SUMMARY
This publication offers a review of the pharmacological interventions studied for Parkinson’s disease psychosis. Before initiating drug therapy for psychosis, possible contribution of antiparkinsonian medications to psychosis must be minimized by reducing their dose and completely switching them to levodopa if indicated. As a group, second-generation antipsychotics have been studied the most for Parkinson’s disease psychosis. Evidence of efficacy for psychosis and safety for motor side effects is strongest for clozapine but routine use of clozapine is limited by its potential to cause agranulocytosis and the stringent monitoring requirements. Based on several open-label studies, quetiapine appeared to be a reasonable alternative, but recent double-blind studies create uncertainty about its efficacy. Olanzapine and aripiprazole have limited efficacy and are associated with worsening of motor symptoms. Literature is limited and lacks clarity about the utility of risperidone and ziprasidone in this scenario. Recently, encouraging literature has emerged on the use of donepezil and rivastigmine in patients with Parkinson’s disease dementia and psychosis. There is a considerable need to further study the existing drugs and explore other pharmacotherapies in Parkinson’s disease psychosis. Future research should ensure sound methodological quality and control for confounding variables to provide results that could be used reliably in clinical practice.
INTRODUCTION

Parkinson’s disease (PD) is the second most common neurodegenerative disease after Alzheimer’s disease, affecting about 1 to 2% of the population over the age of 65 years (1). The cardinal features of PD are “motor” in nature (tremor, rigidity and bradykinesia) but “non-motor” features including neuropsychiatric symptoms, sleep disturbances and autonomic dysfunction are present in most patients with PD (2).

Psychosis is a common neuropsychiatric complication of PD resulting from a complex interaction between factors related to the disease and medications used to treat its motor features (3). It presents usually as visual hallucinations and occasionally as delusions or hallucinations in other modalities. Estimates about the prevalence of psychosis or individual psychotic symptoms in PD patients on anti-PD drug treatment vary greatly depending upon the definition of psychosis used, method of assessment and the patient population studied. On average, about one-third of patients with PD experience visual hallucinations, 20% experience auditory hallucinations and 5% suffer from delusions (4). The overall prevalence of psychosis in patients with PD over the last few days to several months approaches 75% when psychosis is defined loosely to include a variety of unusual perceptual phenomenon and the patient population studied has advanced PD with cognitive deficits (3). PD psychosis (PDP) adds to patient distress and disability, is associated with increased caregiver burden and is predictive of nursing home placement (5-7).

Treating PDP could be very challenging. Attempts to switch patient’s anti-PD medications to levodopa only and decrease its dose to the lowest effective level could worsen patient’s motor symptoms and may not result in resolution of psychosis. Pharmacotherapy to treat psychosis is thus inevitable in most cases. Second-generation antipsychotics (SGAs) have been used over the last couple of decades as an initial intervention. More recently, cholinesterase inhibitors (ChEIs) appear promising in PDP patients with dementia. This article reviews the literature on pharmacotherapy of PDP, provides guidance on clinical management of PDP and makes suggestions about future research on pharmacotherapy of PDP.

METHODS OF LITERATURE SEARCH

Literature was searched during the later part of November 2010 using PubMed and Scopus. Without setting limits for publication year, PubMed was searched for English literature indexed as “clinical trial”, “randomized controlled trial” or “case report” for the term “Parkinson’s disease” in combination with “psychosis, hallucinations or delusions”. From the 392 results, publications relevant to this article were identified either by reading the abstract or the publication if it did not have an abstract. The PubMed search was substantiated by searching Scopus for English literature using the same search settings and search phrases. The Scopus search identified several older relevant literature that were not included in the PubMed results. To keep the review focused, reports published as abstracts or presented as posters, and other publications not specifically discussed in this review are not cited individually.

ANTIPSYCHOTIC DRUGS FOR PARKINSON’S DISEASE PSYCHOSIS

Clozapine

Scholz and Dichgans (8) first reported successful treatment of PDP in four PD patients with clozapine (dose range 25-100 mg/day) without worsening of their motor symptoms. Numerous publications with similar findings followed. Factor et al. (9) reviewed 16 reports published between 1985 and 1994. A total of 136 patients were treated with clozapine 3.125 mg/day to 400 mg/day (mostly less than 175 mg/day) for 1 to 36 months. A total of 111 (82%) patients responded with complete or partial resolution of psychosis; 24 (18%) patients withdrew from treatment mostly because of adverse effects, or due to lack of efficacy. Parkinsonism worsened in eight patients (six were in a study in which mean dose of clozapine was 170.8 mg/day) and improved in five patients. Agranulocytosis was reported in one patient. Auzou et al. (10) reviewed 25 publications (1985 through 1995) reporting the use of clozapine for PDP. All together, more than 200 patients received clozapine. Overall efficacy of clozapine was about 90%. In most studies, clozapine was effective at doses less than 125 mg/day. Psychosis mostly resolved within a couple of weeks of clozapine treatment. Efficacy tended to diminish over time, which could be explained either by the necessity to increase the dose of anti-PD medications or the progression of dementia. Aggravation of parkinsonism occurred very rarely with doses less than 100 mg/day.

Several case reports, open-label trials and retrospective reviews have been published since the review by Auzou et al. (10) replicating previous observations. Widman et al. (11) reported a positive experience with the use of clozapine in 27 patients with PDP, 14 of whom were treated for longer than a year. In a well-designed, 12-month open-
label trial performed on 36 patients with PDP who continued to have psychotic symptoms despite adjustment of their anti-PD medications, Ruggieri et al. (12) documented sustained efficacy (measured by Brief Psychiatric Rating Scale [BPRS] scores) of very low doses of clozapine (mean dose 10.59 mg/day, range 6.25-25 mg/day) over the study period. Unified Parkinson’s Disease Rating Scale (UPDRS) scores remained unchanged but patients required a small, insignificant increase in the dose of levodopa. Daily clozapine doses correlated significantly with BPRS scores. Side effects were transient and manageable, and did not result in patient dropout.

Trosch et al. (13) reviewed the medical records of 172 consecutive PD patients treated with clozapine. Visual hallucinations were reported by 114 patients, auditory hallucinations by 9 patients and delusions by 64 patients. Response rates of these symptoms to clozapine (mean dose 30.5 mg/day titrated over a mean duration of 52 days) were 89.5, 88.9 and 90.6%, respectively. In all, 23% of patients withdrew as a result of adverse events or treatment failure. Common adverse effects reported by the entire sample were sedation (46%), diarrhea (11%) and postural hypotension (10%). Motor worsening occurred in nine patients (5.2%) and lead to discontinuation of clozapine in four of them. Four patients (2.3%) developed neutropenia that resolved without a need to discontinue clozapine. Inpatient clozapine initiation did not improve therapeutic efficacy, or reduce adverse events or the withdrawal rate.

The first placebo-controlled trial (14) failed to document clozapine efficacy and safety due to a very small sample size (six patients), “clozapine to placebo lead-in” design (clozapine was titrated over 10 days, maintained over the next 10 days, and then replaced with placebo over the next 4 days), and rapid titration of clozapine to high doses (mean dose 170.8 mg/day) within 10 days. All subsequent randomized, double-blind, placebo-controlled trials of clozapine for PDP (15-17) (Table I) using lower doses and slower titration schedules have demonstrated clozapine efficacy for PDP and safety for motor side effects. The two trials with an open clozapine lead-in follow-up (i.e., patients in the placebo group were started on clozapine during the open-study period) (15, 17) (one reported as a separate publication [18]) observed therapeutic response comparable to the clozapine group after initiation of clozapine in patients originally in the placebo group.

**Risperidone**

The first open-label trial (19) reported risperidone (mean dose 0.67 mg/day) causing resolution of psychosis in all six patients without worsening their motor symptoms. The enthusiasm about having a possible replacement for clozapine was quickly dampened by the discouraging findings of two subsequent publications (20, 21). Ford et al. (20), in an open-label trial on six patients, found risperidone (mean dose 1.5 mg/day) effective for psychosis, but it caused motor worsening in all patients. The findings of Rich et al. (21) portrayed an even bleaker picture. In their experience on six patients with parkinsonism, risperidone (dose ≥ 2 mg/day in five patients), five of the six patients experienced intolerable exacerbation of parkinsonism requiring immediate discontinuation of risperidone.

Three years after their first publication, Meco et al. (22) reported results of their long-term (mean duration of follow-up 34.8 weeks) open-label trial on 10 patients with advanced PD (with dementia in most) and psychosis. Risperidone (mean dose 0.73 mg/day, range 0.25-1.25 mg/day) was found to be effective in 9 out of 10 patients in short-term but treatment was discontinued or interrupted in 7 patients after week 16 due to recurrence of psychiatric symptoms (1 patient), motor worsening (2 patients), hospitalization for agitation (1 patient) and for confusion (1 patient), death (1 patient) and personal reasons (1 patient).

In an open-label design, Mohr et al. (23) found risperidone (mean dose 1.1 mg/day, range 0.5-2.0 mg/day) to be effective in 17 patients with PDP and dementia (median Mini-Mental State Examination [MMSE] score 22.5) over a 12-week period. They did not observe a significant decrease in the UPDRS total and motor score but hypokinesia was reported as an adverse effect in 10 out of 17 patients.

The trial by Leopold et al. (24) is the biggest in terms of patient number. In this open-label study, 39 patients with parkinsonism and psychosis were treated prospectively for 6 months with risperidone. Thirty-two patients had PD, six had dementia with Lewy bodies (DLB) and one had multiple system atrophy. Risperidone treatment (mean dose 1.10 mg/day, range 0.5-3 mg/day) resulted in complete or almost complete resolution of hallucinations and delusions in 23/39 patients and an estimated 50-75% reduction in another four patients. Response was limited in six patients and risperidone was stopped in another six patients (two of whom had PD) due to motor deterioration. For the 16 patients who completed the 26-week trial, mean UPDRS did not change significantly. Response to treatment was not influenced by the MMSE score prior to treatment.
### Table I. A summary of major randomized, placebo-controlled trials of clozapine (15-17), olanzapine (30, 31) and quetiapine (43-45) for Parkinson’s disease psychosis.

<table>
<thead>
<tr>
<th>Study (year; ref.); description</th>
<th>Patient characteristics and baseline values of outcome variables*</th>
<th>Antipsychotic drug treatment</th>
<th>Outcome with regards to psychosis and motor symptoms</th>
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<tbody>
<tr>
<td><strong>Clozapine</strong></td>
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<tr>
<td>The French Clozapine Parkinson Study Group (1999; 16)</td>
<td>Mean baseline values for the entire sample were as follows: age: 72 years; duration of PD: 12 years; PANSS positive subscore: 16.6; UPDRS motor score: 33.5; and H&amp;Y stage 3.2. Mean baseline CGIS score not reported. Mean MMSE score was significantly higher in the clozapine (26.1) than the placebo group (24.1).</td>
<td>The initial clozapine dose of 6.25 mg/day was titrated over at least 10 days to a maximum of 50 mg/day. At the end of the study, the mean daily dose of clozapine was 36 mg.</td>
<td>Patients in clozapine group showed significant improvement on the CGIS score and PANSS positive subscore. The UPDRS or MMSE mean scores did not change significantly.</td>
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<tr>
<td>A 4-week, multicenter trial; 32 patients in the clozapine group, 28 in the placebo group.</td>
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<tr>
<td>The Parkinson Study Group (1999; 17)†</td>
<td>Mean baseline values for placebo and clozapine groups, respectively, were age: 71.9 and 70.8 years; duration of PD: 10.4 and 10.8 years; H&amp;Y stage: 2.8 and 2.6; UPDRS motor score: 37.1 and 32.8; BPRS score: 35 and 33.1; SAPS score: 22.4 and 20.9; CGIS score: 4.4 and 4.4; and MMSE score: 21.7 and 23.8.</td>
<td>Clozapine was started at 6.25 mg/day. The dose could be increased (up to a maximum of 50 mg/day) or decreased by 6.25 mg/day once between weekly office visits or at the visit. The final mean dose of clozapine was 24.7 mg/day.</td>
<td>Clozapine was significantly superior to placebo on all measures of psychosis (BPRS, SAPS and CGIS scores). Change in UPDRS (tremor, motor and all) and MMSE scores did not differ between groups.</td>
</tr>
<tr>
<td>A 4-week, multicenter trial; 30 patients each in clozapine and placebo groups.</td>
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<tr>
<td>Pollak et al. (2004; 15)†</td>
<td>Mean values for clozapine and placebo groups, respectively, were age: 71.2 and 72.8 years; duration of PD: 12.1 and 11.3 years; H&amp;Y stage: 3.3 and 3.1; UPDRS motor score: 31.5 and 31.4; positive PANSS score: 17.8 and 15.3; CGIS score: 5.1 and 4.9; and MMSE score: 26.1 and 24.1.</td>
<td>Starting daily dose of 6.25 mg, followed, if necessary, by progressive dose increases up to a maximum daily dose of 50 mg, which could not be reached within less than 10 days. Final mean dose of clozapine was 35.8 mg/day.</td>
<td>CGIS and positive PANSS scores decreased significantly in the clozapine group only. The between-group difference was significant. The UPDRS and MMSE scores were unchanged in both groups.</td>
</tr>
<tr>
<td>A 4-week trial; 32 patients in the clozapine group and 28 in the placebo group.</td>
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<tr>
<td><strong>Olanzapine</strong></td>
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<td>Ondo et al. (2002; 31)</td>
<td>For the entire sample, mean values were age: 71 years; duration of PD: 9.1 years; H&amp;Y score (during off periods): 3.2; and MMSE score: 26.8. Hallucination severity was assessed by a structured interview.</td>
<td>Olanzapine was started at 2.5 mg/day with an option to increase the dose to 5 mg/day in week 3 and again in week 6. The final mean dose of olanzapine was 4.6 mg/day.</td>
<td>Olanzapine was started at 2.5 mg/day with an option to increase the dose to 5 mg/day with no significant improvement in olanzapine versus placebo. Scores on measures of psychosis improved on olanzapine but not significantly.</td>
</tr>
<tr>
<td>A 9-week trial; 18 patients in the olanzapine group and 12 in the placebo group.</td>
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<tr>
<td>Breier et al. (2002; 30)</td>
<td>For the entire sample the range for mean age was 70.5-73.5 years and for age of onset of PD was 55.4-61.1 years. Most had moderate to severe H&amp;Y stage of parkinsonism. Slightly &gt; 1/3 had MMSE score &lt; 24. BPRS positive and NPI total scores indicated mild levels of psychopathology.</td>
<td>Starting dose was 2.5 mg/day. Patients could have their dose increased by 2.5 mg/day every 3 to 4 days up to a maximum of 15 mg/day. Dosage decreases could occur at any time by any number of decrements. Mean modal doses of olanzapine were 4.2 (US) and 4.1 (Europe) mg/day.</td>
<td>No significant improvement in the olanzapine group compared with the placebo group. Olanzapine performed significantly worse than placebo in both studies on measures of motor functioning.</td>
</tr>
<tr>
<td>A multicenter 4-week trial; center/olanzapine group/placebo group: US/41/42; Europe/49/28.</td>
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</table>

*Continued*
Wolters et al. (25) were the first to report use of olanzapine to treat psychosis in 15 patients with PD without dementia over a period of 2 months. Olanzapine was started at 1 mg/day and slowly optimized between day 8 and day 50 to a maximum of 15 mg/day. The final daily dose was 2-15 mg/day (mean 6.5 mg/day). Olanzapine significantly reduced psychotic symptoms within 2-5 weeks without any motor worsening. The therapeutic challenge of increase in the dose of anti-PD medications between days 50 and 64 was well tolerated and improved residual motor symptoms.

The encouraging findings by Wolters et al. could not be replicated in several subsequent studies. In a trial by Friedman (26), 5 out of 9 (or 10!) patients with presumed PD benefited from olanzapine but mild worsening of parkinsonism was noted in 3 of them. Similarly, Graham et al. (27) based on a case series of 5 patients with PDP...
and Molho et al. (28) based on a retrospective review of 12 patients with anti-PD drug-induced psychosis observed that olanzapine may be beneficial for PDP but is poorly tolerated with regards to motor symptoms, particularly in doses above 5 mg/day. The results were even more disappointing in a 6-week open-label trial (29) in which four of the five patients terminated trial early due to adverse effects.

In the three randomized, double-blind placebo-controlled trials on olanzapine for PDP (30, 31) (the publication by Breier et al. [30] reported findings of two trials—one conducted in U.S. and the other in Europe), olanzapine was not better than placebo for psychosis and was significantly worse than placebo in terms of motor side effects (Table I).

**Quetiapine**

A few initial small reports (32-34) described successful use of quetiapine to treat psychosis in patients with advanced PD without worsening their motor symptoms, but one case report (35) described it to worsen parkinsonism in two patients even at doses less than 75 mg/day.

Fernandez et al. (36) performed an open-label trial on 35 patients with PDP. The patients were 58-89 years old, had PD from 1-24 years, and severity of their PD ranged between Hoehn and Yahr stage 2.5-5. Twenty of the 35 patients were demented. Among the 24 antipsychotic-naive patients, psychosis improved or resolved in 20 patients (83% efficacy) with quetiapine (dose range 12.5 mg to 75 mg/day) without motor worsening over 8 weeks. Three patients could not tolerate quetiapine due to orthostatic hypotension, headache, nausea and persistence of hallucinations. For the 11 patients previously taking clozapine (8 patients) or olanzapine (3 patients), switch to quetiapine was not possible in 6 (5 on clozapine, 1 on olanzapine) because of confusion, erratic behavior and increased hallucinations.

Fernandez et al. (37, 38), based on chart reviews, reported long-term efficacy of quetiapine for PDP to be about 80% and risk of motor worsening with it to be approximately 32%. In the authors’ observation, the motor worsening represented natural progression of disease, not side effects of quetiapine. Klein et al. (39) followed 35 PDP patients being treated with quetiapine for 2 years. Overall treatment response at the end of the study was 43% (mean dose 93 mg/day). Major reasons for discontinuation were lack of efficacy and somnolence. In another long-term study on 35 patients (40), response rate at 12 months was 31% for hallucinations (mean dose 110 mg/day) and 38% for delusions (mean dose 265 mg/day). Quetiapine was not associated with significant changes in motor or cognitive function. A 24-week open-label trial (41) also reported quetiapine to be effective in patients who had failed treatment with clozapine, risperidone or olanzapine.

Among all these positive studies, one 6-month open-label study (42) on 35 consecutive PDP patients reported quetiapine to have limited efficacy for PDP with a potential to worsen motor symptoms in PD patients with dementia at a mean dose of 150.9 mg/day (mean dose in patients without dementia was 76.3 mg/day). In all the randomized, double-blind, placebo-controlled studies so far (43-46), quetiapine did not worsen motor symptoms but had very limited efficacy for PDP (Table I; one study [46] not shown because its small sample size does not allow any conclusive interpretation of the results).

**Ziprasidone**

In all case reports combined (47-50), use of oral ziprasidone for PDP has been described in seven patients. In most cases, ziprasidone was used after a trial of another SGA had failed. Doses of ziprasidone used ranged from 40 to 80 mg/day. Psychosis improved in six out of seven patients without motor deterioration. In one of these reports (49), two of four patients developed pathological laughing, apparently as an adverse effect of ziprasidone. Successful use of parenteral ziprasidone (10-20 mg) to control acute psychosis and agitation in five PD patients without their motor worsening has also been reported (51).

Gomez-Esteban et al. (52) conducted a 12-week open-label trial on 12 patients with PDP. One patient withdrew due to somnolence and one due to gait difficulties within the first week. In the remaining 10 patients, measures of psychosis improved significantly over the study period. Motor symptoms did not worsen significantly but score on Abnormal Involuntary Movement Scale tended to decline \( (P = 0.063) \). The final mean dose of ziprasidone in this study was 32 mg/day.

**Aripiprazole**

Lopez-Meza et al. (53) reported successfully treating PDP in three patients with aripiprazole 15 mg/day without worsening of their motor symptoms. Others (54, 55) found it to be ineffective and associated with motor worsening.
Fernandez et al. (56) reported their preliminary experience in use of aripiprazole for PDP in eight patients. Five patients were “quetiapine failures”, one patient was switched from olanzapine to aripiprazole and two were antipsychotic-naive. Aripiprazole was started at 5-10 mg/day and slowly increased over 3 to 7 days until side effects or improvement of psychosis occurred. Only two out of eight patients experienced near complete resolution of their psychosis. The other six patients discontinued aripiprazole within 40 days, two due to motor worsening. An open-label study by Friedman et al. (57) gave similar results. Eight out of 14 patients enrolled in the 6-week trial dropped out prematurely because of adverse effects including worsening of motor and psychotic symptoms. Aripiprazole (dose less than 5 mg/day) was marginally effective in the remaining six. Only four subjects had improvement in psychosis without any motor worsening.

**Comparison between SGAs for PDP**

It is obvious from studies on individual SGAs that they differ in their efficacy and safety in PDP. Case reports and open-label studies describing patients not responding or showing poor tolerance to one SGA but responding to or better tolerating another SGA provide further support to their differential effect (39, 41, 58, 59). Furthermore, several double-blinded or rater-blinded trials have specifically compared two SGAs with each other on their relative efficacy and safety in PDP (60-63). These studies, summarized in Table II, affirm the superior efficacy of clozapine and the potential of olanzapine to worsen motor symptoms in PDP patients.

### Table II. Major studies comparing second-generation antipsychotic medications on their efficacy and safety in Parkinson’s disease psychosis (60-63).

<table>
<thead>
<tr>
<th>Study; (year; ref.); description</th>
<th>Drug (mean dose): patients (recruited/completed)</th>
<th>Outcome measures</th>
<th>Final outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ellis et al. (2000; 60)</td>
<td>Clozapine (62.5 mg/day): 5/3 Risperidone (1.2 mg/day): 5/4 Data from 4 subjects on clozapine and 5 on risperidone were used for the analyses.</td>
<td>BPRS UPDRS</td>
<td>Mean improvement in the BPRS psychosis score was similar in both groups. The mean motor UPDRS score worsened in the risperidone group and improved in the clozapine group but the difference did not reach statistical significance.</td>
</tr>
<tr>
<td>Goetz et al. (2000; 61)†</td>
<td></td>
<td>BPRS UPDRS</td>
<td>Between-groups change in the UPDRS scores from baseline to study end was significant. Number of subjects was not enough to test fully for significant differences between olanzapine and clozapine efficacy on psychosis.</td>
</tr>
<tr>
<td>Randomized, double-blind trial of up to 2 months.</td>
<td>Clozapine (25.8 mg/day): 8/5 Olanzapine (11.4 mg/day): 7/1 The trial was terminated because of exacerbated parkinsonism in olanzapine-treated subjects.</td>
<td>BPRS SAPS UPDRS</td>
<td></td>
</tr>
<tr>
<td>Morgante et al. (2004; 63)*</td>
<td>Clozapine (26 mg/day): 23/20 Quetiapine (91 mg/day): 22/20 Final analysis was done on patients completing the study.</td>
<td>BPRS CGIC UPDRS AIMS</td>
<td>No between-group differences on UPDRS and AIMS scores.</td>
</tr>
<tr>
<td>A 12-week, randomized, open-label, rater-blinded trial.</td>
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<tr>
<td>Merims et al. (2006; 62)</td>
<td>Clozapine (13.1 mg/day): 14/7 Quetiapine (90.9 mg/day): 13/9</td>
<td>NPI-(H,D) CGIC</td>
<td>NPI-(H,D) scores showed greater improvement with clozapine than quetiapine. Decrease in CGIC-Q scores was comparable between groups. UPDRS scores did not change much in either group.</td>
</tr>
</tbody>
</table>

*The publication reporting preliminary results by Morgante et al. (108) is not shown in this table to prevent duplication. †Safety stopping rules were invoked because of exacerbated parkinsonism in olanzapine-treated subjects. AIMS, Abnormal Involuntary Movement Scale; BPRS, Brief Psychiatric Rating Scale; CGIC-Q, Clinical Global Impression of Change; CGI-Q, Clinical Global Impression Scale; NPI-(H,D), Neuropsychiatry Inventory - hallucination and delusion items; SAPS, Scale for the Assessment of Positive Symptoms; UPDRS, Unified Parkinson’s Disease Rating Scale.

M. Hasnain

**PSYCHOSIS IN PARKINSON’S DISEASE**

THOMSON REUTERS – Drugs of Today 2011, 47(5)
Relative potential of SGAs to cause extrapyramidal side effects in patients without PD

Rummel-Kluge et al. (64) recently performed a systematic review and meta-analysis of 54 randomized, blinded studies comparing various SGAs in the treatment of schizophrenia or related disorders to determine their extrapyramidal side effect (EPS) safety profile. Primary outcome measure was “use of antiparkinson medication” and the secondary outcome measures were changes in the Barnes Akathisia Scale and the Simpson Angus Scale from baseline to the end of the study. Mean age of the study participants was in the mid-30s. Risperidone was associated with more use of antiparkinson medication than clozapine, olanzapine, quetiapine and ziprasidone. Ziprasidone showed more use of antiparkinson medication than olanzapine and quetiapine, aripiprazole more than olanzapine, and zotepine more than clozapine. There was no significant difference between amisulpride and its comparators (olanzapine, risperidone or ziprasidone). Quetiapine showed significantly less use of antiparkinson medication than the other three SGAs it was compared with (olanzapine, risperidone and ziprasidone). Scale-derived data were limited but generally substantiated these findings. The comparisons of risperidone and olanzapine and risperidone and ziprasidone did not remain significant when all risperidone studies with a mean daily dose over 6 mg were excluded.

Relative potential of SGAs to cause EPS in individuals with dementia

SGAs are frequently used in older adults to control psychotic and behavioral symptoms associated with dementia. Rochon et al. (65) performed a retrospective cohort study on adults 66 years and older who had dementia and were not exposed to an antipsychotic medication in the previous year. Individuals with a history of PD, defined as those dispensed drug therapy specific for PD were excluded. The final cohort consisted of 11,571 individuals receiving an atypical antipsychotic, 14,198 receiving a typical antipsychotic and 32,069 receiving neither agent. The antipsychotic drug group was followed up for evidence of parkinsonism (new PD diagnosis or the dispensing of an antiparkinsonian drug) during their period of continuous drug use for up to 1 year after their index claim. None of the patients had side effects or deterioration of parkinsonian symptoms. The beneficial effect of donepezil on psychosis in patients with PD with dementia (PDD) is also noted in the 20-week open-label study by Thomas et al. (69) comparing the efficacy of donepezil in patients with PDD and DLB. UPDRS motor scores did not change significantly from baseline in either group.

CHOLINESTERASE INHIBITORS

Donepezil

Kurita et al. (66) reported successful resolution of visual hallucinations with donepezil 5 mg/day in three PD patients without their motor worsening. One patient developed delusions while on donepezil. The delusions disappeared after discontinuation of donepezil but visual hallucinations recurred. Fabbrini et al. (67) conducted a 2-month open-label study in eight PDP patients using donepezil 5 mg/day. Patients had PD for a mean duration of 7.5 years and their baseline MMSE score was 25.2. Antipsychotic drugs were not allowed, and the dose of levodopa was maintained stable during the study period. Hallucinations and delusions improved significantly in all patients. Donepezil was overall well tolerated, but motor worsening was noted in two of eight patients.

Bergman et al. (68) studied donepezil (up to 10 mg/day) in six patients with PD (range of duration 3–7 years) and dementia (baseline mean MMSE score 22.2) complicated by psychosis. All patients were taking anti-PD medications. Five patients had clinically significant (more than 53%) improvement on measures of psychosis and one patient had minimal (24%) improvement after 6 weeks of the treatment. None of the patients had side effects or deterioration of parkinsonian symptoms. The beneficial effect of donepezil on psychosis in patients with PD with dementia (PDD) is also noted in the 20-week open-label study by Thomas et al. (69) comparing the efficacy of donepezil in patients with PDD and DLB. UPDRS motor scores did not change significantly from baseline in either group.

Rivastigmine

Bullock et al. (70) reported a case series of five patients with PD treated with rivastigmine. Four patients had dementia, and visual hallucinations were present in the
four. Duration of treatment with rivastigmine ranged from 5 to 13 months. Dose of rivastigmine was slowly increased to 6 mg twice a day after 13 weeks. Visual hallucinations resolved in two patients and improved in the other two. Overall, rivastigmine was well tolerated.

In a well-designed, open-label study, Reading et al. (71) evaluated rivastigmine for neuropsychiatric symptoms of PDD in 15 patients who had no psychiatric or cognitive symptoms for at least 2 years prior to the diagnosis of PD, were on stable anti-PD medications, were not taking antipsychotic or anticholinergic medications, and had an MMSE score of over 10. Rivastigmine was initiated at 1.5 mg twice a day and titrated every 2 weeks to a maximum of 6 mg twice a day or the highest tolerated dose. Patients were reassessed 8 weeks after the highest dose, then 6 weeks later (experimental session). At this point, the drug was discontinued and a final assessment undertaken 3 weeks later (withdrawal session). Patients improved significantly on measures of psychosis and cognition from baseline to the experimental session and deteriorated significantly after withdrawal of rivastigmine. Rivastigmine did not cause motor worsening. The only significant side effect was nausea which limited the dose escalation in nine patients.

A large double-blind, placebo-controlled study (72) on patients with PDD has documented a significant benefit of rivastigmine (assessed 6 months from baseline) on the neuropsychiatric symptoms of hallucinating PDD patients but not in nonhallucinating patients without worsening of their motor symptoms. The authors did not specify whether the improvement was specifically due to a decrease in hallucinations. Similarly, Emre et al. (73) reported a decrease in the Neuropsychiatry Inventory Scores of PDD patients treated with rivastigmine without specifying the reason for this decrease. In both these studies, rivastigmine was not associated with a decrease in the use of antipsychotic medications.

**Galantamine**

Relative to donepezil and rivastigmine, literature on possible utility of galantamine in PDP is very limited. In an 8-week, open-label trial of galantamine (final dose 8 mg twice a day) in 16 patients with PDD (74), hallucinations improved in 7 of the 9 patients. Improvement of global mental symptoms was noted in eight patients, whereas worsening was reported in four. Parkinsonism improved in six patients, but a mild worsening of tremor was noted in three.

**RARELY STUDIED DRUGS WITH SOME EVIDENCE OF EFFECTIVENESS**

Melperone is an older “atypical” antipsychotic with both serotonin 5-HT₂A receptor and dopaminergic D₂ receptor blocking properties. A 2-year open-label study on 30 patients found it to be effective for PDP as measured by BPRS score without worsening of motor symptoms that were monitored by UPDRS. Only two patients dropped out over the course of the study (75).

One open-label study (76) of 4-8 weeks on patients with advanced PD found ondansetron quite effective for PDP without any adverse effects, but another 2- to 6-week open-label study (77) on seven clinically similar patients found it ineffective.

Mianserin, an older antidepressant with 5-HT₂A receptor blocking properties, has also been reported to be effective (based on slightly modified BPRS scores) in PDP. It improved average UPDRS scores slightly but significantly and was well tolerated overall. Its effectiveness was maintained in 10 out of 12 patients initially responding to it over several months of follow-up (78).

Pimavanserin, an experimental compound with inverse 5-HT₂A receptor agonist activity and no significant affinity for dopaminergic receptors, was recently reported in a multicenter, double-blind, placebo-controlled, 28-day study to cause significantly greater improvement in psychosis than placebo in patients with PDP without impairing motor function or causing significant side effects (79). But, as disclosed by the company researching the compound, results from the pivotal phase III trial with pimavanserin did not meet its primary endpoint of antipsychotic efficacy in patients with PDP (80).

Memantine has also been reported to diminish hallucinations in patients with PDD (81).

**DISCUSSION**

Despite the best evidence of efficacy for over a decade, clozapine could not become the first-line treatment for PDP in routine practice because of its potential to cause agranulocytosis and the stringent monitoring requirements. Risperidone, the first of the “new” SGAs, appeared promising initially but soon a series of studies reported its limited efficacy in PDP and potential to worsen motor symptoms. The same sequence of events was repeated after the introduction of olanzapine. Several case reports and open-label studies documenting the efficacy and safety of quetiapine helped it become the preferred treatment (82), but recent double-
blind studies (44, 45) failing to document its efficacy diminish its role in PDP.

Management of suspected PDP should start with a comprehensive assessment. Psychosis in a patient with PD may be a feature of another psychopathology, e.g., a mood or primary psychiatric disorder, which would be managed differently than PDP. A thorough review of presenting complaints, alcohol and substance abuse history, past psychiatric history, family history, and a detailed assessment of the mental status would help make this differentiation. The risk of delirium increases with aging and patients with PD may be particularly vulnerable to it due to the underlying neuropathology (83). Delirium should be ruled out as a potential cause for the psychotic symptoms in patients with PD by a thorough medical assessment, review of medications and investigations deemed necessary.

Psychosis was rarely observed in PD patients in the pre-levodopa era (84). Several reports of psychosis associated with the use of levodopa (85) and bromocriptine (86) followed the availability of these agents. Now we know that virtually all anti-PD medications can contribute to psychosis in PD (87) in a “dose-response” manner (88). Anti-PD medications are thus a modifiable risk factor for PDP (3) and should be the focus of initial clinical intervention. Because of their adverse cognitive effects, anticholinergics should not be used in PD patients at risk of cognitive problems because of age or progression of PD, irrespective of presence or absence of concurrent psychosis. Among anti-PD medications, levodopa is believed to have the lowest potential to cause or contribute to psychosis in PD patients. If a patient is on anti-PD medications besides levodopa, their dose should be gradually decreased one at a time while closely monitoring for improvement in psychosis and worsening of motor symptoms. The ultimate goal would be resolution of psychosis without motor worsening, which may entail gradually stopping all anti-PD medications except levodopa and optimizing the dose of levodopa (89, 90).

Selection of a medication for PDP will be guided by several factors. For mild hallucinations that are not distressing or disabling, clinical monitoring is usually the preferred strategy, although a recent publication showing relatively rapid progression of hallucinations to delusions in PDP patients not receiving treatment for psychosis compared to those who were raises concern if that would be the best approach (91).

Quetiapine is the preferred initial intervention in PDP patients without dementia. Starting at 12.5 to 25 mg at bedtime, the dose can be increased by increments of 12.5 to 25 mg every several days to a few weeks while monitoring for potential adverse effects and response. Lack of response to doses between 100-150 mg/day would signal treatment failure in most cases but higher doses may be tried cautiously. The best evidence-based option for PDP patients failing a trial would be clozapine. Patient (and family if indicated) must be educated about the potential adverse effects of clozapine and need for regular blood work-up for monitoring of agranulocytosis before initiation of clozapine. The usual starting dose of clozapine would be 6.25 mg/day that could be increased by increments of 6.25 mg every several days to accomplish resolution of psychosis. Doses above 100 mg/day would be rarely required.

Due to limited efficacy and risk to worsen motor symptoms, olanzapine (27, 28) and aripiprazole (54-57) are not good options for “quetiapine failure” PDP patients without dementia who would prefer to try something besides clozapine. A trial of either ziprasidone or risperidone could be considered in such patients. The expected effective dose for ziprasidone and risperidone would be between 80-120 and 0.5-1.25 mg/day, respectively, in most cases. Use of a higher dose should be cautious with close monitoring of motor symptoms.

For patients with PDP with dementia, donepezil or rivastigmine may be preferred over quetiapine as an initial intervention. Both these drugs have been found effective and safe in PDP and they would have a positive impact on dementia as well (66-74). It could be several weeks before response to ChEIs is observed. ChEIs can rarely cause worsening of motor symptoms. ChEI nonresponders would be candidates for trial of quetiapine.

Patient (and family) should be informed about the potential adverse effects of the medication being prescribed and monitored accordingly. Besides possible worsening of motor symptoms, all antipsychotic medications can cause varying degrees of somnolence, dizziness, orthostasis, weight gain and metabolic problems. In patients with dementia, all antipsychotics are associated with a slightly increased risk of mortality. Aripiprazole, olanzapine and risperidone are also associated with an increased risk of cerebrovascular events in patients with dementia. Clozapine is associated with a 1 to 2% risk of agranulocytosis that is not dose dependent. Patients prescribed clozapine must be registered with the national Clozapine Registry and regularly monitored for their blood counts using registry guidelines. It can also decrease seizure threshold in a dose-dependent
manner and is rarely associated with myocarditis. Common adverse effects of ChEIs include gastrointestinal symptoms, dizziness, orthostasis, bradycardia and diminished bladder control.

**DIRECTION FOR FUTURE RESEARCH**

Increased dopaminergic activity, particularly in the mesolimbic pathways, and dysfunction in the dopaminergic and serotonergic systems have been implicated in various types of psychosis (92, 93). For schizophrenia and related psychosis, SGAs are believed to work through these neurochemical systems, but they differ in their impact on these systems (e.g., strength of binding to dopamine D2 receptors, relative binding to D2 versus 5-HT2A receptors) and effect on other neurochemical (e.g., histaminic and muscarinic) systems. These differences in the SGAs probably account for their varying effect in PDP. Literature is currently limited and inconclusive for risperidone and ziprasidone. Well-designed studies are needed to clarify their utility in patients with PDP (and psychosis associated with other parkinsonian conditions). It may be worthwhile to study melperone further given the encouraging findings of the only study on it in PDP (75). Zotepine (and possibly amisulpride) would also be a candidate for study in PDP considering its low potential for EPS (64).

A few years ago, Diederich et al. (94) had suggested that visual hallucinations should be considered as a dysregulation of the gating and filtering of external perception and internal image production. Others (95-97) have substantiated this observation showing that visual hallucinations are associated with impairment in attention and visual processing. The central cholinergic system plays an important role in this processing (98) and is assumedly impaired in patients with PD. The cholinergic deficits worsen as PD progresses to PDD (99) further impairing the attentional and perceptual processes and increasing the likelihood of visual hallucinations. Given these data, it would be desirable to study ChEIs (and substances with cholinergic properties) in PDP patients with and without dementia.

There is strong evidence for the involvement of the serotonergic 5-HT2A receptor system in PDP. Clozapine is effective for PDP at doses which mostly provide an anti-5-HT2A effect (100). Recent data (101) also suggest that the serotonergic system affects striatal dopamine release in a state-dependent manner associated with the conditional involvement of various serotonergic receptors. Furthermore, involvement of the 5-HT2A receptor system in PDP is substantiated by functional radiological and post-mortem studies (102, 103). Serotonergic substances, especially those with 5-HT2A receptor-blocking properties, may be worth exploring in PDP.

Glutamatergic system dysregulation is implicated in schizophrenia (104) as well as in PD (105) but its contribution to PDP is not known so far. Memantine, an Alzheimer’s disease medication that works on the central glutamatergic system by blocking NMDA-glutamate receptors, has been shown to have some beneficial effect in PDP (81). The glutamatergic system could be a potential target for PDP development.

Common reasons for parkinsonism in old age include PD, DLB and Alzheimer’s disease. These three populations are likely to vary in how they respond to and tolerate an antipsychotic (or any other study drug). Duration of PD, presence or absence of dementia, and severity of parkinsonism would also impact upon the study outcome. Besides, efficacy rates of the study drug would most likely be different for “drug-naive” patients versus patients who had failed a trial of another medication. Controlling these variables and aiming at a homogeneous study population in individual studies would improve the validity of findings. The definition of psychosis used for patient inclusion and the tool(s) used to monitor it would also impact upon the study findings. Using the definition of PDP provided by National Institute of Neurological Disorders and Stroke workgroup in future research would help maintain consistency across studies and help exclusion of non-PD psychosis patients (106). The Movement Disorder Society task force report guides on scales suitable for use in research related to PD.

**DISCLOSURES**

The author states no conflicts of interest.

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