Switching From Depot Antipsychotic Drugs to Olanzapine in Patients With Chronic Schizophrenia

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Background: Patients with chronic schizophrenia (DSM-IV criteria) often receive depot antipsychotic medications to assure longer administration and better compliance with their treatment regimen. This study evaluated whether patients stabilized on depot antipsychotic medication could be successfully transitioned to oral olanzapine.

Method: In a 3-month open-label study, 26 clinically stable patients with schizophrenia taking depot antipsychotics for over 3 years were randomly assigned to continue on their current depot dose or to switch to oral olanzapine. Clinical ratings (Positive and Negative Syndrome Scale [PANSS], Global Assessment of Functioning [GAF] scale, and Clinical Global Impressions [CGI] scale) and side effect parameters (Abnormal Involuntary Movement Scale [AIMS], Barnes Akathisia Scale, AMDP-5 scale, vital signs, and weight) were obtained monthly.

Results: Oral olanzapine patients (N = 13) demonstrated significant clinical improvement over the depot control group (N = 13) from baseline to 3-month endpoint (PANSS total, p = .012; PANSS general, p = .068; PANSS negative, p = .098; CGI-Improvement, p = .007; CGI-Severity, p = .026; GAF, p = .015). Side effect rating scales showed no statistical differences between the 2 groups (AIMS, Barnes Akathisia Scale, AMDP-5, vital signs). The depot control group showed no statistical superiority in any measure except weight change (p = .0005). After 3 months, all olanzapine patients preferred olanzapine to their previous depot medications and chose to continue on olanzapine treatment.

Conclusion: Clinicians may expect clinical improvement when switching chronically psychotic patients from traditional depot antipsychotic drugs to oral olanzapine. Switching may be completed within a 4-week period with relative compliance being maintained and patients preferring oral olanzapine to their previous depot medications.

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Current practices for optimizing treatment of patients with chronic psychosis include (1) switching patients from older (conventional) to newer (atypical or novel) antipsychotic drugs,[1] and (2) switching patients from newer antipsychotic drugs with less favorable side effect profiles to newer antipsychotic drugs with more favorable side effect profiles.[2] We know less about switching patients with chronic psychosis from long-acting depot conventional antipsychotic drug injections to newer oral antipsychotic drugs.[3] In an effort to better understand the switching process from a depot to an oral antipsychotic and to define the efficacy and safety of this process, we studied chronically psychotic patients receiving depot antipsychotic drugs as we switched them to orally administered olanzapine over a 3-month period.

METHOD

Study Sample

Study patients received depot antipsychotic drugs for at least 3 years before entering into the study. All study participants (N = 26) were outpatients, between ages 18 and 65 years, and met DSM-IV[4] criteria for schizophrenia. Most had historically been placed on the depot form of antipsychotic medication secondary to noncompliance, often complicated by substance abuse. Patients were considered competent and gave informed consent following an explanation of the study and possible side effects, as approved by the Louisville Veterans Affairs Medical Center Research and Development Committee and Human Studies Subcommittee. Treating psychiatrists

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referred stable patients who were not optimally functioning and might benefit from a trial of oral olanzapine.

Treatment Schedule

In this open-label study, patients were randomly assigned to either continue their current depot antipsychotic drug (control group, N = 13) or to switch to oral olanzapine (N = 13). The control group continued on depot drugs for 3 months without change in dosage. The olanzapine patients were started on olanzapine, 10 mg/day, while simultaneously receiving depot drugs during the first month. After the first month, olanzapine patients received no further depot medication but continued on olanzapine alone for a total of 3 months of olanzapine. The treating psychiatrist titrated the medication dosage as clinically warranted in increments/decrements of 5 mg/day each month, not exceeding a total of 20 mg/day. In addition, patients who were randomized to olanzapine were followed for 3 additional months to further evaluate treatment outcomes, the results of which will be reported in a separate publication.

Concomitant Drugs

Study patients continued to receive all other prestudy baseline medications, including psychotropic drugs. An attempt was made to maintain concomitant drugs, including anticholinergic medications, constant at the prestudy doses in all patients so that only 1 variable (depot preparation vs. oral olanzapine) was changed.

Assessments

Clinic time and frequency of clinic visits during the study were generally constant at 1 to 2 hours per month, similar to prestudy treatment for both the control and olanzapine patients.

Clinical parameters were assessed using the Positive and Negative Syndrome Scale (PANSS),[5] the Clinical Global Impressions (CGI) scale,[6] and the Global Assessment of Functioning (GAF) scale[4] at baseline and monthly intervals.

Safety was assessed by the AMDP-5 scale,[7] which measures 40 comprehensive somatic signs consistent with untoward effects of psychotropic drugs, the Abnormal Involuntary Movement Scale (AIMS),[8] the Barnes Akathisia Scale (BAS),[9] and vital signs including weight.

Statistical Methods

We summarized and compared the 2 study groups at baseline and monthly for the duration of the study. Because of some small cell sizes, we compared frequencies using the Fisher exact test. In the case of non-Gaussian distributions, we used Mann-Whitney U tests to compare groups and reported medians. To compare Gaussian data over time, we used repeated-measures analysis of variance. Contrasts of interest were compared using t tests. Line or profile plots were generated to depict changes over time. A p value of less than or equal to .05 was considered statistically significant, and p values between .05 and .10 were also noted as potentially significant in this pilot study.

Table 1. Characteristics of Patients in the Olanzapine Group Versus the Control Group

Characteristic	Olanzapine (N = 13)		Control (N = 13)		p Value
Age, median, y	45		48		.223
Age at onset of psychosis, median, y	26		23		.579
Duration of illness, median, y	19		23		.113
Sex	N	%	N	%	
Male	13	100	13	100	1.0
Female	0	0	0	0	
Race					
White	9	69	6	46	.428
African American	4	31	7	54	
Schizophrenia subtype					
Paranoid	13	100	12	92	1.0
Disorganized	0	0	1	8	
Course of schizophrenia					
Episodic with interepisode residual symptoms	13	100	12	92	1.0
Episodic with interepisode residual symptoms with prominent negative symptoms	0	0	1	8	1.0
No. of hospitalizations					
< 10	3	23	4	31	1.0
≥ 10	10	77	9	69	

RESULTS

Demographics

There were no statistically significant differences between control and olanzapine patients in terms of sex, ethnicity, diagnoses, age at illness onset, illness duration, or number of hospitalizations (Table 1). The majority of patients were white with a mean ± SD age of 45.9 ± 7.6 years, a mean age at illness onset of 25.6 ± 6.8 years, and a mean duration of illness of 20.3 ± 7.9 years.

Efficacy

Clinical improvement in baseline-to-endpoint (3-month) data was significantly superior in the olanzapine group compared with the decanoate patients (Table 2) as seen in PANSS total scores (p = .012), PANSS general scores (p = .068), PANSS negative scores (p = .098), CGI-Improvement (CGI-I) scale (p = .007) and CGI-Severity of Illness (CGI-S) scale scores (p = .026), and GAF scores (p = .015). There was no statistical difference for PANSS positive scores (p = .141).

Safety

Side effect rating scales demonstrated no statistical difference between the decanoate and olanzapine groups in

Table 2. Mean Change in Efficacy Measures, Baseline to Endpoint in Depot (N = 13) and Olanzapine (N = 13) Patients

	Baseline		Endpoint		Change		
Measure	Mean	SD	Mean	SD	Mean	SD	p Value
PANSS							
Total							
Depot	66.00	13.44	72.46	13.98	6.46	7.89	.012
Olanzapine	68.08	16.95	64.85	17.09	–3.23	10.13	
Positive							
Depot	14.85	5.0	16.00	4.93	1.15	2.67	.141
Olanzapine	16.23	6.46	15.38	4.63	–0.85	3.91	
Negative							
Depot	15.31	5.47	18.23	6.31	2.92	4.73	.098
Olanzapine	16.08	7.18	15.61	6.05	–0.46	5.29	
General							
Depot	35.85	7.51	38.23	8.56	2.38	5.09	.068
Olanzapine	35.62	8.12	33.85	10.24	–1.77	5.95	
CGI-Severity							
Depot	4.85	0.72	4.85	0.72	0.00	0.41	.026
Olanzapine	4.85	0.66	4.42	0.70	–0.42	0.49	
GAF							
Depot	45.00	9.10	43.85	9.64	1.15	3.95	.015
Olanzapine	42.77	6.03	44.85	6.21	–2.08	2.06	

Abbreviations: CGI = Clinical Global Impressions scale, GAF = Global Assessment of Functioning scale, PANSS = Positive and Negative Syndrome Scale.

baseline-to-endpoint changes including AIMS (p = .947), BAS-objective (p = .479), BAS-subjective awareness (p = .545), BAS-subjective distress (p = .153), BAS-global (p = .448), and AMDP-5 (p = .139).

Vital signs showed no statistical differences between control and olanzapine groups from baseline to endpoint (systolic blood pressure, p = .687; diastolic blood pressure, p = .587; pulse, p = .900; temperature, p = .492; and respirations, p = .315).

Weight gain was statistically greater in the oral olanzapine group compared with the decanoate group at the end of the 3-month study period (p = .0005). Mean ± SD weight at baseline was 196.38 ± 35.33 lb (89.08 ± 16.03 kg) for olanzapine patients and 197.00 ± 47.98 lb (89.36 ± 21.76 kg) for controls. The olanzapine-treated patients experienced a mean weight gain of 8.00 ± 7.36 lb (3.63 ± 3.34 kg) over the 3-month treatment period while the control group lost 1.69 ± 4.48 lb (0.77 ± 2.03 kg).

Drug Dose

For control depot patients, prestudy depot doses remained constant throughout the study: mean ± SD fluphenazine decanoate = 67.9 ± 40.7 mg intramuscular (IM) total 4-week dose (7 patients) and mean haloperidol decanoate = 173.7 ± 116.2 mg IM total 4-week dose (6 patients). For olanzapine patients, mean prestudy depot drug doses were fluphenazine decanoate = 76.7 ± 25.27 mg IM total 4-week dose (5 patients) and haloperidol decanoate = 150.0 ± 83.45 mg IM total 4-week dose (8 patients). The mean third-month final olanzapine daily dose was 12.31 ± 4.39 mg.

Compliance

Medication compliance, assessed by documentation of each depot drug IM injection, was 100% for the control group, which was greater than their historical levels. For the olanzapine group, patients were questioned about medication use, a pill count was done, and patient logs were reviewed at each visit. Our best estimate is that olanzapine patients took their study drugs approximately 90% of the time.

Outcomes

After 3 months, all olanzapine patients preferred that drug to their previous depot medications and chose to continue to receive olanzapine. All study patients completed the 3-month trial. During this time, 1 patient from the control group was hospitalized; no patient from the olanzapine group was hospitalized.

DISCUSSION

This study is one of the first to compare conventional depot antipsychotic medication to any atypical antipsychotic drug, and to olanzapine in particular. Previous investigations comparing depot antipsychotics with atypical oral agents either were anecdotal,[10] were retrospective,[11] did not have a depot control group,[3] or used atypical antipsychotic drugs other than olanzapine.[3,11,12]

The switch from depot to olanzapine in our study population was marked by superior efficacy of olanzapine with comparable compliance within the constraints of a 3-month study, despite a history of refractoriness and noncompliance to treatment on previous oral antipsychotics. All patients in the olanzapine arm of our study successfully completed the 3-month switch from depot to olanzapine, with each patient preferring the oral olanzapine and opting to stay on olanzapine treatment beyond the 3 months of the evaluation period. The search for predictive factors favoring olanzapine administration was preempted by successful transition from depot drugs for all patients.

Baseline to 3-month measures demonstrated significant improvement in the olanzapine group compared with decanoate in PANSS total, PANSS general, PANSS negative, CGI-I, CGI-S, and GAF scores. Both subjective and objective evidence of clinical improvement occurred as early as the first month of olanzapine treatment. During the remainder of the study, olanzapine patients continued to improve compared with the control group, which was consistent with findings of previous investigations comparing olanzapine with the conventional antipsychotic haloperidol.[13,14]

Furthermore, there was no worsening of adverse events including akathisia or dyskinetic movements as

measured by the AMDP, AIMS, or Barnes Akathisia Scale ratings in the olanzapine group after the switch, and there were no statistical changes in vital signs when comparing the 2 groups. Weight gain was the only parameter where the depot group showed a result superior to olanzapine patients. Most of the weight gain appeared to occur in the first 4 weeks of olanzapine treatment. These findings were similar to other studies where weight gain decreased after the first 6 weeks and was minimal at the end of the first year after initiation with olanzapine.[15]

Switching

Our switching strategy was one of gradual withdrawal of the depot drug while simultaneously starting oral olanzapine at an initial full dose of 10 mg/day. This approach has demonstrated the greatest efficacy and tolerability when switching oral antipsychotics to oral olanzapine as opposed to (1) the abrupt withdrawal of the other oral antipsychotic drug while switching to olanzapine or (2) the gradual increase of olanzapine while switching from conventional oral antipsychotic drugs.[1,16,17] It was not known, however, if this gradual decrease of an antipsychotic in depot form would work while simultaneously starting oral olanzapine at the full 10-mg/day dose.

Olanzapine patients tolerated the switch quite well, with no significant increase in side effects even during the first transitional month when both depot agents and olanzapine were on board. This strategy when switching patients from depot to oral olanzapine may be more successful than older cross-titration methods such as slowly reducing the dose of the older drug while gradually increasing the dose of the newer drug[18] or starting olanzapine when the next depot drug is due.[19]

Study Limitations

Our study sample was small, and the study duration for the comparison of the 2 treatment groups was only 3 months; therefore, important questions such as the rates of relapse associated with a depot preparation versus an oral medication could not be compared. Though our raters were initially blinded to the drug, they became unblinded as patients in the study often revealed whether they were receiving parenteral or oral drug, given the obvious difference in route of administration. Additionally, compliance was measured by counting pills and historical data from patients rather than by more reliable methods such as measuring olanzapine serum concentrations. Likewise, depot serum concentrations were not measured, which could have given a clearer estimate of duration of the effect of the depot medication after its cessation.

CONCLUSION

We demonstrated clinical stability when switching chronically psychotic patients from conventional depot antipsychotic drugs to oral olanzapine in a select group of patients. Of further clinical importance, we found that switching may be completed within a 4-week period with relative compliance being maintained and patients preferring oral olanzapine to their previous depot medications.

Additional studies with larger sample size and greater study duration are needed to more definitively confirm our observations and extend our recommendations to the main body of chronically psychotic patients. Larger study samples comparing different treatments may show significant differences in relapse/rehospitalization rates only after 1 or more years.

Drug names: fluphenazine (Permitil, Prolixin, and others), haloperidol (Haldol and others), olanzapine (Zyprexa).

REFERENCES

1. Kinon BJ, Basson BR, Gilmore JA, et al. Strategies for switching from conventional antipsychotic drugs or risperidone to olanzapine. J Clin Psychiatry 2000;61:833–840
2. Littrell KH, Johnson CG, Hilligoss NM, et al. Switching clozapine responders to olanzapine. J Clin Psychiatry 2000;61:912–915
3. Desai NM, Hug Z, Martin SD, et al. Switching from depot antipsychotics to risperidone: results of a study of chronic schizophrenia. Adv Ther 1999;16:78–88
4. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association Press; 1994
5. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Schizophr Bull 1987;13:261–276
6. Guy W. Clinical Global Impressions scale. ECDEU Assessment Manual for Psychopharmacology. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976:218–222
7. Association for Methodology and Documentation in Psychiatry. The AMDP system in clinical psychopharmacology. Br J Psychiatry 1986; 148:467–468
8. Guy W. Abnormal Involuntary Movement Scale. ECDEU Assessment Manual for Psychopharmacology. US Dept, Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976:534–537
9. Barnes TRE. A rating scale for drug-induced akathisia. Br J Psychiatry 1989;154:672–676
10. Strauss AJ, Bailey RK, Dralle PW, et al. Conventional psychotropic-induced tremor extinguished by olanzapine [letter]. Am J Psychiatry 1998;155:1132
11. Malla AK, Norman RMG, Kotteda V, et al. Switching from therapy with typical antipsychotic agents to risperidone: long-term impact on patient outcome. Clin Ther 1999;21:806–817
12. Kirov GK, Murray RM, Seth RV, et al. Observations on switching patients with schizophrenia to risperidone treatment. Acta Psychiatr Scand 1997;95:439–443
13. Tollefson GD, Beasley CM, Tran PV, et al. Olanzapine versus haloperidol in the treatment of schizophrenia and schizoaffective and schizophreniform disorders: results of an international collaborative trial. Am J Psychiatry 1997;154:457–464
14. Beasley CM Jr, Tollefson G, Tran P, et al. Olanzapine versus placebo and haloperidol: acute phase results of the North American double-blind olanzapine trial. Neuropsychopharmacology 1996;14:111–123
15. Beasley CM. Safety of olanzapine. J Clin Psychiatry 1997;15:19–21
16. Weiden PJ, Aquila R, Dalheim L, et al. Switching antipsychotic medications. J Clin Psychiatry 1997;58(suppl 10):63–72
17. Masand PS, Berry SL. Switching antipsychotic therapies. Ann Pharmacother 2000;34:200–207
18. Amery W, Marder SR. Safety and switching issues of novel antipsychotics. Int J Psychiatry Clin Pract 1998;2:S43–S49
19. Taylor D. Switching from typical to atypical antipsychotics. CNS Drugs 1997;8:285–292