Course, prognosis, and management of psychosis in Parkinson's disease: Are current treatments really effective?

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Abstract

It is essential to recognize and treat psychosis in Parkinson disease (PD) for several reasons. Multiple studies have shown that psychosis in PD patients is a strong risk factor for nursing home placement. Psychosis may be the single greatest stress for caretakers of PD patients, it is often persistent, and its presence markedly increases the risk of mortality.

Treatment of psychotic symptoms should occur only after potential medical and environmental causes of delirium have been eliminated or addressed. Initial pharmacologic changes should include limiting the patient's anti-PD medications to those that are necessary to preserve motor function. Should that fail, an atypical antipsychotic agent is presently the treatment of choice. An emerging treatment option is the use of acetylcholinesterase inhibitors. This article reviews what is currently known about the course, prognosis and treatment strategies in PD psychosis.

Introduction

As highlighted by the other authors in this supplement, non-motor and behavioral complications are commonly seen throughout the course of Parkinson's disease (PD). Psychotic features such as hallucinations have long been identified as possible side effects of dopaminergic medications and, more recently, have come to be regarded as products of the disease process itself. Research into their course and utility as prognostic indicators has expanded, and strategies for their management within the context of the patient's comprehensive motor and non-motor sequelae have yet to be optimally refined, as psychosis represents a distinct challenge for the clinician, patient, and family.

Prognostic indicators

The meaning of psychosis and hallucinosis as prognostic indicators in PD varies depending upon when symptoms are seen during the disease course. If symptoms are evident at time of diagnosis or very early on in the disease, then a pre-existing psychiatric disorder or another parkinsonian syndrome such as dementia with Lewy bodies (DLB) is likely to be present, and additional symptoms of such disorders will manifest. In one study, all patients identified as having early-onset (within three months of initiating levodopa therapy) hallucinations were later found to carry a diagnosis other than or in addition to PD that could account for their baseline psychotic symptoms.[1] However, most psychotic features arise later in the disease course and are often prognostic of additional complications such as cognitive impairment[2] and weight loss[3] as well as negative outcome variables such as caregiver distress[4], nursing home placement[5], and mortality.[6]

Psychotic symptomatology has been considered by some to represent a "harbinger to cognitive decline."[7] Indeed, data seem to support the clinical observation that PD patients who present with visual hallucinations are more likely to develop cognitive impairments later on.[8,9,10] Psychosis and cognitive decline often co-occur, and both have been related to the development of the other. These symptoms severely impact on caregiver burden and patient quality of life and may partly explain the increased risk for nursing home placement and related mortality in PD patients who manifest them.[11]

A 1993 case-control study identified hallucinosis as the number one factor differentiating PD patients who were placed in a nursing home from those who were not, as variables including motor and cognitive impairment did not differ between the groups.[12] In a 2-year follow-up study, the authors found that 100% of nursing home PD patients had died.[13] Recent reports have documented more conservative nursing home mortality rates, which have been attributed in part to the increasingly common use of atypical antipsychotic agents for the treatment of psychosis.[14,15] However, the finding that hallucinations and other psychotic phenomena are predictive of negative outcome has been well-replicated and underscores the importance of both treating PD psychosis as well as its utility as a prognostic indicator. When psychosis and dementia co-exist in PD, it is perhaps the greatest limiting factor for the optimal treatment of motor symptoms.

Course

On average, PD patients manifest psychotic symptoms ten or more years after the initial diagnosis.[16] In its early stages, PD psychosis tends to occur within a context of a clear sensorium and retained insight.[17] At this stage, support and counseling may be determined sufficient in managing psychotic symptoms. However, these symptoms usually recur and worsen over time, and insight may be lost.[18] Psychosis in PD had long been conceptualized as occurring along a continuum in that minor experiences such as vivid dreaming and illusions herald more frank hallucinations and delusions, which ultimately lead to florid psychosis and dementia.[19] However, recent evidence suggests that this conceptualization may not be accurate.[20,21] While the specific course of PD psychosis remains to be adequately described, it seems clear that psychotic symptoms, once present, are persistent and distressing.

Once it appears, hallucinosis is robust in PD, and the existence of hallucinations at baseline is a strong predictor of their presence at follow-up evaluations.[22] While treatment with antipsychotic agents has been shown to provide some degree of symptom relief, data regarding the effects of treatment on the long-term course of psychosis have been variable. Some studies documented no differences in hallucinations between patients who received treatment compared to those who did not, and many treated patients were still experiencing

hallucinations at long term follow-up.[23,24] Other reports suggest that many patients receiving antipsychotic treatment experience continued efficacy, especially those who responded to their medication early on.[25] However, aside from the relatively lower mortality rates documented since the establishment of atypical antipsychotic treatment as a standard of practice in treating PD psychosis, there is little data to suggest that antipsychotic treatment improves long term functional outcome.

Once patients initiate antipsychotic therapy, continued treatment may be necessary to maintain symptom control and avoid exacerbation of psychosis. One study that attempted to wean psychosis-free PD patients off of their antipsychotic medications was aborted after enrolling only six patients because 5 out of the 6 subjects experienced "rebound psychosis."[26] Furthermore, 3 out of these 5 patients experienced a worsening of psychotic episodes (compared to their original psychotic episode that prompted anti-psychotic use) in the form of paranoid delusions or threatening auditory hallucinations. Additional research is needed to confirm the utility and necessity of continued antipsychotic treatment.

Management

Reduction/Simplification of Parkinson's Disease Medications

General consensus and clinical practice support a reduction in anti-PD medications as the most appropriate first-line treatment for PD psychosis. If a patient is on multiple medications, most authorities would recommend the gradual removal of anti-PD medications in the following order: anticholinergics, amantadine, MAO-B inhibitors, dopamine agonists, catechol-O-methyltransferase (COMT) inhibitors, and lastly, levodopa. [27,28] Furthermore, although not extensively and systematically studied, the short-acting formulation of levodopa, as compared to the continued-release version, may reduce the risk of accumulating adverse side effects.

Aside from PD medications, polypharmacy has been identified as an independent risk factor for psychosis in PD.[29] Because various commonly-prescribed agents (e.g. narcotics, hypnotics, antidepressants, and anxiolytics) can contribute to the development of psychotic symptoms, it is important for the clinician to consider the patient's complete pharmacological regimen when combating PD psychosis.

Due to adverse side effects, the addition of an antipsychotic agent should be considered only if the strategy of medication reduction to the lowest tolerated dosages causes significant motor worsening or does not improve psychosis. Because reducing a patient's medications will likely lead to a re-emergence of unendurable motor dysfunction, the clinician and patient are faced with a difficult challenge in minimizing symptom burden and optimizing quality of life.

Atypical Antipsychotics

After medication simplification, prescription of an atypical antipsychotic (AA) represents the most common clinical response to PD psychosis. Because the differences between the six atypical antipsychotic agents currently marketed in the US lie in their relative propensities to exacerbate motor symptoms, the choice of an AA is based largely on its distinct side effect profile. Table 1 summarizes the methods and results of double-blind and select open-label trials of atypical antipsychotics for the treatment of PD psychosis.

According to a 2007 meta-analysis, clozapine is the only AA fully recommended for the treatment of PD psychosis due to its demonstrated efficacy and tolerability in both 2 well-designed randomized, controlled and numerous open-label trials.[30,31,32,33] Additionally, longitudinal studies have shown clozapine to be well-tolerated and effective in the long

term.[34,35] However, despite its established effectiveness, clozapine is often avoided because of the cumbersome monitoring required to catch agranulocytosis, which has been shown to occur in only 0.38% of a sample of over 99,000 US patients with schizophrenia.[36] Weekly WBC count monitoring during the first six months and bi-weekly monitoring thereafter is required with use of clozapine. In addition, sedation, orthostatic hypotension and sialorrhea may also occur.[37] Therefore, research has increasingly shifted toward identifying more practical agents to treat PD psychosis.

Although risperidone was released in the US as an atypical antipsychotic, research suggests that it more closely resembles "typical" neuroleptics in that it exhibits a dose-dependent incidence of extrapyramidal side effects and prolactin elevation.[38,39] The majority of the studies on risperidone in PD demonstrate significant improvements in psychosis.[40,41,42,43] However, most are open-label, which may partly contribute to the variability in reports of motor side effects in the extant literature. [44,45] Due to numerous reports of motor worsening and the agent's documented "typical" antipsychotic behavior, it is often avoided by clinicians in the treatment of PD psychosis.

In addition to being more chemically similar to clozapine than is risperidone, olanzapine appears to be more atypical in that it does not cause significant prolactin secretion, and extremely high doses are required to induce catalepsy.[46] While the first published report in PD was an open-label trial that documented improvement in drug-induced psychosis without motor worsening,[47] three controlled trials have since documented both a lack of significant improvements in psychosis and a deterioration of motor functioning, and a fourth was discontinued after 6 of 7 olanzapine treated subjects experienced significant motor decline. [48,49,50] A 2003 review estimated that olanzapine led to motor worsening in about 40% of PD patients.[51] Thus, olanzapine is generally considered to be ineffective in treating PD psychosis and is associated with intolerable motor deterioration even at low doses.

Among the AAs, quetiapine is most chemically similar to clozapine but does not show a risk of agranulocytosis. Despite results from numerous open-label studies involving more than 400 patients that have shown quetiapine to be well-tolerated and efficacious in the treatment of PD psychosis,[52,53] two double-blind trials reported no significant improvements in psychosis.[54,55] A third, in which 40 patients were randomized to either quetiapine or clozapine, did show efficacy in treating psychosis; and the two groups did not differ in mean improvement.[56] In sum, quetiapine appears to be slightly less effective than clozapine for the treatment of PD psychosis, and it may also induce mild motor worsening, but not to the extent seen with risperidone and olanzapine.[51] Unlike those seen with olanzapine and risperidone, none of the motor declines reported in PD patients taking quetiapine have required hospitalization. Additionally, quetiapine does not carry an associated risk of agranulocytosis and thus does not require vigilant monitoring like clozapine. As a result, quetiapine, by default, is a common choice among many clinicians treating PD psychosis.

The use of ziprasidone has been limited due to its effects on the heart's electrical cycle (i.e. prolonging the QT interval), but there have been no reported cases of its causing torsades de pointes.[57] Case reports and series suggest that ziprasidone may be a relatively safe treatment for psychosis in PD, especially when other atypical antipsychotics have proven ineffective or caused intolerable side effects.[58,59,60,61] However, after reviewing data on ziprasidone for the treatment of schizophrenia, a panel of expert psychiatrists concluded that its extrapyramidal side effects profile is "better than risperidone, the same as olanzapine but not quite as good as quetiapine or clozapine".[62]

Unlike other atypical antipsychotics, aripiprazole is a "partial agonist" at both D_2 and $5\text{-}HT_1$ receptors and is believed to carry a relatively low risk of extrapyramidal side effects due to

its high 5-HT$_2$/D$_2$ affinity ratio.[63] Available data from several case reports and two open-label trials on aripiprazole in PD suggest that its efficacy and tolerability in PD patients is variable.[64,65,66,67,68] While aripiprazole may be efficacious for some patients, it carries a considerable risk of adverse effects, and there is a need for further controlled trials of aripiprazole in the PD population.

While atypical antipsychotics continue to be the most commonly-prescribed pharmacological agents in the treatment of PD psychosis, the US Food and Drug Administration (FDA) has mandated that all manufacturers provide a boxed warning on product labels stating that AAs have been found to be associated with a higher risk of mortality when used in elderly patients with dementia.[69] This finding is particularly relevant for the management of PD psychosis considering the age and frailty of the late-stage PD patients who typically experience psychosis. Since the mechanism by which AAs cause increased mortality has not been fully elucidated, they will likely continue to be used in the treatment of PD psychosis, especially when the consequences of inaction are taken into account. However, studies involving alternative therapies such as cholinesterase inhibitors are currently ongoing.

Cholinesterase inhibitors

Table 2 summarizes the methods and results of double-blind and select open-label trials of atypical antipsychotics for the treatment of PD psychosis. The first published report of a cholinesterase inhibitor in PD described an open-label trial of tacrine in which psychotic symptoms completely resolved in 5 out of 7 demented patients and improved in the remaining 2, and no patients experienced motor worsening despite previous accounts of an exacerbation of parkinsonism in one patient treated with tacrine.[70,71] However, today tacrine is rarely used for the treatment of PD psychosis due its tendency to cause hepatic toxicity.

Open-label studies using donepezil in PD patients have shown improvements in psychosis and variability in motor side effects.[72,73,74] However, in general, placebo-controlled trials published to date have shown non-significant improvements in psychosis, perhaps as a consequence of small sample sizes and/or low baseline symptom severity.[75,76]

Unlike other cholinesterase inhibitors, galantamine also acts on nicotinic acetylcholine (Ach) receptors. According to some authors, activity at these receptors may prevent the down-regulation of acetylcholine that accompanies treatment with cholinesterase inhibitors. It has been suggested that in the striatum, increasing activity at nicotinic receptors on presynaptic dopamine neuron terminals may facilitate the release of dopamine, thereby improving motor symptoms. Only one study using galantamine in PD psychosis has been published, and it reported that 3 out of 9 patients experienced a complete resolution of their hallucinations, and 4 additional patients reported an improvement.[77] While parkinsonism improved in 6 of the patients, the remaining 3 experienced a worsening of tremor. Further studies are necessary to explicate the value of galantamine in treating PD psychosis.

Rivastigmine, the only one in its class now FDA approved for the treatment of PD dementia, is unique from the other cholinesterase inhibitors in that it inhibits not only acetyl, but also butyryl cholinesterase. One open-label trial showed that caregiver distress, MMSE scores, and scores on NPI subscales measuring hallucinations and sleep disturbances improved.[78] Also, rivastigmine was well-tolerated, and motor symptom severity remained stable. Recently, Burn *et al.* published results from a large, double-blind, placebo-controlled trial using rivastigmine to treat visual hallucinations in patients with Parkinson's disease and dementia.[79] The authors reported that hallucinating patients experienced a significant improvement in both total NPI score and the agitation/aggression item. Additional double-

blind, controlled trials using this promising agent for the treatment of visual hallucinations in PD are warranted and are underway.

Memantine

Recently, interest regarding pharmacological treatments for PD has turned to memantine, a relatively new agent developed for use in dementia and approved by the FDA for the treatment of moderate to severe Alzheimer's disease in 2003. Memantine is a selective, uncompetitive antagonist at NMDA receptors and reduces glutamatergic excitotoxicity.[80] Memantine's potential neuroprotective effects are thought to be due to its partial blockage of NMDA receptor sites and subsequent prevention of the overstimulation of these receptors by excess glutamate that is thought to ultimately lead to cell death and disruption from excessive intracellular calcium.[81]

While most clinical trials published to date were not expressly designed to identify changes on neuropsychiatric measures, there are limited data to suggest that memantine may have positive behavioral effects in neurodegenerative disorders, especially in the domains of agitation/aggression, eating/appetite, and irritability/lability.[82,83,84] Similarly, a recent case study described an antipsychotic dose-sparing effect in one patient with AD.[85] However, memantine has also been reported to cause a worsening of psychotic symptoms in a subset of patients with Dementia with Lewy Bodies and Alzheimer's disease.[86,87] Further research is needed to explore the potential for memantine as a treatment of Parkinson's disease and its related behavioral symptoms.

Ondansetron

Ondansetron, an antiemetic, was tested as a possible treatment for schizophrenia due to its action as an antagonist at the 5-HT$_3$ receptors, but it has not been found to be efficacious for this purpose. However, there are several early reports that it may have utility in the treatment of psychosis in PD without the worsening of motor symptoms, presumably due to its high selectivity. Two open-label trials conducted by Zoldan, *et al*. reported an improvement in psychosis with limited side effects (e.g. headache, constipation).[88,89] However, these positive results have not been reproduced by others.[90] Furthermore, the cost of the drug has kept it from being tested further in the PD population.

Potential value of a Parkinson's non-dopaminergic/non-anticholinergicmedication

All anti-PD medications have been implicated in the development of psychotic features in PD, not just levodopa.[91] As highlighted earlier, optimal management of the Parkinson patient implies a delicate balance between controlling cardinal motor symptoms and minimizing medication-related side effects. The clinician is often faced with the challenge of combating one symptom with an agent that is known to exacerbate others. For example, anticholinergic medications, which attenuate cholinergic activity, are frequently prescribed as adjunct treatments for PD motor symptoms, while cholinesterase inhibitors, which enhance cholinergic activity, are the most common agents used to manage cognitive deficits.

In addition, while PD is most commonly conceptualized as a disorder of dopamine depletion in the substantia nigra, various other neuronal fields and neurochemical systems are affected: the locus coeruleus, dorsal motor nucleus, substantia innominata, the autonomic nervous system and the cerebral cortex.[92] Additionally, Lewy bodies are commonly found outside of the basal ganglia, and their deposition is heterogeneous amongst patients.[93] Non-motor symptoms of PD are at least partly attributable to this non-striatal neuropathology and are often reported by patients and their caregivers to be even more distressing than cardinal

motor symptoms.[94,95] Indeed, a recent 15-year longitudinal study concluded that the most disabling long-term problems that develop in PD are those related to the emergence of symptoms not improved by levodopa.[96]

Multicentric neurodegeneration in PD and its resultant non-motor complications inevitably necessitate non-dopaminergic treatment.[97] Also, the potential for non-dopaminergic and non-cholinergic agents to treat motor deficits with fewer side effects is desirable, and researchers are actively engaged in exploring new strategies and pharmacological agents in order to optimize the management of the whole Parkinson patient.[98]

Conclusion

The inherent tension between treating PD motor symptoms with agents known to facilitate the emergence of psychotic features and managing psychosis in order to maximize patient quality of life presents an interesting dilemma for researchers and clinicians. While a variety of current treatments have demonstrated limited effectiveness in research studies and improved the lives of many patients, the variability in response patterns and frequency of side effect expression highlight the progress that still needs to be made in both reducing the incidence of PD psychosis and treating psychotic features once they emerge.

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Table 1

Open label and double-blind trials of atypical antipsychotics for PD psychosis

Agent	Design	No. of Patients	Dosage	Psychosis outcome	Motor worsening
Clozapine					
Parkinson Study Group (31)	Double-blind	60	24.7 mg/d	Significant improvement on total BPRS	None
Pollak et. al. (33)	Double-blind	60	36 mg/d	Significant improvement on CGI-S & PANSS subscore	None
Risperidone					
Workman et. al. (40)	Open label	9	1.9 mg/d	Symptoms improved in 9 pts	None
Meco et. al. (41)	Open label	10	0.73 mg/d	Symptoms improved in 9 pts	3 pts exhibited motor worsening
Leopold (42)	Open label	39	1.1 mg/d	Symptoms improved in 33 pts	6 pts exhibited motor worsening
Mohr et. al. (43)	Open label	17	1.1 mg/d	Significant improvement on CGI- S, CGI-I & PANSS. Symptom improvement in 16 pts	1 pt exhibited motor worsening
Ellis et al. (45)	Double blind	5	1.2 mg/d	Significant improvement on total BPRS	Worsening on UPDRS motor subscale, but no sig. difference with clozapine group
Olanzapine					
Wolters et. al. (47)	Open label	15	6.5mg/d	Significant improvement on total BPRS and core symptom subscore	None
Lilly US trial (48)	Double-blind	41	4.2 mg/d	Significant improvement overall on total, positive cluster, and hallucination item BPRS, total and hallucination item NPI, & CGI-S psychosis scores	Worsening on UPDRS total and motor subscale
Lilly European trial (48)	Double-blind	49	4.1 mg/d	Significant improvement overall on total, positive cluster, and hallucination item BPRS, total and hallucination item NPI, & CGI-S psychosis scores	Worsening on UPDRS total and motor subscale
Ondo et. al. (49)	Double-blind	16	4.6 mg/d	No significant improvement on UPDRS item 2 or structured interview for hallucinations	Worsening on UPDRS motor subscale and timed tapping
Quetiapine					
Reddy et. al (52)	Retrospect.	43	54 mg/d	Symptoms improved in 32 pts as per pt and caregiver interviews	5 pts worsened on UPDRS motor subscore, but no sig. group change
Fernandez et. al. (53)	Retrospect.	87	60.8 mg/d	Symptoms improved in 70 pts as per chart review	28 pts experienced mild worsening over 15 months, as per chart review
Ondo et. al. (54)	Double- blind	21	75–200 mg/d	No significant improvement on BPRS or Baylor PD Hallucination Questionnaire	No difference compared to placebo
Rabey et. al. (55)	Double- blind	30	119.2 mg/d	No difference compared to placebo on BPRS or CGI	No difference compared to placebo
Morgante et. al. (56)	Double- blind	22	91 mg/d	Significant improvement on BPRS (total & specific items) and CGIS	3 pts worsened, butno sig. group difference on UPDRS motor subscale
Aripiprazole					

Agent	Design	No. of Patients	Dosage	Psychosis outcome	Motor worsening
Fernandez et. al. (68)	Open label	8	12.8 mg/d	Symptoms improved in 4 pts as per pt report	3 pts as per pt report
Friedman et. al. (69)	Open label	14	1–5 mg/d	Symptoms improved in 6 pts; Significant improvement on BPRS (total & positive cluster)	5 pts discontinued study due to motor worsening

BPRS = Brief Psychiatric Rating Scale; CGI-I and -S = Clinical Global Impression Scale–Improvement and Severity; PPRS = Psychosis Rating Scale for Parkinson's disease; UPDRS–Unified Parkinson's Disease Rating Scale

Table 2

Open label and double-blind trials of cholinesterase inhibitors for PD psychosis

Agent	Design	No. of Patients	Dosage	Psychosis outcome	Motor worsening
Tacrine					
Hutchinson et. al. (72)	Open label	7		Psychosis resolved in 5 pts, improved in 2 pts	None
Donepezil					
Fabbrini et al. (73)	Open label	8	5 mg/d	8 pts improved; significant improvement on PPRS	2 pts worsened, but no sig. group difference on UPDRS motor subscale
Bergman et. al. (74)	Open label	6	5–10 mg/d	5 pts improved; significant improvement on SAPS and CGI	None
Kurita et. al. (75)	Open label	3	5 mg/d	Hallucinations improved in 3 pts, but delusions emerged in 1 pt, as per pt report	None
Ravina et al. (77)	Double-blind	10	5–10 mg/d	No mean improvement on BPRS	None
Galantamine					
Aarsland et. al. (78)	Open label	16 total; 9 with VH	4–8 mg/d	7pts in VH group improved on NPI hallucination item	3 pts worsened total
Rivastigmine					
Reading et. al. (79)	Open label	15	1.5–6 mg/d	Significant improvement on NPI total and hallucinations & sleep disturbance subscales; significant improvement in caregiver distress on NPI	None
Burn et. al. (80)	Double-blind	357 total; 118 with VH	8.9 mg/d in VH group	Significant improvement on NPI total and agitation/aggression item in VH group	Worsening tremor in 10/2% of VH group, but no sig. group difference on UPDRS motor subscale

BPRS = Brief Psychiatric Rating Scale; CGI-I and -S = Clinical Global Impression Scale–Improvement and Severity; PPRS = Psychosis Rating Scale for Parkinson's Disease Rating Scale; SAPS = Scale for the Assessment of Positive Symptoms; VH = Visual Hallucinations