Treatment of Parkinson's disease psychosis

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Abstract

Early in the course of Parkinson disease (PD), treatment usually goes well. However, after five to ten years, things start to change as treatment requires higher doses of medications and side effects become more problematic. One of the most difficult problems is the development of hallucinations or delusions. Throughout the 20th century, treatment options were unproven and unsatisfactory, but the past 20 years have brought important changes. Two medications that are well tolerated in PD have now proved efficacious in randomized, controlled trials, and others are in development. Here I summarize this history briefly and provide a general plan for treating the patient with PD complicated by psychotic symptoms.

Keywords

Hallucinations/therapy, Delusions/therapy, Parkinsonian Disorders, Delirium, Antipsychotic Agents, pimavanserin

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Introduction

James Parkinson's original description of the illness that now bears his name focused on motor signs. However, the 200 years since that description first appeared have revealed that nonmotor features are important in Parkinson's disease (PD) [1]. Among these, one of the most problematic is the development of psychosis. Psychosis primarily refers to hallucinations or delusions; a hallucination is a sensory perception in the absence of a real stimulus, and a delusion is a firm belief in something that is not true despite clear evidence to the contrary. Risk factors for psychosis in PD include duration of illness, the presence of dementia, sensory impairments or insomnia, the use of dopamine agonist medications, and perhaps the ACE (angiotensin converting enzyme) or DAT (dopamine transporter) genes [2-5]. A working group convened by the U.S. National Institutes of Health proposed diagnostic criteria for PD psychosis that included not only these typical psychotic symptoms but also illusions (a misinterpreted real percept, such as thinking that one's bathrobe hung on the door is an intruder) and "presence hallucinations" (the sense that someone else is in the room without seeing anyone) [6]. A broad and inclusive case definition is appropriate when the phenomenon under investigation is not well described, but time will tell the appropriate nosological position of these less obviously abnormal features. Although most people with PD do not have psychotic symptoms when assessed cross-sectionally, over time a majority of PD patients will eventually develop psychosis [7].

First steps

The first step in treating psychosis in PD is diagnosis (see Box 1). First one must exclude other causes of psychosis. Appropriate medical history usually can exclude schizophrenia and psychotic mood disorders fairly easily. Excluding delirium is more important. Delirium is characterized by inattention and disorientation, but often is complicated by hallucinations or delusions. Common causes of delirium include infections, recently-added medications, and electrolyte abnormalities, but the diagnosis is made by the clinical syndrome; one cannot always identify a specific single cause. History, mental status and physical examination often suffice for diagnosis of delirium, supplemented as appropriate by laboratory studies [8].

Once PD psychosis is diagnosed, the next step is to prune the list of antiparkinsonian medications. I generally remove them in the following sequence: anticholinergics, amantadine, and then dopamine agonists. Some clinicians also stop monoamine oxidase inhibitors and

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catechol-*O*-methyl transferase (COMT) inhibitors. Parkinsonian symptoms often will increase as a result of these medication changes, requiring increases in levodopa dosage. If psychosis persists after thus simplifying antiparkinsonian treatment, levodopa dosage can be reduced if possible, but often patients already are at the minimum dose tolerated for motor function.

At this stage, adding a medication to treat the psychosis is usually necessary. Of course, as with all treatment decisions in medicine, one must weigh the risks and benefits. Initially, some psychotic symptoms may appear relatively benign, for instance seeing an old friend when no one is present. Such symptoms may not require treatment when they are infrequent and accompanied by insight. However, psychotic symptoms tend to worsen over time in terms of frequency, complexity and loss of insight, and some hallucinations and delusions can lead to dangerous behavior. Thus at a minimum, even "benign" hallucinations should be monitored carefully, and treatment is often indicated.

Box 1
Diagnostic criteria for psychosis in Parkinson's disease
Adapted from ref. [6], © 2007, by permission of John Wiley and Sons

- Presence of any of the following:
  - ◊ hallucinations
  - ◊ delusions
  - ◊ illusions
  - ◊ false sense of presence
- Parkinson's disease (UK Brain Bank criteria for PD) prior to development of psychosis
- Symptoms must be recurrent or continuous for at least 1 month
- Not better explained by another illness, such as dementia with Lewy bodies, delirium, major depression with psychosis, or schizophrenia
- May occur with or without any of the following features:
  - ◊ insight
  - ◊ dementia
  - ◊ treatment for Parkinson's disease

Specific treatment
Medications with proven efficacy for psychosis in PD

In 1999, two studies independently showed clozapine to be superior to placebo for psychosis in PD [9-12]. Some trials reported minor worsening of parkinsonism with clozapine [10,12], but others found improvement in motor signs [13,14]. Expert consensus is that clozapine does not substantially worsen motor signs in PD. One study even suggested that clozapine may reduce mortality [15]. However, along with various dose-related side effects, clozapine carries the risk of severe neutropenia in about 0.3%-1.0% of patients, unrelated to dose [16,17]. This risk is mitigated by weekly to monthly blood tests, but the frequent venipuncture and the coordination between prescriber, laboratory and pharmacy are difficult for many patients. In this population, clozapine is usually started at 6.25 at bedtime. Scheduled monitoring of neutrophil counts must be followed as per accepted guidelines (www.clozapinerems.com). The final total daily dose of clozapine in PD psychosis typically ranges from 12.5mg to 150mg.

Recently pimavanserin, a serotonin 2A receptor inverse agonist, was approved by the U.S. Food and Drug Administration (FDA) for treatment of psychosis in PD. Phase II studies had shown good tolerability and a nonsignificant trend for better efficacy compared to placebo [18]. The pivotal clinical trial was a randomized double-blind study in which pimavanserin at 34mg daily reduced psychotic symptoms significantly more than placebo [19,20]. The decrease in psychotic symptoms was evident at 2 weeks, but separated from placebo only at the 4-week follow-up visit, with further improvement at 6 weeks. Therefore 4-6 weeks at full dose likely are required for a reasonable trial of pimavanserin. Sleep pattern, caregiver burden and other exploratory outcome measures also improved significantly more with active drug. Importantly, pimavanserin did not worsen motor function.

Poorly tolerated or unproven treatments

Until recently, the only available treatments for psychosis consisted of reducing dopaminergic tone. At its extreme, this consisted of removing all antiparkinsonian medications for a period of time, a so-called "drug holiday." As Friedman observed, however, this was "not a holiday in the usual sense," since motor function quickly worsened [21]. In fact, patients could

develop a neuroleptic malignant syndrome–like presentation, which occasionally could be lethal. Dopamine D2-like receptor (D2R) antagonists prior to the 1990s all had unacceptable motor side effects.

In the 1990s and 2000s, newer ("atypical") antipsychotics were tried eagerly in PD psychosis in hopes of better tolerability [22]. Like their predecessors, they block dopamine at D2-like receptors, but have more complex pharmacology, often including serotonin 5HT2 receptor antagonism or lower affinity for striatal D2Rs, and cause fewer motor side effects in patients with schizophrenia [23]. Small, open trials with remoxipride and zotepine generally seemed positive, but several patients experienced intolerable motor side effects [24-28]. Risperidone at low dose showed some promise in early reports [29-31], but intolerable motor side effects in others [32]. In the only controlled trial with risperidone in PD, it was more effective than clozapine but less well tolerated [33]. In controlled trials, olanzapine proved superior to placebo for PD psychosis [34], but worsened motor function [35-37].

Ziprasidone showed minimal deterioration in motor signs in open studies [38,39] and in a blind comparison with clozapine [40]. However, some patients do show motor worsening on ziprasidone, e.g. 1 of 5 patients in a small series [41], and the drug is not widely accepted as benign in this population. Melperone was well tolerated in a double-blind, placebo-controlled trial in 90 PD patients with psychosis, but unfortunately the groups did not differ significantly in terms of psychotic symptoms [42] (see also ClinicalTrials.gov, https://clinicaltrials.gov/ct2/show/NCT00125138). The D2R partial agonist aripiprazole produced mixed results in small, open series, with worsening of parkinsonism in 25-36% of patients [43,44].

Case series and open trials of quetiapine in PD psychosis reported good tolerability and overall improvement in psychosis. Some measures of psychosis improved in one RCT of quetiapine [45], and comparative studies found similar benefit with quetiapine and clozapine [14,46]. However, other studies found greater antipsychotic benefit from clozapine than from quetiapine [47], or found improvement with clozapine in most patients who had not improved on quetiapine [48]. Finally, no controlled trials of quetiapine in PD have yet found superiority to placebo on the primary outcome measure [45,46,49-53]. Nevertheless, given its good tolerability, many physicians still turn first to quetiapine in PD. Typical final doses range from 25-150mg nightly, though daily doses as high as 600mg have been used [52].

A number of other drugs, and electroconvulsive therapy, have been reported to be helpful for PD psychosis in case series or open studies [54-56], but none of these has proven better than placebo in a controlled trial [57]. Some clinicians recommend a trial of cholinesterase inhibitors, suggested by experience in Lewy body dementia, though evidence for efficacy in PD is limited [58-63]. Various nonsomatic treatments have also been suggested, from keeping a light on at night to a caregiver-implemented psychosocial support intervention [54,64]. Optimizing the environment to maximize orientation is often recommended, and is a benign and inexpensive intervention. However, none of these nonsomatic interventions have been tested in a controlled trial for efficacy in PD.

Conclusion

With the background above, one can lay out a reasonable plan for treatment of psychosis in PD

Box 2

Treatment strategy for psychosis in Parkinson's disease

1. Psychosis in Parkinson's disease is a serious medical condition, and treatment should be directed by an appropriately trained physician who can adapt the suggestions below to the specific situation of the individual patient
2. Confirm the diagnosis
   - ◊ careful history and mental status examination
   - ◊ exclude or treat delirium
3. Simplify antiparkinsonian medications
   - ◊ remove anticholinergics, amantadine and dopamine agonists
   - ◊ increase dose of levodopa as needed for motor function
4. If symptoms persist, add medication targeting psychotic symptoms
   - ◊ pimavanserin is an appropriate first choice in most cases
   - ◊ switch to clozapine if an adequate trial of pimavanserin is ineffective
5. If these treatments are ineffective, review diagnosis and medication list and consider quetiapine or other treatment options

(see Box 2). As in all of medicine, patients' symptoms and response to treatment vary, and individual adaptation may be needed. None of the currently available treatments is effective in every patient, and new treatment research is needed. Several clinical trials are currently active as of this writing (http://bit.ly/PDP_clinical_trials). Additional future studies could include testing higher doses of pimavanserin if the usual dose is ineffective, or identifying patient characteristics that predict better response to clozapine. In summary, for Parkinson's disease patients who develop psychosis, the prognosis is much better now than 20 years ago, and one can reasonably expect further progress over the next 20 years.

Resumo

Frue dum la evoluado de malsano de Parkinson (MP), traktado kutime sukcesas. Tamen, post kvin aŭ dek jaroj, la stato komencas ŝanĝi pro tio, ke la paciento bezonas pli altaj dozoj de medikamentoj, kaj kromefikoj fariĝas pli problemaj. Unu el la plej seriozaj problemoj estas la apero de halucinoj aŭ iluzioj. Dum la 20-a jarcento, kuracadoj estis nepruvita kaj nekontentiga, sed la pasintaj 20 jaroj alportis gravajn ŝanĝojn. Du medikamentoj, kiuj estas bone tolereblaj en MP jam montriĝis efikaj en lotumataj, kontrolitaj provoj, kaj oni disvolvas aliajn. Ĉi tie mi mallonge resumas tiun historion kaj provizas ĝeneralan planon por trakti MP komplikata de psikozaj simptomoj.

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Competing interests

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