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Brief Report

Worsening of Motor Features of Parkinsonism With Olanzapine

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Summary: Clozapine is the current treatment of choice for drug-induced psychosis (DIP) occurring in Parkinson's disease. However, alternative medications have been sought because of the small but significant risk of agranulocytosis and the need for frequent blood testing. The new "atypical" antipsychotic olanzapine (OLZ) has recently been proposed as a safe and effective option for treating psychosis in this setting. To investigate this, we retrospectively evaluated all 12 of our patients treated with OLZ for DIP. Symptoms of psychosis were improved in nine of 12 patients, but nine of 12 patients also experienced worsening of motor functioning while on OLZ. The worsening was considered dramatic in six of these patients. Overall, there was no significant increase in levodopa doses on OLZ. Only one patient remained on OLZ at the time of the analysis. Nine patients were switched to alternative treatment for DIP. We conclude that although OLZ may improve symptoms of psychosis in parkinsonian patients, it can also worsen motor functioning. In some patients, the degree of motor worsening may be intolerable. **Key Words:** Parkinsonism—Psychosis—Olanzapine.

Drug-induced psychosis (DIP) is a common and often disabling complication of advancing Parkinson's disease (PD). The subgroup of patients with PD who have this problem are at increased risk for nursing home placement,[1] have an increased morbidity,[2] and pose a difficult management problem for families and physicians. In recent years, clozapine (CLZ) has become the treatment of choice for DIP in patients with PD. Its antipsychotic efficacy has been demonstrated in numerous studies and, because of its unique pharmacologic profile, it can be safely used in patients with PD without the risk of motor deterioration.[3] The results of a multicenter, placebo-controlled trial have recently been published and have confirmed its use in PD.[4] However, because of the small but significant risk of agranulocytosis associated with its use and the need for frequent blood monitoring, alternative medications have been sought.

Risperidone was the first "atypical" neuroleptic introduced as a potential alternative to CLZ in 1994. Early reports that extrapyramidal side effects were negligible at lower doses (<8 mg)[5] fueled enthusiasm for trying this medication in patients with PD who have DIP. However, it soon became obvious in clinical practice that risperidone could cause parkinsonism de novo and worsen motor features in patients with PD. This clinical experience was confirmed in the literature.[6,7]

Olanzapine (OLZ) is another recently introduced "atypical" neuroleptic (1997) which has been proposed as a safe and effective alternative to CLZ. Wolters et al.[8] reported that OLZ was effective in treating DIP in 15 nondemented patients with PD. They found no significant worsening of motor functioning in these patients. However, again subsequent reports in the literature have been less favorable.[9–13] In our own clinical practice we have seen some patients who, despite improvement of psychiatric symptoms, have had to discontinue OLZ treatment because of significant motor deterioration. We review this experience to better define the risks and benefits of using OLZ in this setting.

METHODS

We retrospectively evaluated the records of all 12 patients who were treated at the Albany Medical Center Movement Disorder Clinic for DIP with OLZ. Eleven

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patients had a diagnosis of idiopathic PD based on the presence of at least three of four cardinal features of PD and dopamine responsivity. One patient (patient no. 12) was thought to have diffuse Lewy body disease based on clinical features. Seven of the 11 patients with idiopathic PD had no cognitive impairment, two had mild memory loss, and three had more disabling symptoms of dementia. In all of the patients with idiopathic PD, the psychiatric symptoms were consistent with chronic dopaminomimetic psychosis. All patients were treated with OLZ in an open-label fashion as part of their routine care. OLZ was the first antipsychotic agent used in all 12 patients. It was started at a dose of 2.5 mg per day and increased in 2.5-mg increments as needed. The entire dose was given at bedtime. No attempt was made to keep antiparkinsonian medications stable and they were adjusted, if necessary, based on clinical need. Chart review was used to obtain demographic and clinical information. Data concerning improvement of psychosis and worsening of motor function is reported as a physician global impression based on patient and family report and, when possible, Unified Parkinson's Disease Rating Scale (UPDRS) motor scale scores, which were gathered prospectively during patient office visits. Scores were not available in those patients started on the drug prior to a visit or when OLZ was stopped between visits. Information was also obtained on whether OLZ was continued or if the patient was switched to an alternative antipsychotic medication.

RESULTS

Demographic and clinical data is presented in Table 1. Symptoms of psychosis were improved in nine of 12 patients (75%). In four of these the improvement was partial and in five there was a total resolution of psychotic symptoms. Psychosis improved in all five patients with dementia and four of seven (57%) nondemented patients. Worsening of motor function was reported in nine of 12 patients (75%) while on OLZ. In six patients, the worsening was considered to be dramatic and one patient had to be hospitalized because of immobility (patient no. 2). In six patients, UPDRS motor examination scores were available before and while on OLZ. In these patients, there was an average worsening of 9 points. One patient experienced a 54-point worsening (patient no. 8) which returned to baseline 1 week after switching to CLZ. Six of the nine who experienced motor worsening were nondemented. The average L-dopa dose was 734.1 mg prior to OLZ and decreased to 711.4 mg on OLZ. This change was not significant ($p < 0.3$; paired *t* test). Levodopa dose increased in three of 11 patients treated, decreased in five patients, and stayed the same in three patients. Only one of 12 patients remained on OLZ at the time of the analysis (patient no. 4). Two patients were switched to quetiapine and seven patients were switched to clozapine. UPDRS motor examination scores were available in four patients on OLZ and after being switched to clozapine (data not shown). In these patients, there was an average improvement in the UPDRS motor scale of 13 points. One patient died and one patient was lost to follow up.

DISCUSSION

OLZ was developed in an effort to create an "atypical" antipsychotic medication which, like clozapine, would treat both positive and negative symptoms of schizophrenia without the risk of extrapyramidal side effects. Studies have, in fact, shown that OLZ has a receptor binding

TABLE 1. *Clinical features of 12 patients treated with olanzapine*

Patient no.	Sex	Age (yrs)	Duration of PD (yrs)	Duration of psychosis (mos)	Duration of OLZ treatment (mos)	Maximum dose of OLZ (mg)	Psychosis improved on OLZ?	Motor function worsened on OLZ?	UPDRS motor before OLZ (L-dopa dose)	UPDRS motor on OLZ (L-dopa dose)	Was OLZ continued? (motor score)
1	F	79	6	12	12	5.0	Yes	No	54 (450 mg)	47 (650 mg)	No, QTP started
2	F	71	7	18	1	5	Yes	Yes	38 (300 mg)	45 (100 mg)	No, CLZ started (40)
3	M	74	14	24	1.5	7.5	No	Yes	NA (1100 mg)	NA (1100 mg)	No, CLZ started
4	M	48	7	1	12	2.5	Yes	No	40 (1400 mg)	26 (1600 mg)	Yes
5	M	80	3	12	10	5	Yes	No	45 (400 mg)	38 (350 mg)	No, died
6	F	69	8	16	4	5	Yes	Yes	30 (700 mg)	NA (500 mg)	No, QPT started
7	M	73	17	48	4	2.5	No	Yes	26 (1875 mg)	46 (1875 mg)	No, CLZ started
8	F	70	12	12	2.5	10	Yes	Yes	17 (700 mg)	71 (500 mg)	No, CLZ started (26)
9	F	87	23	24	2	10	Yes	Yes	35 (700 mg)	NA (350 mg)	NA
10	M	84	6	1	10	10	Yes	Yes	NA (NA)	56 (350 mg)	No, CLZ started (43)
11	M	64	10	.75	.5	10	No	Yes	21 (450 mg)	NA (800 mg)	No, CLZ started (23)
12	F	74	7	12	11	5	Yes	Yes	NA (0.0 mg)	50 (0.0 mg)	No, CLZ started (43)
Total (Average)		(72.8)	(10)	(15.1)	(5.9)	(6.5)	9/12	9/12	(734.1 mg)	(711.4 mg)	

UPDRS, Unified Parkinson's Disease Rating Scale; PD, Parkinson's disease; OLZ, olanzapine; QTP, quetiapine; CLZ, clozapine; NA, not available.

Motor score is the total of the UPDRS motor subscale.

profile and behavioral pharmacology similar to clozapine.[14,15] In contrast to clozapine, however, OLZ has not been associated with a significant occurrence of agranulocytosis. As a result, OLZ has been proposed as an alternative to clozapine for the treatment of DIP in PD.

The results of the first published prospective open trial in PD[8] suggest that OLZ can effectively treat DIP without worsening motor symptoms. In contrast, subsequent publications of open-label data have indicated that significant worsening of motor symptoms can be seen in patients with PD treated with this drug.[9–13] In agreement with these latter reports, the results of our retrospective analysis lead us to also conclude that although OLZ is effective in reducing symptoms of psychosis, it may worsen motor functioning in a majority of patients with PD who have DIP. Seventy-five percent of our patients experienced worsening of motor symptoms after being placed on OLZ. In 50%, the worsening was profound enough to cause additional disability and one patient had to be hospitalized. Graham et al.[12] speculated that the worsening seen in their patients who were given open-label OLZ was the result of the relatively high starting dose of 5 mg per day compared with the 1 mg per day starting dose used in the favorable report of Wolters et al.[8] Our patients were started on 2.5 mg per day which is currently the lowest commercially available pill size in the United States. Despite this lower starting dose and careful upward titration, dictated by the need for better control of psychosis, most of our patients still experienced motor worsening. Our average maximum OLZ dose (6.5 mg) was identical to that of Wolters et al.[8] Additionally, only three of 11 patients on L-dopa were able to increase their dose while on OLZ. This contrasts sharply with the well-established experience with CLZ. Finally, and perhaps most troubling, is the finding that only one of 12 patients treated with OLZ was still on this medication at the time of the analysis. Nine patients were switched to alternative antipsychotic treatment even though six of them had experienced some improvement in their psychotic symptoms.

Wolters et al.[16] have suggested that a favorable outcome is more likely when OLZ is used to treat typical dopaminomimetic psychosis in nondemented idiopathic patients with PD and that the observation by Friedman[9] of frequent motor deterioration was the result of poor patient selection. Our results call this idea into question because nondemented patients were just as likely to experience motor worsening (six of nine, 66%) as those with some degree of dementia (three of five, 60%).

Obviously, there are limitations to this type of uncontrolled retrospective analysis. In addition, biases in favor of and against treatment success can influence investigators with extensive prior experience in treating DIP with CLZ. Despite these shortcomings, the results reported here strongly suggest that the idea that OLZ is free of extrapyramidal side effects should now be viewed with skepticism. In our own practice, we have abandoned the use of OLZ in this setting. Additional prospective, controlled clinical trials are needed to more clearly delineate the role, if any, of OLZ treatment in patients with PD who have DIP.

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