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Treatment of Psychosis in Parkinson's Disease

Safety Considerations

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Abstract

Psychosis only rarely occurs in patients with untreated Parkinson's disease. Much more commonly, psychosis is induced by drug therapy for Parkinson's disease and is the strongest known risk factor for nursing home placement. Delusions are less frequent than hallucinations, but are more concerning as they are often paranoid in nature. Treatment begins with a search for correctable infectious, toxic, and metabolic aetiologies. If symptoms persist, anti-Parkinson's

disease medications are slowly reduced. However, withdrawal of these drugs usually worsens parkinsonism and is often not tolerated. Certain atypical antipsychotics can be used to treat psychosis without compromising motor function.

The choice of atypical antipsychotic is largely based on ease of use and adverse effect profile as most have comparable efficacy in improving psychosis. Currently, there are five marketed atypical drugs – clozapine, risperidone, olanzapine, quetiapine and ziprasidone. Ziprasidone is the only agent whose adverse effect profile has not been reported in Parkinson's disease.

The most common adverse effects of clozapine in Parkinson's disease are sedation, orthostatic hypotension and sialorrhoea. Sedation is generally helpful since these patients are frequently awake at night and tend to have worse behavioural problems then. Clozapine does not induce deterioration of motor function, but it has the potential to cause agranulocytosis, which is idiosyncratic and not dose-related.

In risperidone-treated Parkinson's disease patients, reported adverse effects include somnolence, sialorrhoea, dizziness, palpitations, constipation, delirium, fatigue, leg cramps, depression, urinary incontinence and hypotension. Although in some Parkinson's disease studies, risperidone has been well tolerated, others have shown that many patients are unable to tolerate the drug due to deterioration of motor function.

While an initial study of olanzapine in Parkinson's disease psychosis showed the drug to be effective without deterioration of motor function, succeeding reports demonstrated a deleterious effect of the drug on motor functioning.

The most common adverse effects of quetiapine in Parkinson's disease patients are sedation and orthostatic hypotension. There is a lack of double-blind trials; however, cumulative reports involving >200 Parkinson's disease patients strongly suggest that quetiapine is well tolerated and effective. Unlike clozapine, it does not improve tremor and may induce mild deterioration of motor function.

Recently, cholinesterase inhibitors have been reported to alleviate psychosis in Parkinson's disease. Although ondansetron, an antiemetic with antiserotonergic properties, has been reported to relieve psychosis in Parkinson's disease, its prohibitive cost has prevented further study in this population. Electroconvulsive treatment is generally reserved for the patient with psychotic depression who is unable to tolerate any pharmacological therapy.

Psychotic symptoms only rarely occur in untreated Parkinson's disease[1,2] or emerge in a Parkinson's disease patient with a concomitant psychiatric illness such as schizophrenia.[3] Much more commonly, psychotic symptoms occur as a complication of drug therapy for Parkinson's disease,[4-6] and all anti-Parkinson's disease drugs have been implicated.[7-9] It is the single most important factor precipitating nursing home placement,[10,11] an often irreversible medical and social decision[12] that carries a grave prognosis.[13] Psychotic symptoms in Parkinson's disease can be subdivided into three general categories – hallucinations, delusions and delirium.

In some patients, psychosis may be preceded by abnormal dream phenomena that include vivid dreams, nightmares and night terrors.[14,15] These occur in more than 30% of patients with Parkinson's disease and can be perceived as risk factors for psychosis.[16,17] One study noted that 39% of patients with sleep disturbances, such as insomnia, sleep

fragmentation, excessive daytime sleepiness, altered dreams and parasomnias, had hallucinations compared with only 4% of those with normal sleep patterns.

Hallucinations are usually visual, benign, and associated with preserved insight but can sometimes be perceived as very real. Estimates of the prevalence of visual hallucinations vary from 20–40% in treated patients with Parkinson's disease.[18,19] Auditory hallucinations are less common. When present, they are usually accompanied by visual hallucinations[19,20] and are unlike the persecutory auditory hallucinations that characterise schizophrenia.

Delusions affect about 8% of treated patients with Parkinson's disease.[4-6] They are usually paranoid in nature and commonly involve suspicions of spousal infidelity. Other paranoid themes include people stealing money, intruders living in the house, or nurses planning harmful plots. Thought broadcasting, ideas of reference, loosened associations, and 'negative' symptoms, all common in schizophrenia, do not seem to occur in anti-Parkinson's disease drug-induced psychosis.

Delirium is a form of psychosis with clouded sensorium. The patient has lost touch with reality, often with severe disturbance of arousal. It may start as nocturnal confusion or 'sun-downing', which, when left untreated, can carry over to daytime behaviours that affect the entire family. When full blown, this 'toxic' mental state can be accompanied by agitation or aggression and can represent the final straw that triggers nursing home placement.

Besides the presence of abnormal dream phenomena, reported risk factors for anti-Parkinson's disease drug-induced psychosis include: advanced age, a longer disease duration, and the presence of dementia, sleep disorders and depression or a history of depression.[18,21] The type, duration and dosage of anti-Parkinson's disease drug therapy have not been found to be associated with an increased risk of psychosis.

1. General Treatment

As in any geriatric patient, urinary and pulmonary infections, metabolic and endocrine derangements, cerebral hypoperfusion states and even social stress, such as a change in environment, are common precipitating factors for delirium and psychosis in Parkinson's disease. A search for these correctable causes is required and resolution of the underlying medical illness may be all that is necessary to reverse psychosis.[22,23] Another aetiology is the addition of medications with CNS effects, such as opioids, hypnotics, antidepressants, anxiolytics and virtually any other drug that crosses the blood-brain barrier, including anti-Parkinson's disease medications. If psychotic symptoms persist, anti-Parkinson's disease medications are slowly reduced then discontinued. We recommend reducing anti-Parkinson's disease drugs in the following order: anticholinergic agents, selegiline, amantadine, dopamine agonists, then catechol-*O*-methyltransferase (COMT) inhibitors, and finally, levodopa.[9,15] If psychosis improves, the patient is then maintained on the lowest possible dose of anti-Parkinson's disease medications. However, withdrawal of anti-Parkinson's disease drugs usually worsens parkinsonism and may not be tolerated. The use of an atypical antipsychotic agent is then recommended.

The choice of an atypical antipsychotic agents is largely based on its ease of use and adverse effect profile, as most drugs probably have comparable efficacy rates in improving psychosis (see table I, table II, table III and table IV). The main difference in atypical antipsychotic agents lies in their propensity to worsen motor functioning in this frail and already vulnerable population. Thus far, five drugs – clozapine, risperidone, olanzapine, quetiapine and ziprasidone – have been marketed in the US as 'atypical'. Ziprasidone is the only atypical antipsychotic agents that has not been reported in drug-induced psychosis in Parkinson's disease.

An emerging drug class is the cholinesterase inhibitor. Because patients with dementia with Lewy bodies experience improvement of psychosis when treated with cholinesterase inhibitors for dementia, this class of drug might be an alternative to atypical antipsychotic agents.[61-64]

Although ondansetron, an antiemetic with antiserotonergic properties, has been described in the

Table I. Summary of double-blind and selected larger open label study reports on clozapine in the treatment of psychosis in Parkinson's disease (PD)

Reference	Study design	No. of patients	Dosage (mg/day)[a]	No. of patients with improved psychosis	No. of patients with a deterioration in PD
Wolters et al.[24]	Double blind	6	75–250	3	3
Parkinson Study Group[25]	Double blind	60	24.7	Improved mean BPRS	0
French Clozapine Study[26]	Double blind	60	36	Improved mean CGIS, PANSS	7
Ostergaard and Dupont[27]	Open label	16	12.5	14	0
Kahn et al.[28]	Open label	11	56	8	0
Factor et al.[29]	Open label	19	35	Improved mean BPRS	1
Rabey et al.[30]	Open label	27	42	Not documented	0
Ruggieri et al.[31]	Open label	36	10.6	Improved mean BPRS	0

a Dosage is given as a mean or a range.

BPRS = Brief Psychiatric Rating Scale; **CGIS** = Clinical Global Impression Scale; **PANSS** = Positive and Negative Symptom Scale.

past to relieve psychosis in Parkinson's disease,[65,66] its cost has prohibited further study and application in this population.

Electroconvulsive treatment (ECT) is generally reserved for the severely psychotic Parkinson's disease patient who is unable to tolerate any pharmacological therapy.[67-70]

2. Clozapine

2.1 Pharmacokinetics

Clozapine is a dibenzodiazepine. The drug is highly protein bound and is excreted in both urine and faeces. At steady state, the drug has a half-life of approximately 12 hours. Although it acts at other dopamine receptors as well, clozapine is unique in its high affinity for dopamine D_4 receptors. In addition, it also acts at adrenergic, cholinergic, histaminergic, and serotonergic receptors.[71]

2.2 General Adverse Effects

The adverse effect profile of clozapine in the treatment of psychosis in Parkinson's disease is quite different from that in schizophrenia, presumably because of the markedly reduced dosage used in Parkinson's disease and the different patient populations and concomitant medications. One notable difference is in weight gain. While weight gain in patients with Parkinson's disease receiving low-dose clozapine has been reported, it was only 0.7 kg over 12 weeks (average) in a double-blind, placebo-controlled trial.[25] It is rarely significant at the lower doses administered in anti-Parkinson's disease drug-induced psychosis. In part, this may be due to the natural trend towards weight loss in many patients with Parkinson's disease. The higher clozapine dos-

Table II. Summary of reports on risperidone in the treatment of psychosis in Parkinson's disease (PD)

Reference	No. of patients	Dosage (mg/day)[a]	No. of patients with improved psychosis	No. of patients with a deterioration in PD
Meco et al.[32]	6	0.67	6	0
Ford et al.[33]	6	1.5	6	6
Rich et al.[34]	6	0.5–4	4	5
Meco et al.[35]	10	0.73	9	3
Workman et al.[36]	9	1.9	9	0
Leopold[37]	39	1.1	33	6
Mohr et al.[38]	17	1.1	16	1

a Dosage is given as a mean or a range.

Table III. Summary of reports on olanzapine in the treatment of psychosis in Parkinson's disease (PD)

Reference	No. of patients	Dosage (mg/day)[a]	No. of patients with improved psychosis	No. of patients with a deterioration in PD
Wolters[39]	15	6.5	15	0
Jimenez-Jimenez et al.[40]	2	5	1	2
Friedman and Goldstein[41]	19	N/A	7	10
Friedman et al.[42]	12	4.4	12	7
Molho and Factor[43]	12	6.3	9	10
Weiner et al.[44]	21	5	13	9
Churchyard and Iansek[45]	22	7.5	17	N/A
Graham et al.[46]	5	5	5	3
Stover and Juncos[47]	22	N/A	12	8
Goetz et al.[48]	7	11.2	N/A	6
Aarsland et al.[49]	21	4.5	16	0
Gimenez-Roldan et al.[50]	9	4.7	6	9

a Dosage is given as a mean or a range.

N/A = data not available.

age used in the treatment of tremor, however, may be associated with troublesome weight gain.[72]

Seizures have occurred infrequently in patients with Parkinson's disease receiving clozapine, with only one published case[73] involving a patient receiving low-dose clozapine for more than one year. This may not have been related to clozapine, as seizures are dose related and generally occur at a daily dosage of more than 600 mg/day.[74]

One striking feature of the adverse effect profile of clozapine in Parkinson's disease has been the absence of typical anticholinergic effects. Anticholinergic agents are poorly tolerated by the elderly, who are prone to memory dysfunction, blurred vision due to impaired lens accommodation, constipation and urinary retention, especially in men with benign prostatic hypertrophy. Clozapine is rarely associated with any of these. Two anticholinergic effects that are virtually universal with the drugs used to treat Parkinson's disease are dry mouth and constipation. For reasons still unexplained, clozapine produces sialorrhoea rather than dry mouth. Since many patients with Parkinson's disease already experience drooling, clozapine may produce

Table IV. Summary of reports on quetiapine in the treatment of psychosis in Parkinson's disease (PD)

Reference	No. of patients	Dosage (mg/day)[a]	No. of patients with improved psychosis	No. of patients with a deterioration in PD[b]
Parsa and Bastani[51]	2	200–400	2	1
Evatt et al.[52]	10	50	10	0
Juncos et al.[53]	15	70	15	0
Juncos et al.[54]	40	25–800	40	8
Samanta and Stacy[55]	10	37.5	6	7
Fernandez et al.[56]	15	62.5	12	4
Targum and Abbott[57]	10	107	7	0
Reddy et al.[58]	43	54	32	5
Dewey and O'Suilleabhain[59]	75	86	40	0
Fernandez et al.[60][c]	106	60.8	87	34

a Dosage is given as a mean or a range.

b Deterioration of motor function in all reports was described as minor.

c Eleven patients had dementia with Lewy bodies, two patients had progressive supranuclear palsy and one patient had dementia pugilistica.

intolerable worsening.[28,31,72,73,75-77] The sialorrhoea caused by clozapine is due to increased saliva production, whereas drooling in Parkinson's disease is due to hypokinesia, a reduced rate of spontaneous swallowing, causing saliva accumulation.

Myocarditis has not been reported in patients with Parkinson's disease receiving clozapine. Whether this is due to the lower dosage used in patients with Parkinson's disease, their older age, or the rarity of the condition is unknown, especially as clozapine is administered to significantly fewer patients with Parkinson's disease than patients with schizophrenia.

Altered glucose metabolism has been a recent concern with clozapine and olanzapine (see section 4.2). While this is partly due to weight gain, it is also thought to represent a direct effect of clozapine or olanzapine on insulin and therefore to be unrelated to weight gain.[78] The emergence of glucose intolerance or worsening of diabetes mellitus has not been described in patients with Parkinson's disease. Only study has specifically addressed the question of glucose intolerance in clozapine-treated patients with Parkinson's disease (given for psychosis and tremor).[79] This retrospective study involved 44 subjects with Parkinson's disease who took a mean dosage of clozapine of 50.6 mg/day for an average duration of 41 months. The comparator group was 82 patients with schizophrenia who took clozapine for at least 1 year.[80] Thirteen of the Parkinson's disease patients had been taking clozapine for >60 months and of these patients, one (7.7%) was diagnosed with new-onset diabetes; in comparison 30 of the 82 (36.6%) patients with schizophrenia receiving clozapine for >60 months were diagnosed with diabetes. Thus, Parkinson's disease patients tended to have a lower occurrence of new-onset diabetes. Six of the 44 (13.6%) Parkinson's disease patients had altered glucose metabolism (two were placed on hypoglycaemic agents and four had a fasting blood glucose level of > 140 mg/dL), which was fewer than in the group with schizophrenia (43 of 82; 52.4%). However, the mean clozapine duration in the Parkinson's disease cohort (41 months) was less than that of the schizophrenia cohort (>60 months). Hence the question remains unanswered.

The most common adverse effects of clozapine, even at a low dosage, are sedation, orthostatic hypotension and sialorrhoea, which has already been discussed.[25] The sedation caused by clozapine is generally helpful since these patients are frequently awake at night and tend to have worse behavioural problems then. Since clozapine has a once-daily dose administration schedule, giving the medication at bedtime may improve both the psychosis and nocturnal awakening. This has the added benefit of reducing daytime somnolence. However, some patients experience intolerable sedation with a dosage of clozapine that is not sufficient to ameliorate psychosis.[25] Orthostatic hypotension is common in Parkinson's disease, presumably as a direct effect of the illness, and is often exacerbated by anti-Parkinson's disease medications. This may amplify the orthostatic hypotension-inducing effects of clozapine. Treatment is with hypertensive agents, such as added salt, fludrocortisone or midodrine. Fainting is uncommon but may occur and is of particular concern at night when patients awaken from sleeping in their beds to walk to the toilet.[25]

Delirium may occur and causes significant problems since many of the patients have psychosis as part of a global confusional state. Clozapine may worsen this condition, either because of its anticholinergic properties, or perhaps simply because it is sedating and therefore interferes with attention, thus offsetting any improvements in the psychosis.[9]

The number of deaths reported in association with clozapine use requires comment. The open-label trials have not reported this problem but the two placebo-controlled multicentre trials did.[26,29] In one study, 6 of 60 patients died during the study period, although one of the six actually died shortly after drug discontinuation.[29] Since both studies were of less than 20 weeks duration, this is surprising. No deaths were attributed to adverse effects of clozapine, however. The deaths were either unexplained or due to pneumonia, sudden death (presumably arrhythmia or pulmonary embolus) or coronary ischaemia. There were no indications of myocardi-

tis, uncontrolled diabetes, leucopenia or neuroleptic malignant syndrome (NMS). It is thought that these elderly frail patients, who often have advance directives (a form that they sign beforehand that orders 'do not resuscitate'), are not treated aggressively once they fall ill.[25] The mortality for patients with Parkinson's disease with drug-induced psychosis is thought to be high.[13] Some of these patients had been in nursing homes during the trial. What remains unexplained is the discrepancy between the open-label reports, which often had follow-up of more than 20 weeks duration, and the two blinded trials.

Despite the advantage of clozapine in that it does not induce deterioration of motor function in Parkinson's disease, the use of clozapine is complicated by its potential for inducing agranulocytosis. The problem is idiosyncratic and, unfortunately, not dose related, so that even the small doses administered in Parkinson's disease do not exempt patients from this adverse effect. Nonetheless, leucopenia is usually transient, and there have been only two reports of frank agranulocytosis in patients with Parkinson's disease,[4,81] both transient. The small numbers involved, along with the variability of reporting, suggests that there is a lack of evidence to indicate that patients with Parkinson's disease are more or less likely than age-matched controls to experience clinically significant abnormalities in white blood cell (WBC) counts. There have been two reports of low platelet levels; in one report the patient also had agranulocytosis,[81] while in the other, the patient had no other blood disorder.[82] As far as we are aware, no deaths due to agranulocytosis have occurred in patients with Parkinson's disease. In the US, for the first 6 months of treatment, each patient on clozapine is required to have a weekly WBC count, verified by the pharmacy, and can receive only 1 week's supply of the drug at a time. After 6 months the process becomes bi-weekly. Thus, because of the cumbersome process required to maintain a patient on clozapine, each newly released atypical antipsychotic agent has been tried in Parkinson's disease in the hope of reducing clozapine to being a back-up drug rather than the drug of choice.

Recently, a task force that considered all well designed peer-reviewed reports on clozapine in Parkinson's disease concluded that 'low-dose clozapine is *efficacious* in the short-term improvement of psychosis in Parkinson's disease with *acceptable risk with specialized monitoring* but there is *insufficient evidence* of its long-term efficacy.'[83] A retrospective analysis of 39 patients with Parkinson's disease receiving long-term clozapine for a mean duration of 60 months showed that 85% achieved a continued partial/good response and 13% a complete resolution of psychosis. Thirty-three percent were eventually admitted to nursing homes while 28% died over a span of 5 years[84] – a significantly improved mortality rate compared with previous 2-year mortality rate reports approaching 100% among Parkinson's disease residents with psychosis in the nursing homes.[13]

2.3 Extrapyramidal Adverse Effects

Clozapine-induced NMS seems to be a very uncommon event in patients with schizophrenia and has not yet been described in patients with Parkinson's disease. Since patients with Parkinson's disease may develop an NMS-like syndrome upon abruptly stopping levodopa[85] or amantadine,[86] distinguishing clozapine-induced NMS and NMS due to discontinuation of a Parkinson's disease medication may not be possible. On rare occasions, motor decline does occur with clozapine.[87] Whether this is a nonspecific effect due to sedation or represents an idiosyncratic sensitivity to clozapine is unknown but, fortunately, it appears to be a very uncommon occurrence. In all studies but one,[24] clozapine ameliorated psychosis in Parkinson's disease without exacerbating parkinsonism, making it still the gold standard treatment for drug-induced psychosis in Parkinson's disease.[9] The one negative report was the first double-blind, placebo-controlled trial which used a starting dose of 25 mg/day and daily increases of the same amount.[24] The patients were unable to tolerate this dose, perhaps due to excessive sedation more than increased

parkinsonism, and the study was stopped with only 6 patients enrolled. The results of this study were refuted by two large, double-blind studies performed in the US and France which demonstrated that starting clozapine treatment at a dosage of 6.25 mg/day with a mean dose of about 25 mg/day improved psychosis without deterioration of motor function.[25,26]

3. Risperidone

3.1 Pharmacokinetics

Risperidone is a benisoxazole derivative with a high affinity for serotonin 5-HT_2 and D_2 receptors as well as histamine H_1 receptors and α_1- and α_2-adrenergic receptors. The drug is metabolised in the liver to an active metabolite, 9-hydroxyrisperidone, that acts similarly to risperidone. Overall, the mean half-life of both components is approximately 20 hours.[71]

3.2 General Adverse Effects

In a US study of risperidone in schizophrenia, compared with patients receiving placebo, somnolence, extrapyramidal symptoms, dizziness, constipation, and tachycardia were reported with an increased incidence of at least 5% in patients receiving risperidone 16 mg/day.[88] Of these known adverse effects, only somnolence, extrapyramidal symptoms, and dizziness were statistically significant.[89] Significant dose-related symptoms (by patient report) included fatigue, sedation, accommodation disturbances, orthostatic dizziness, palpitations or tachycardia, weight gain, decreased libido, and erectile dysfunction.[88]

In risperidone-treated patients with Parkinson's disease, reported adverse effects included somnolence, sialorrhoea, dizziness, palpitations, rash, constipation, delirium, fatigue, leg cramps, depression, urinary incontinence, and hypotension.[32,37,38] Studies in patients with dementia with and without Parkinson's disease have not shown risperidone to cause cognitive impairment.[36,89] Although Meco et al. reported a decline in Mini-Mental Status Examinations (MMSE) scores in risperidone-treated Parkinson's disease patients, the examiners did not believe it was related to risperidone.[35]

Risperidone is known to prolong the QT interval but is not associated with any other clinically significant ECG changes.[89,90] Studies in patients with Parkinson's disease have not revealed any significant changes in laboratory data,[91] although there is one case report of hyponatraemia occurring in a risperidone-treated patient.[92]

3.3 Extrapyramidal Adverse Effects

Although some studies have reported risperidone to be well tolerated in patients with Parkinson's disease,[35,36] other studies have shown that many patients are unable to tolerate the drug because of deterioration of motor function.[33,34] An early report of risperidone use in Parkinson's disease showed no significant deterioration of motor function by Unified Parkinson's Disease Rating Scale (UPDRS) scores over 16 weeks of treatment. However, three patients eventually withdrew from the study because of increased parkinsonism.[35] Subsequent reports demonstrated less promising outcomes. Ford et al. described six patients with Parkinson's disease, all of whom experienced deterioration of motor function while receiving risperidone.[33] In a report by Rich et al., five of six risperidone-treated patients with akinetic-rigid syndromes had to discontinue the drug due to deterioration of motor function.[34] Four of the five improved when their treatment was switched to clozapine.

Further studies have continued to show mixed results and may have been confounded by limitations. A open label study of risperidone in nine patients with Parkinson's disease demonstrated an improvement in psychosis without deterioration of motor function as measured by the Rating Scale for Side Effects (RSSE) over 37 days.[36] However, the RSSE is not the most sensitive scale for assessing parkinsonism.[36,93] The largest study of risperidone in parkinsonism included 39 patients. Sixteen patients completed the trial with no significant change in their UPDRS scores over 6 months but six patients experienced worsening of motor symptoms and had to discontinue treatment.[37] In the only

double-blind study of risperidone in Parkinson's disease psychosis, Ellis et al. compared risperidone with clozapine in 10 patients with Parkinson's disease over 3 months. Parkinsonism was worsened in one clozapine-treated patient and in three risperidone-treated patients. Mean UPDRS scores worsened with risperidone and improved with clozapine. While this difference was clinically significant, it was not statistically significant, and the study serves as an illustration of over-interpretations of a small, albeit double-blind, study.[91] Mohr et al. examined risperidone use in 17 patients with Parkinson's disease with psychosis and concluded that the drug did not worsen motor symptoms,[38] but this study, too, had several limitations. Parkinsonism was exacerbated in one patient, and 'hypokinesia' and drooling were described adverse events even among patients experiencing benefit. Why these adverse effects from a drug not known to induce sialorrhoea were not ascribed to the worsening of parkinsonism is unclear and the study's conclusions have been challenged.[94] A meta-analysis of 82 patients with Parkinson's disease treated with risperidone showed 23 (33%) experienced deterioration of motor function.[94]

Thus, controversy remains over the safety of risperidone in patients with Parkinson's disease. Many experts believe that the adverse effect profile of risperidone in patients with Parkinson's disease is more similar to typical than atypical antipsychotic agents.[94-96] In a comparative trial of clozapine, risperidone, and typical antipsychotics in schizophrenia, risperidone caused significantly more akathisia than clozapine, both according to patient reports and objective scores on the Barnes Akathisia Scale.[94] Similarly, patients receiving risperidone scored significantly higher on the Simpson Angus Scale than patients receiving clozapine, and there was no significant difference between the scores associated with risperidone and those associated with conventional antipsychotics.[94] On the Subjective Extrapyramidal Rating Scale, patients receiving typical antipsychotic agents actually scored better than patients taking risperidone. Finally, a study comparing risperidone and haloperidol in antipsychotic-naive patients with schizophrenia did not demonstrate any significant difference between the extrapyramidal adverse effects of risperidone and haloperidol.[95]

Despite reports of the use of risperidone in the treatment of tardive dyskinesia (TD),[97] there have also been several reports of the drug causing TD.[93,96,98-100] However, most patients had chronic psychiatric illnesses and had been treated with other antipsychotics in the recent past.

There have been no reports of NMS specifically in patients with Parkinson's disease receiving risperidone.

4. Olanzapine

4.1 Pharmacokinetics

Like clozapine, olanzapine is a dibenzodiazepine.[101] It has a high affinity for 5-HT_2, D_1, D_2, D_3, D_4, muscarinic, H_1, and α_1-adrenergic receptors. Metabolised primarily by the liver, the drug has a half life of 21–54 hours. Daily administration achieves steady state concentrations in about 1 week.[71]

4.2 General Adverse Effects

Most reports of adverse effects in patients receiving olanzapine come from studies in patients with schizophrenia. Somnolence, constipation, dizziness, pharyngitis, paraesthesia, dry mouth, weight gain, increased appetite, akathisia, headache, insomnia, agitation, asthenia, and nervousness have all been reported.[102-105] All four pivotal schizophrenia trials showed weight gain in patients treated with olanzapine.[102-104,106] A meta-analysis by Allison et al. showed olanzapine to cause an estimated weight gain of 4.15kg over 10 weeks, an increase second only to that of clozapine.[107] Olanzapine has not been shown to have any significant effect on orthostatic blood pressure,[102,103,105] and no clinically significant ECG changes have been noted.[103,105]

Other than deterioration of motor function, few adverse effects have been specifically reported in the Parkinson's disease population. In the study by

Friedman et al., two olanzapine-treated patients experienced excessive somnolence and one became agitated and combative.[41] Wolters et al. reported significantly increased sleep time in patients with Parkinson's disease receiving olanzapine without an increase in complaints of drowsiness, but this was generally considered to be a beneficial effect.[39]

Recently, olanzapine treatment of schizophrenia has been associated with a few cases of new onset diabetes.[108] However, no formal studies investigating the effects of olanzapine on glucose metabolism have been performed among patients with Parkinson's disease.

4.3 Extrapyramidal Adverse Effects

An initial open-label study by Wolters et al.[39] of 15 non-demented patients with Parkinson's disease with psychosis who were treated with olanzapine 2–15 mg/day (mean dose 6.5 mg/day) showed it to be effective in the treatment of drug-induced psychosis without associated deterioration of motor function. Succeeding reports, however, demonstrated a deleterious effect of olanzapine on motor functioning in Parkinson's disease.[41-43,49,91,93,108-110] In an open-label study by Friedman et al., 10 of the 19 patients with parkinsonian syndromes experienced deterioration of motor function when treated with olanzapine.[41] An open label, crossover study, also by Friedman et al., described 12 patients with Parkinson's disease who were switched from clozapine to olanzapine.[42] Nine of the 12 experienced increased parkinsonism and were unable to tolerate olanzapine. Similarly, Molho et al. reported that 9 of 12 patients with Parkinson's disease in a retrospective study experienced deterioration of motor function on olanzapine.[43] Finally, a double-blind comparative study of clozapine versus olanzapine in drug-induced psychosis in patients with Parkinson's disease had to be aborted prematurely because six of seven olanzapine-treated patients experienced a significant decline in motor function.[49] These and other studies strongly suggest that olanzapine exacerbates motor functioning in Parkinson's disease.[93,109] It is important to note that the motor dysfunction in patients receiving olanzapine was clear to the patient and the caregiver and was not merely a minor change noted incidentally in a battery of Parkinson's disease assessment instruments, or a result of the natural progression of disease. The task force on evidence-based review of the treatment of psychosis in Parkinson's disease concluded 'there is *insufficient evidence* to demonstrate efficacy of olanzapine and at low conventional doses it carries an *unacceptable* risk of motor deterioration'.[83]

5. Quetiapine

5.1 Pharmacokinetics

Quetiapine is a dibenzothiazepine, a class of drugs related to clozapine and olanzapine.[101] It acts at D_1, D_2, 5-HT_1 and 5-HT_2 receptors, as well as at H_1 and α_1- and α_2-adrenergic receptors. Metabolised by the liver, the half-life is approximately 6 hours and the drug reaches steady state in 2 days.[71]

5.2 General Adverse Effects

The adverse effects of quetiapine in patients with Parkinson's disease appear to be similar to those seen in patients with schizophrenia. These are primarily sedation and orthostatic hypotension. Evatt noted that 'systolic blood pressure drops greater than 20% occurred in 5 of 10 subjects, but only a single subject had described light-headedness'.[52] One patient developed tachycardia that limited drug dose increase. Samanta and Stacy reported a single case of diplopia, but this adverse effects has not been reported in other publications.[55] In the largest retrospective study on quetiapine use for psychosis among patients with Parkinson's disease, 28 of 106 patients in the study discontinued quetiapine for the following reasons: sedation (3 patients), hypotension (2), confusion (2), rash (1) and increased parkinsonism symptoms (10).[60] Seventy-eight of 106 patients (74%) remained on quetiapine for a mean duration of 15 months at an average dose of 60 mg/day. Eighty-seven patients (82%) had partial or complete resolution of their psychosis while 19 patients (18%) experienced no improvement on quetiapine.

5.3 Extrapyramidal Adverse Effects

The effect of quetiapine on motor function is most similar to the effect of clozapine but not quite as benign.[58,60] Unlike clozapine, there are no claims that quetiapine has anti-tremor effects. This is a very important consideration in assessing motor function effects, since a mild negative impact of clozapine on motor function measured on the UPDRS could be masked by its anti-tremor positive effect. Thus, clozapine might cause mild increases in bradykinesia or rigidity while improving tremor sufficiently to reduce the UPDRS motor score. Quetiapine, which does not have an anti-tremor effect, might then have motor effects equivalent to clozapine yet look mildly worse. In one double-blind, placebo-controlled clozapine trial,[25] UPDRS motor scores were 1.8 points better with clozapine than with placebo, of which 1.5 points were a result of tremor benefit.

In a retrospective study of 43 patients, 5 of 20 patients with dementia and 0 of 19 patients without dementia had worsening of UPDRS motor scores, but none severe enough to cause discontinuation of the quetiapine.[58] Parsa reported one of two patients with mild deterioration of motor function.[51] Juncos reported 8 of 40 with increased parkinsonism symptoms.[53] Samanta described 7 of 10 patients with a deterioration in motor function on quetiapine.[55] Fernandez et al. described 4 of 15 having deterioration of motor function when clozapine was replaced by quetiapine.[56] Although quetiapine caused a deterioration of motor function in 5–10% of patients, it was rarely deemed clinically significant. In the largest retrospective long-term study of quetiapine in Parkinson's disease involving 106 patients, 10 discontinued the drug due to a deterioration in motor function.[60] An additional 24 patients experienced motor decline over a mean of 15 months, thought to be largely explained by disease progression. Patients with dementia appeared to be at a greater risk of deterioration of motor function.[58,60] In another retrospective study of 84 patients with Parkinson's disease who commenced treatment with quetiapine, the authors stated that 'deterioration of motor function following the institution of quetiapine was not observed.'[59]

There is a single publication describing two cases of 'typical' antipsychotic adverse effects in patients with Parkinson's disease receiving quetiapine. A 73-year-old man with a 27-year history of Parkinson's disease with dementia who presented with persecutory delusions and visual hallucinations developed an oculogyric crisis while receiving quetiapine 37.5mg daily and then tolerated 25 mg/day without difficulty.[111] A 69-year-old woman developed akathisia after around 5 months of treatment with quetiapine 75 mg/day. Akathisia is not uncommon in both treated and untreated idiopathic Parkinson's disease, so its occurrence in association with quetiapine treatment may have been coincidental. Acute dystonic reactions are extraordinarily rare.[112]

With the lack of double-blind trials, the task force for evidence-based review of Parkinson's disease treatment concluded that 'there is *insufficient evidence* to support the efficacy and safety of quetiapine and its use for psychosis in Parkinson's disease should be considered *investigational*.'[83] However, available reports involving over 200 patients with Parkinson's disease strongly suggest that quetiapine appears to be well tolerated and effective. Despite the lack of head-to-head trial, quetiapine appears to be slightly less effective than clozapine in alleviating psychosis. Unlike clozapine, it does not improve tremor and may induce mild deterioration of motor function. The majority of motor decline, especially in long-term trials, was mild or could be attributed to Parkinson's disease progression, and hospitalisation was not required. The mean daily dose was generally below 75 mg/day.

6. Ziprasidone

6.1 Pharmacokinetics

Ziprasidone is a benzisothiazole-piperazine-indolone. The drug has a high affinity for 5-HT_2 and D_2 receptors and reaches steady state after one day. Metabolised in the liver, ziprasidone has a half-life of 3.2–10 hours.[113]

6.2 General Adverse Effects

The newest of the atypical antipsychotic agents, ziprasidone was approved for use in the US in February, 2001. To date, there have been no studies or reports of ziprasidone use in patients with Parkinson's disease, and all of the data on the drug comes from its use in patients with schizophrenia.

There has been concern over prolongation of the QT interval with ziprasidone. A review by Glassman and Bigger demonstrated a modest prolongation of the corrected QT (QTc) interval with ziprasidone, but found no evidence to support an association with torsade de pointes or cardiac death.[114] Moreover, there have been no reports of torsade de pointes in patients receiving ziprasidone, and the major studies showed no significant effect on the QT interval and no clinically significant ECG changes.[114-118]

Unlike most of the other atypical antipsychotics, studies of ziprasidone in schizophrenia have consistently shown minimal weight gain associated with the drug.[115,117,118] The most common and consistently reported adverse effects are somnolence and gastrointestinal complaints.[117]

6.3 Extrapyramidal Adverse Effects

All of the studies on ziprasidone in schizophrenia evaluated the presence of movement disorders with the Simpson-Angus Rating Scale for extrapyramidal symptoms, the Abnormal Involuntary Movement Scale (AIMS) for tardive dyskinesia, and the Barnes Akathisia Scale for akathisia.[115,116,118] Two major studies showed no significant difference on any scale between ziprasidone and placebo. In both studies, however, more ziprasidone patients were also receiving benztropine compared with placebo patients.[115,118] The extrapyramidal effects seen in schizophrenia trials and the minimal effect that ziprasidone has on prolactin levels suggest that its extrapyramidal profile may be similar to that of olanzapine. With respect to extrapyramidal adverse effects, a recent panel ranked the atypical antipsychotic agents as follows, from greatest effects to the least: risperidone > olanzapine = ziprasidone > quetiapine > clozapine.[119] There are no reports in the literature of NMS in a patient on ziprasidone.

7. Other Therapies

7.1 Ondansetron

Ondansetron is an expensive antiemetic and a selective 5-HT_3 receptor antagonist. Zoldan et al. reported that, in two open-label trials, a total of 40 patients with Parkinson's disease experienced an improvement in psychotic symptoms. Only one patient developed a headache and seven patients had constipation.[66,120] However, these positive findings could not be reproduced by others.[121]

7.2 Cholinesterase Inhibitors

To date, four cholinesterase inhibitors – tacrine, donepezil, rivastigmine and galantamine – are approved for the treatment of mild to moderate dementia in Alzheimer's disease only. The cholinergic deficit may be greater in Parkinson's disease than in Alzheimer's disease.[122] Thus, theoretically, cholinesterase inhibitors may have a potentially greater impact in Parkinson's disease than that already seen in Alzheimer's disease. However, since anticholinergic drugs are known to improve tremor in Parkinson's disease, procholinergic drugs such as cholinesterase inhibitors, may, theoretically, worsen parkinsonism symptoms, particularly tremor.

There are only a few reports of the use of cholinesterase inhibitors in Parkinson's disease. The first report of cholinesterase inhibitor use in Parkinson's disease dementia described a series of seven subjects with confusional states and visual hallucinations treated with tacrine.[123] In this open label study, five patients had complete resolution of hallucinations and two patients improved. The MMSE improved by 7.1 points and the UPDRS total and motor scores improved dramatically. None experienced a deterioration in motor function.

In an open label study, 11 consecutive patients with Parkinson's disease with dementia were treated for 26 weeks with tacrine or donepezil. The mean Alzheimer's Disease Assessment Scale-cognitive

portion (ADAS-cog) score improved significantly by 3.2 points. Parkinsonism symptoms were either unchanged or slightly improved, as measured on the Short Parkinson Evaluation Scale.[124] Behavioural symptoms were not mentioned.

In another open label trial of 12 patients with Parkinson's disease with drug-induced psychosis,[125] rivastigmine was initiated at 1.5mg twice daily and increased every 2 weeks until either the maximum of 6mg twice daily or the highest tolerated dose was achieved. The drug was well tolerated. Three patients withdrew, including one who died from unrelated sepsis, one because the caregiver became ill and the third from nausea. The MMSE improved from 20.8 to 25.4 while the UPDRS motor scale did not change, and the mean National Psychiatric Inventory (NPI) score improved on the subscales measuring hallucinations and sleep disturbance but not delusions. Caregiver distress also improved. Repeat measurements after a 3-week withdrawal showed a comparable decline. No worsening of tremor or parkinsonism symptoms was noted. The same group reported another open label trial of donepezil.[126] Nineteen patients with dementia with Lewy bodies, 28 with Parkinson's disease and two 'other' patients were treated with donepezil for dementia. By week 32, 15 of the dementia with Lewy bodies patients, 15 of the Parkinson's disease patients and the two of the 'other' patients were still assessable. The MMSE improved 3.11 ($p < 0.001$), the NPI by 7.53 ($p < 0.004$), without a deterioration in UPDRS scores. In another study, 10 patients with Parkinson's disease with psychosis were treated with rivastigmine up to 6mg twice daily for psychosis, with the majority showing clinical improvement of the psychosis (BPRS improvement >20%) without deterioration of motor function.[127] Adverse effects were minor.

A postmarketing surveillance report of >2000 patients treated with donepezil included 73 patients with both Alzheimer's disease and Parkinson's disease who were observed for over 3 months. Improvement in memory, mood and social behaviour was described, as well as good tolerance.[128] Finally, a double-blind placebo-controlled crossover trial of donepezil in patients with Parkinson's disease and dementia involved 14 subjects studied for 20 weeks, 10 weeks in each arm. Cognitive function improved without a decline in motor function.[129] Three patients had improved scores for delusions, two for hallucinations, nine for agitation, six for depression, and five for apathy. None of these improvements were statistically significant because of low scores on these items at baseline and the small number of subjects involved.

There have been several reports of deterioration of motor function with cholinesterase inhibitors in Parkinson's disease. Reported in abstract form, Pourcher used donepezil in two patients with Parkinson's disease, one with postencephalitic parkinsonism, one with dementia with Lewy bodies, one with vascular parkinsonism and one with carbon monoxide parkinsonism with levodopa-induced hallucinations.[130] The author reported that visual hallucinations tended to improve in a dose-related fashion. Emotion-laden hallucinations did not improve, however, and parkinsonism mildly worsened. Similarly, Richard et al.[131] reported a single case of possible deterioration of parkinsonism symptoms with rivastigmine. Fabbrini et al.[132] reported open label results in eight patients with Parkinson's disease with hallucinations and delusions. All patients experienced some benefit with donepezil but two experienced a worsening of parkinsonism symptoms. Finally, Ott and Lannon described a single case of exacerbation of parkinsonism in a patient on tacrine.[133] More blinded studies on the use of cholinesterase inhibitors and comparative trials comparing them with atypical antipsychotic agents will be important in determining the best approach to the treatment of psychosis in Parkinson's disease.

7.3 Electroconvulsive Therapy

ECT has been reported to be beneficial in drug-induced psychosis in only a handful of patients with Parkinson's disease and it may improve motor symptoms as well.[67-70] However, experience with ECT for Parkinson's disease psychosis is limited. It may require a period of hospitalisation, may cause significant confusion, and its efficacy can be short-

lived. Thus, it should be considered only when drug manipulations have failed.

8. Conclusions

In summary, there are strong data to support the use of low-dosage clozapine in Parkinson's disease patients with psychosis. However, despite the low dosage, clozapine still requires onerous monitoring, making its use problematic and the search for a practical and 'low maintenance' first-line treatment for psychosis in Parkinson's disease an important goal.

There are enough data to suggest that risperidone behaves more like a low to medium potency typical antipsychotic than an atypical antipsychotic even among patients with schizophrenia. Its effect on motor function in Parkinson's disease has been mixed. The low number of reports probably reflects the poor experience neurologists have, making them reluctant to give many Parkinson's disease patients this drug.

The task force on evidence-based review on the treatment of psychosis in Parkinson's disease concluded 'there is *insufficient evidence* to demonstrate efficacy of olanzapine and at low conventional doses it carries an *unacceptable* risk of motor deterioration'.

With the lack of double-blinded trials, the same task force concluded that 'there is *insufficient evidence* to support the efficacy and safety of quetiapine and that its use for psychosis in Parkinson's disease should be considered *investigational*'. Nonetheless, available reports involving over 200 patients strongly suggest that quetiapine appears to be well tolerated and effective.

Odansetron is an expensive antiemetic and a selective 5-HT_3 receptor antagonist. Zoldan et al.[120] reported two open-label trials showing a total of 40 patients with Parkinson's disease with improvement of psychosis. However, these positive findings could not be reproduced by others.

With the improvement of psychosis in patients with dementia with Lewy bodies given cholinesterase inhibitors for dementia, this class of drug might be an alternative to antipsychotic agents. Small open-label trials in Parkinson's disease show cholinesterase inhibitors improved not only dementia but also hallucinations. Blinded, comparative studies on the use of cholinesterase and atypical antipsychotics will be important in determining the best approach to psychosis in Parkinson's disease. ECT should only be considered when drug therapy has been unsuccessful.

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