylcholine in mind: a neurotransmitter correlate of consciousness? Trends neurosci. 1999;22:273–80.
46. Van der Mast RC, Fekkes D. Serotonin and amino acids: partners in delirium pathophysiology? Semin Clin Neuropsychiatry. 2000;5:125–31.
47. Fernandez HH, Trieschmann ME, Friedmann JH. The treatment of psychosis in Parkinson's disease: safety considerations. Drug Saf. 2003;26:643–59.
48. Harding AJ, Broe GA, Halliday GM. Visual hallucinations in Lewy body disease relate to Lewy bodies in the temporal lobe. Brain. 2002;125(Pt2):391.
49. Goetz CJ et al. Intravenous levodopa in hallucinating Parkinson's disease: high-dose challenge does not precipitate hallucinations. Neurology. 1998;50:515–7.
50. Wint DP, Okun MS, Fernandez HH. Psychosis in Parkinson's disease. J Geriatr Psychiatry Neurol. 2004;17:127–36.
51. Henderson MJ, Meilers JDC. Psychosis in Parkinson's disease: "between a rock and a hard place.". Int Rev Psychiatry. 2000;12:319–34.
52. Fernandez HH, Friedman JH. The role of atypical antipsychotics in the treatment of movement disorders. CNS Drugs. 1999;11:467–83.
53. Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. JAMA. 2005;294:1934–43.
54.•• Weintraub D et al. Patterns and trends in antipsychotic prescribing for Parkinson disease psychosis. Arch Neurol. 2011;68:899–904. **Study comparing the use of antipsychotics in Parkinson's disease with psychosis with other dementia with psychosis. Study revealed rare prescription of clozapine and common prescription of high potency antipsychotics despite the FDA 'black box' warning**.
55. Miyasaki JM et al. Quality Substandards Committee of the American Academy of Neurology. Practice parameter: evaluation and treatment of depression, psychosis, and dementia in Parkinson disease (an evidence-based review): report of the Quality Standards Subcommittee of the American academy of Neurology. Neurology. 2006;66:996–1002.
56. Seppi K et al. The Movement Disorder Society evidence-based medicine review update: treatments for the non-motor symptoms of Parkinson's disease. Mov Disord. 2011;26 suppl 3:S42–80.
57. Moskowitz C, Moses H, Klawans HL. Levodopa-induced psychosis: a kindling phenomenon. Am J Psychiatry. 1978;135:669–75.
58. Friedman JH. Atypical antipsychotic drugs in the treatment of Parkinson's disease. J Pharm Pract. 2011;24(6):534–40.
59. Frieling H, et al. Treating dopamimetic psychosis in Parkinson's disease: structure review and meta-analysis. Eur Neuropsychopharmacol. 2007;17(3):165–71
60. Low-dose clozapine for the treatment of drug-induced psychosis in Parkinson's disease. The Parkinson Study Group. N Engl J Med. 1999;340:757–63.
61. Clozapine in drug-induced psychosis in Parkinson's disease. The French Clozapine Study Group. Lancet. 1999;353:2041–2.
62. Wolters EC et al. Clozapine in the treatment of parkinsonian patients with dopaminomimetic psychosis. Neurology. 1990;40:832–4.
63. Fernandez HH, Donnelly EM, Friedman JH. Long-term outcome of clozapine use for psychosis in parkinsonian patients. Mov Disord. 2004;19:831–3.
64. Klein C et al. Clozapine in Parkinson's disease psychosis: 5-year follow-up review. Clin Neuropharmacol. 2003;26:8–11.
65. Pollak P et al. Clozapine in drug induced psychosis in Parkinson's disease: a randomised, placebo controlled study with open follow up. J Neurol Neurosurg Psychiatry. 2004;75:689–95.
66. Richelson E. Preclinical pharmacology of neuroleptics: new generation compounds. J Clin Psychiatry. 1996;57 Suppl 11:4–11.
67. Ondo WG et al. Double-blind, placebo-controlled unforced titration parallel trial of quetiapine for dopaminergic induced hallucinations in Parkinson's disease. Mov Disord. 2005;20:958–63.
68. Rabey JM et al. The effect of quetiapine in Parkinson's disease (PD) psychotic patients: a double-blind parallel study of 3 months duration. Mov Disord. 2005;20:S46.
69. Fernandez HH et al. Quetiapine improves visual hallucinations in Parkinson's disease but not through normalization of sleep architecture: results from a double-blind clinical polysomnography study. Int J Neurosci. 2009;119:2196–205.
70. Morgante L et al. Quetiapine and clozapine in parkinsonian patients with dopaminergic psychosis. Clin Neuropharmacol. 2004;27:153–6.
71. Vanover KE et al. Pharmacological and behavioral profile of N-(4-fluorophenylmethyl)-N-(1-methylpiperidin-4-yl)-N'-(4-(2-methylpropyloxy)phenylmethyl) carbamide (2R,3R)-dihydroxybutanedioate (2:1) (ACP-103), a novel 5-hydroxytryptamine(2A) receptor inverse agonist. J Pharmacol Exp Ther. 2006;317:910–18.
72. Abbas A, Roth BL. Pimavanserin tartrate: a 5-HT2A inverse agonist with potential for treating various neuropsychiatric disorders. Expert Opin Pharmatother. 2008;9:3251–9.
73.•• Cummings J et al. Pimavanserin for patients with Parkinson's disease psychosis; a randomised placebo-controlled phase 3 trial. Lancet. 2014;383:533–40. **This is the randomized controlled trial of pimavanserin, the first FDA-approved drug for the specific indication of Parkinson's psychosis**.
74. U.S. food and Drug Administration. www.accessdata.fda.gov/drugsatfda_docs/nda. Accessed February 2016.
75. U.S. Food and Drug Administration. www.accessdata.fda.gov/drugsatfda. Accessed 25th July 2016.
76. Fernandez HH, Trieschmann ME, Friedman JH. Aripiprazole for drug-induced psychosis in Parkinson disease: preliminary experience. Clin Neuropharmacol. 2004;27:4–5.
77. Friedman JH et al. Open-label flexible-dose pilot study to evaluate the safety and tolerability of aripiprazole in patients with psychosis associated with Parkinson's disease. Mov Disord. 2006;21:2078–208.
78. Breier A et al. Olanzapine in the treatment of dopamimetic-induced psychosis in patients with Parkinson's disease. Biol Psychiatry. 2002;52:438–45.
79. Ondo WG et al. Olanzapine treatment for dopaminergic-induced hallucinations. Mov Disord. 2002;17:1031–5.
80. Ellis T et al. Clozapine and risperidone treatment of psychosis in Parkinson's disease. J Neuropsychiatr Clin Neurosci. 2000;12(3):364–9.
81. Fabbrini G et al. Donepezil in the treatment of hallucinations and delusions in Parkinson's disease. Neurol Sci. 2002;23:41–3.
82. Kurita A et al. The beneficial effect of donepezil on visual hallucinations in three patients with Parkinson's disease. J Geriatr Psychiatry Neurol. 2003;16:184–8.
83. Bergman J, Lerner V. Successful use of donepezil for the treatment of psychotic symptoms in patients with Parkinson's disease. Clin Neuropharmacol. 2002;25:107–10.
84. Reading PJ, Luce AK, McKeith IG. Rivastigmine in the treatment of parkinsonian psychosis and cognitive impairment: preliminary findings from an open trial. Mov Disord. 2001;16:1171–4.

85. Rovers JM, Dautzenberg PL, ter Bruggen JP. Rivastigmine as adjunctive therapy in the therapeutic dilemma for the treatment of hallucinations due to Parkinson disease. Tijdschr Gerontol Geriatr. 2006;37:117–20.
86. Burn D et al. Effects of rivastigmine in patients with and without visual hallucinations in dementia associated with Parkinson's disease. Mov Disord. 2006;21:1899–907.
87. Meco G, Bernadi S. Antidepressant use in treatment of psychosis with comorbid depression n Parkinson's disease. Prof Neuropsychopharmacol Biol Psychiatry. 2007;31:311–3.
88. Ozer F et al. Electroconvulsive therapy in drug-induced psychiatric states and neuroleptic malignant syndrome. J ECT. 2005;21:125–7.