The Use of Risperidone for Psychosis and Agitation in Demented Patients With Parkinson's Disease

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This pilot study investigated effectiveness and tolerability of risperidone for the treatment of psychosis and agitation in 9 inpatients with Parkinson's disease and dementia. Investigators found risperidone to be effective and safe, without worsening extrapyramidal symptoms or further impairing cognition.

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After stroke and Alzheimer's disease, Parkinson's disease (PD) is the most commonly encountered neurological disorder in elderly persons. Dopamine replacement therapy remains the cornerstone of treatment for PD, but it has well-documented, long-term complications. Furthermore, neuropsychiatric side effects occur with all classes of antiparkinsonian (anti-PD) drugs.[1] Factors that predispose patients with PD to neuropsychiatric complications of anti-PD drug treatment include comorbid dementia, prior psychiatric history, advanced age, and exposure to high daily doses of levodopa. Among the neuropsychiatric complications, drug-induced psychotic states are troublesome and frequently contribute to nursing home placement.

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First-line strategies in treating dopaminomimetic psychosis include decreasing anti-PD medications and the "drug holiday," but both have well-known problematic consequences. Standard neuroleptics, even low-dose, low-potency agents, in most cases exacerbate PD symptoms and place the patient at risk for tardive dyskinesia.[2] Clozapine, the first atypical antipsychotic, was initially used for the treatment of psychosis in PD patients in 1985,[3] but its adverse side effect profile and cost make it contraindicated for many geriatric patients.[2]

The introduction in 1994 of risperidone, a new atypical antipsychotic that most closely resembles clozapine, has created another opportunity for the treatment of psychotic symptoms in elderly patients with PD. Risperidone is a benzisoxazole derivative with potent serotonin 5-HT_2 and weak dopamine D_2 receptor antagonist properties. It has low antimuscarinic but high alpha-adrenergic and histaminic blockade. Although the D_2 receptor blocking ability is said to be weak, it is actually dose dependent.[4] Risperidone has superior antipsychotic efficacy for negative symptoms, with much less drug-induced parkinsonism than haloperidol.[5,6]

There have only been two published reports (letters) on the use of risperidone in PD patients with psychosis. The first report, by Meco et al.,[7] suggests that risperidone was effective in treating levodopa-induced hallucinosis in 6 PD patients. In response to Meco, a letter by Ford et al.[8] reported worsening of PD symptoms in 6 patients treated with risperidone. Our pilot study investigates the use of risperidone for the treatment of psychosis and agitation in demented patients with Parkinson's disease, comorbid dementia, and other Axis I disorders.

METHODS

All patients with a diagnosis of PD and psychosis who were prescribed risperidone were selected from consecutive admissions to a geropsychiatric inpatient unit. They received a comprehensive evaluation by a multidisciplinary team. Upon these patients' admission and at discharge, one of the two geriatric psychiatrists on the unit performed a structured assessment that included the Mini-Mental State Examination[9] (MMSE), the Hamilton Rating Scale for Depression[10] (Ham-D), the Brief Psychiatric Rating Scale[11] (BPRS), the Rating Scale for

Side Effects[12] (RSSE), and the Cohen-Mansfield Agitation Inventory[13] (CMAI). Interrater reliability was measured on a random subsample of all consecutive admissions (n = 15) by having both psychiatrists rate the patient. One performed the structured assessments as the other observed and rated independently. Interrater reliability as measured by intraclass correlation coefficients was 0.60 for the BPRS, 0.76 for the CMAI, and greater than 0.90 for the MMSE, Ham-D, and RSSE. Psychiatric diagnoses were established according to DSM-IV criteria[14] at a consensus conference. Paired t-tests were used for statistical analysis. Because of the exploratory nature of this pilot study, we chose a significance level of 0.05.

RESULTS

Of the 378 admissions during the 21 months reviewed, 18 patients (4.8%) had a diagnosis of PD and psychosis. Of these, 9 male patients (8 white, 1 black) were prescribed risperidone after it was approved by the Food and Drug Administration. The mean age of these patients (± SD) was 72.7 ± 4 years (range 66–78), and the number of comorbid medical problems was 5.4 ± 3.1. The mean discharge dose of risperidone was 1.9 ± 0.65 mg. Three patients were switched from typical antipsychotics (2 were on loxapine, 1 was on haloperidol) to risperidone because of potential worsening of their PD. Four patients were not on antipsychotics before risperidone, and 2 patients had been started on risperidone as outpatients only a few days prior to admission on the inpatient unit.

Patients had a mean of 3.2 ± 1 consensus-conference psychiatric diagnoses. Table 1 shows the Axis I diagnoses of the 9 patients. Five patients were admitted because of psychosis secondary to anti-PD medications, 2 because of behavioral disturbance related to dementia, 1 for exacerbation of schizophrenia, and 1 for a depressive episode with psychotic features. The average length of stay in the hospital was 37.3 ± 11.5 days. Only 2 patients required readmission: 1 due to exacerbation of his schizophrenia and the other due to onset of dementia and caregiver burden.

The CMAI, the total BPRS, and the Thought Disorder (THOT) BPRS subscales scores decreased significantly from admission to discharge, indicating reductions in agitation and general psychiatric symptoms, particularly psychotic symptoms (Table 1). Mean GAF scores increased from admission to discharge, reflecting an improvement in patients' global functioning (Table 1). There was also a slight decrease in the RSSE from admission to discharge, indicating no worsening of side effects (Table 1).

Eight patients were living at home at the time of admission. Of these, 3 were discharged to nursing homes secondary to progression of their dementia and inability to be cared for safely at home, and the remaining 5 were able to return home after hospitalization. One patient who was admitted from a nursing home was discharged to the same nursing home.

All of the patients were on an average of 1.5 ± 0.88 anti-PD medications on admission and 1.4 ± 0.53 at discharge (not significant). Seven were prescribed carbidopa with levodopa, 4 were prescribed anticholinergic agents, and 2 were prescribed selegiline. Mean dosage of levodopa was 550 ± 335 mg on admission and was 535 ± 221 mg on discharge (not significant).

DISCUSSION

We found a significant improvement in general psychiatric symptoms, agitation, and global functioning in 9 patients with PD, comorbid dementia, and other Axis I diagnoses. This occurred without worsening extrapyramidal symptoms, further impairing cognition, or necessitating an increase in antidyskinetic medications. Instead, we found no change in the number of anti-PD medications prescribed at discharge or in the amount of levodopa prescribed. Our results are consistent with those of Meco et al.,[7] who also found that risperidone effectively and safely controlled neuropsychiatric complications of anti-PD treatment.

Although the largest study of PD patients with psychosis and agitation to date, this pilot study was limited in that it comprised a small number of all-male subjects and the treating psychiatrists also administered the assessments. Furthermore, 2 of our subjects had been started on risperidone prior to our admission assessment and may have skewed the admission data. Another limitation is that side effects were measured with the RSSE, which is neither the most sensitive nor the most specific measure of extrapyramidal side effects. Future studies should examine the influence of demographic variables and comorbid medical conditions on the effectiveness of risperidone in PD patients.

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TABLE 1. Psychiatric measures at admission (AD) and discharge (DI) for patients with Parkinson's disease ($N=9$) treated with risperidone

Pt ID	Age	Diagnoses	Dose (mg)	MMSE		BPRS		HOST		THOT		CMAI		GAF		RSSE	
				AD	DI	AD	DI	AD	DI	AD	DI	AD	DI	AD	DI	AD	DI
1	73	Dementia due to PD; adjustment disorder; substance hallucinosis	1.0	19	20	37	26	4	3	8	4	36	32	30	45	25	38
2	70	Schizophrenia; dementia due to PD	1.0	23	27	28	26	3	3	4	5	31	41	35	45	7	8
3	70	Organic delusional disorder; organic mood disorder	2.0	25	28	43	22	5	3	11	4	31	31	40	75	22	14
4	71	Alzheimer's with delusions; alcohol dependence; PTSD	2.0	21	19	18	31	3	4	4	4	35	31	20	30	2	10
5	77	Substance hallucinosis; dementia due to PD; alcohol- induced persisting dementia	2.5	27	28	39	29	3	5	10	5	66	39	15	50	23	14
6	66	Major depressive disorder with psychosis; anxiety disorder; dementia due to PD; dysthymia	2.0	25	23	41	32	3	4	4	4	35	31	30	50	34	15
7	77	Substance delusional disorder; Alzheimer's dementia; dementia due to PD	3.0	21	14	52	31	10	3	11	8	46	33	30	40	27	17
8	78	Alzheimer's dementia with delusions; dementia due to PD; substance-induced psychotic disorder	1.5	13	20	42	33	10	7	8	7	65	36	20	25	35	10
9	72	Alzheimer's dementia; dementia due to PD; alcohol-induced persisting dementia; alcohol dependence; PTSD	2.0	0	0	47	31	8	3	9	4	87	72	10	15	4	6
		Mean		19.3	19.8	38.5	29.0	5.4	3.9	7.7	5.0	48	38.4	25	42	19.9	14.7
		SD		8.3	1.8	10.2	3.6	3.0	1.4	2.9	1.5	19.9	13.1	9.8	17.3	12.5	9.4
		P-value		0.69		0.02*		0.16		0.02*		0.05*		0.00*		0.24	

Note: MMSE = Mini-Mental State Examination; BPRS = Brief Psychiatric Rating Scale; HOST = Hostility subscale of BPRS; THOT = Thought Disorder subscale of BPRS; CMAI = Cohen-Mansfield Agitation Inventory; GAF = Global Assessment of Functioning; RRSE = Rating Scale for Side Effects; PD = Parkinson's disease; PTSD = posttraumatic stress disorder.
*Significant change from admission to discharge.

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