Strategies for Switching From Conventional Antipsychotic Drugs or Risperidone to Olanzapine

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Background: This study compared the efficacy and safety of 4 therapeutically relevant strategies for switching clinically stable patients from a conventional antipsychotic drug or risperidone to olanzapine.

Method: Two hundred nine outpatients with a DSM-IV diagnosis of schizophrenia or schizoaffective disorder who were clinically stable while being treated with a conventional antipsychotic drug or risperidone were openly randomly assigned to either abrupt or gradual discontinuation of their prior antipsychotic drug. Patients were further randomly assigned in a double-blind fashion to immediate olanzapine initiation (olanzapine, 10 mg q.d. for 3 weeks) or stepwise initiation (a sequence of 1 week each on placebo; olanzapine, 5 mg q.d.; and olanzapine, 10 mg q.d.). The efficacy of these 4 switching paradigms was assessed using the Clinical Global Impressions (CGI)-Improvement scale, Patient's Global Impressions (PGI)-Improvement scale, and Positive and Negative Syndrome Scale (PANSS). Safety assessments included ratings for extrapyramidal symptoms, cognitive impairment, adverse events, laboratory parameters, weight change, and vital signs.

Results: The paradigm of gradual antipsychotic drug discontinuation combined with an initial full dose of olanzapine, 10 mg/day, had the most favorable efficacy and tolerability profile overall. By week 3, the majority of completing patients on all 4 switching paradigms were either improved or clinically unchanged (≥ 90%). No clinically significant differences between switching paradigms were seen in laboratory values or vital signs.

Conclusion: In this study, switching clinically stable outpatients with a diagnosis of schizophrenia or schizoaffective disorder to olanzapine was most successful when a full therapeutic dose of olanzapine was immediately initiated while gradually discontinuing prior conventional antipsychotic drug or risperidone treatment. Overall, switching was achieved without increased vulnerability to relapse or to occurrence of clinically burdensome antipsychotic drug withdrawal symptoms in the majority of patients.

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Currently, few reported studies provide insight on a preferred strategy of switching patients from one antipsychotic drug to another.[1–7] Because novel antipsychotic drugs, such as olanzapine, are rapidly evolving as the standard of care owing to the possibility for greater clinical improvement and a more favorable safety profile, defined methods for switching patients from prior antipsychotic drugs to newer agents are needed. Further, a better understanding of the potential benefits and risks gained from switching across atypical antipsychotic drugs is required to address problems associated with patients who may be experiencing a less-than-optimal clinical response from their current atypical antipsychotic drug.

Although seeking further therapeutic benefit may be warranted for some clinically stable patients, in certain cases, clinicians may be reluctant to switch from the present antipsychotic drug to a novel antipsychotic drug such as olanzapine. Potential events known or hypothesized to occur during drug transition periods include relapse of psychotic symptoms due to inadequate antipsychotic drug treatment[8,9]; neuroleptic "withdrawal syndrome" as the present antipsychotic drug is rapidly discontinued[10]; and the potential for adverse drug-drug interactions characterized by excessive sedation, confusion, motor incoordination, and cognitive worsening[1] as a newly initiated atypical antipsychotic drug is added to the current therapy. Hesitancy over switching antipsychotic drugs may be compounded in an outpatient setting by the lack of clinical control over the patient's treatment response. After deciding that the benefit of switching therapies is greater than the risk of any untoward events that may result, the clinician may be further reluctant to start the new antipsychotic drug at the recommended therapeutic dose, preferring instead to start low and titrate up.

The purpose of this study was to compare 4 different methods of switching partially remitted, clinically stable outpatients diagnosed with schizophrenia or schizoaf-

fective disorder from their current oral antipsychotic drug (either a conventional antipsychotic drug or risperidone) to olanzapine. These switching paradigms included abrupt versus gradual discontinuation of prior antipsychotic drug in conjunction with immediate (full therapeutic dose) versus stepwise initiation of olanzapine.

METHOD

Patient Population

Male or female outpatients 18 years or older who fulfilled the criteria for schizophrenia or schizoaffective disorder as defined in the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV)[11] were screened for inclusion in this study. Patients were required to be clinically stable for 8 weeks on a consistent dose of only 1 antipsychotic drug (either a conventional antipsychotic drug or risperidone) prior to study entry and to be rated no worse than moderately ill on the Clinical Global Impressions (CGI)-Severity scale[12] (≤ 4) at 2 time points, 2 weeks apart, before randomization. Patients were not included if they had serious, unstable medical illnesses or were treated with an injectable depot neuroleptic within 12 weeks prior to study entry. Because of clozapine's reported necessity to be withdrawn more slowly,[13] patients taking clozapine within 6 weeks prior to study entry were excluded. This study was conducted at 17 sites in the United States from July 1997 to May 1998. Written informed consent was obtained from all participants. Institutional review board approval was given at each of the study sites.

Study Design

This study consisted of a baseline observation and screening phase and a 3-week treatment phase, designed specifically to observe the transition period of switching from a prior antipsychotic drug to olanzapine. At the beginning of the treatment phase, patients were openly randomly assigned to either abrupt or gradual discontinuation of their prior antipsychotic drug. Those patients undergoing abrupt discontinuation had their prior antipsychotic drug completely stopped at the time of random assignment (week 0). Those patients randomly assigned to gradual discontinuation had their dose of prior antipsychotic drug reduced to 50% by the end of the first week of observation and completely discontinued by the end of the second week. Simultaneously, patients were further randomly assigned in a double-blind fashion to receive either (1) olanzapine, 10 mg q.d., or (2) a sequence of 1 week each on placebo, olanzapine, 5 mg q.d., and olanzapine, 10 mg q.d. Figure 1 summarizes the 4 paradigms used to switch patients from their prior antipsychotic drug to olanzapine.

The use of benzodiazepines and antiparkinsonian drugs was permitted during the study, although the dose was limited and only clinically essential use was recommended.

Assessments

The primary efficacy measure was the CGI-Improvement scale,[12] which was evaluated weekly, using a 1- to 7-point scale, to record changes in the patient's condition since baseline. The Patient's Global Impressions (PGI)-Improvement scale[12] and the Positive and Negative Syndrome Scale (PANSS)[14] were also measured weekly as secondary efficacy assessments. The Brief Psychiatric Rating Scale (BPRS)[15] and the BPRS-Positive subscale were extracted from the PANSS and individual items were scored 0–6.

Medical and psychiatric history and physical examinations were taken at study entry, and weight and vital signs were measured at study entry and at all subsequent visits. Standard laboratory parameters were measured at the beginning and at the end of the study.

The collection of adverse events was based on an objective adverse event scale (Association for Methodology and Documentation in Psychiatry [AMDP-5]),[16,17] which was administered and recorded weekly. Changes in cognition and level of consciousness were assessed by weekly Mini-Mental State Examinations (MMSE).[18] Extrapyramidal symptoms (EPS) were assessed weekly using the Simpson-Angus Scale,[19] the Barnes Akathisia Scale,[20] and the Abnormal Involuntary Movement Scale (AIMS).[12]

Statistical Methods

Data from all randomly assigned patients were included in the analyses. Total scores on rating scales were derived from individual item scores; if any single item score was missing, the total score was treated as missing. Where a single endpoint was analyzed for each patient, the last measure after randomization was used (LOCF).

For continuous efficacy and safety parameters, analysis of variance (ANOVA) was used to compare treatment effects among the 4 switching paradigms. For LOCF change from baseline analyses, the independent variables in the ANOVA included treatment and site. Visitwise analyses were performed using ANOVA on observed cases at each timepoint including terms for treatment and site. Within-group analyses used 1-sample t tests or Wilcoxon signed rank tests.

Categorical comparisons used either chi-square or Fisher exact tests. In the categorical analysis of laboratory analytes, the subset of patients with normal laboratory values for a given analyte at baseline was analyzed according to whether patients were above or below the normal range at endpoint. The frequency with which patients gained or lost more than 7% of their body mass was also determined.

Treatment-emergent adverse events were defined as events that worsened or first occurred after baseline, and frequencies were compared using chi-square tests.

Switching groups were also compared with respect to concomitant use of benzodiazepines and antiparkinsonian medications. The mean daily dose (diazepam equivalents

Table 1. Baseline Patient Characteristics

Variable	Abrupt Antipsychotic Drug Discontinuation: Immediate Olanzapine Initiation	Abrupt Antipsychotic Drug Discontinuation: Stepwise Olanzapine Initiation	Gradual Antipsychotic Drug Discontinuation: Immediate Olanzapine Initiation	Gradual Antipsychotic Drug Discontinuation: Stepwise Olanzapine Initiation	Total	p Value
Sample size, N	52	53	54	50	209	
Age, mean ± SD, y	43.6 ± 12.4	46.2 ± 11.3	42.4 ± 12.5	43.9 ± 13.6	44.0 ± 12.4	.453[a]
Gender, N (%)						
Male	27 (51.9)	32 (60.4)	34 (63.0)	29 (58.0)	122 (58.4)	.695[b]
Female	25 (48.1)	21 (39.6)	20 (37.0)	21 (42.0)	87 (41.6)	
Prior antipsychotic,[c] N (%)						
Haloperidol	16 (30.8)	15 (28.3)	15 (27.8)	11 (22.0)	57 (27.3)	.635[b]
Risperidone	17 (32.7)	13 (24.5)	11 (20.4)	16 (32.0)	57 (27.3)	
Other	19 (36.5)	25 (47.2)	28 (51.8)	23 (46.0)	95 (45.4)	
Duration of illness, mean ± SD, y	17.9 ± 9.4	18.9 ± 10.2	16.5 ± 10.5	19.5 ± 12.0	18.2 ± 10.5	.477[a]
CGI-Severity,[d] mean ± SD score	3.5 ± 0.6	3.4 ± 0.8	3.4 ± 0.7	3.5 ± 0.7	3.4 ± 0.7	.839[a]

[a]F test.
[b]Fisher exact test.
[c]Single antipsychotic drug taken prior to study entry.
[d]Only patients with post-baseline Clinical Global Impressions-Severity measure (N = 204).

and benztropine equivalents, respectively) of patients taking each medication in addition to study therapy was summarized for each treatment group and analyzed using ANOVA.

All hypothesis tests were 2-sided using a significance level of $\alpha = .05$, unless otherwise specified.

RESULTS

Patient Demographics

Of 243 patients screened at baseline, 209 patients were randomly assigned to a switching paradigm. Of 209 patients randomized, 152 had been treated with a conventional antipsychotic drug and 57 with risperidone. The mean age in this study was 44.0 years (range, 18 to 83 years). There were no significant differences in age, gender, previous antipsychotic medication, duration of illness, or CGI-Severity score among the 4 switching paradigms at baseline (Table 1). Ten patients (5%) were over 65 years of age.

Patient Disposition

One hundred seventy-two patients (82.3%) completed the study. No significant differences in discontinuation rates overall ($p = .181$) or for any specific reason were seen between the switching paradigms ($p \geq .162$). Fourteen patients (6.7%) discontinued the study due to adverse events; however, there were no significant differences between switching paradigm groups in discontinuation rate either overall ($p = .542$) or for any given adverse event. Numerically, the most discontinuations due to adverse events occurred in the "*abrupt* antipsychotic drug (APD) discontinuation + *stepwise* olanzapine (OLZ) initiation" group (6/53 patients; 11.3%). Four patients (1.9%) discontinued the study due to lack of efficacy.

Efficacy Results

Endpoint (LOCF). The median CGI-Improvement score at endpoint was 3 (minimally improved) for all 4 switching groups. There were no significant between-group differences in mean CGI-Improvement at endpoint ($p = .672$). Across all patients (completing and non-completing patients), 65% at endpoint had better CGI-Improvement scores (32% minimally improved, 30% moderately improved, 3% much improved), 22% were unchanged, and 13% were worse. Switching by "*gradual* APD discontinuation + *immediate* OLZ (10 mg) initiation" resulted in the numerically greatest proportion of improved patients (68.6%; of which 31.4% were minimally improved, 33.3% were moderately improved, 3.9% were much improved).

Table 2 displays mean change at endpoint (LOCF) for secondary efficacy parameters. Mean change from baseline to endpoint in BPRS Total and PANSS Negative scores improved significantly within-group for all 4 switching paradigms ($p \leq .010$), although no significant between-group differences were seen ($p = .387$ and $p = .219$, respectively). Mean changes in BPRS Positive score indicated significant differences between switching paradigm groups ($p = .001$). All switching paradigms showed significantly greater improvement in BPRS Positive scores at endpoint as compared to the "*abrupt* APD discontinuation + *stepwise* OLZ initiation" regimen ($p \leq .044$). Patients switched by "*gradual* APD discontinuation + *immediate* OLZ (10 mg) initiation" showed the greatest numerical improvement in BPRS Positive scores.

Table 2. Mean ± SD Change From Baseline in Efficacy Rating Scale Results (LOCF)[a]

Rating	Abrupt Antipsychotic Drug Discontinuation: Immediate Olanzapine Initiation	Abrupt Antipsychotic Drug Discontinuation: Stepwise Olanzapine Initiation	Gradual Antipsychotic Drug Discontinuation: Immediate Olanzapine Initiation	Gradual Antipsychotic Drug Discontinuation: Stepwise Olanzapine Initiation	p Value
BPRS Total					
N	50	51	50	50	
Baseline	19.5 ± 9.6	18.9 ± 10.3	19.1 ± 9.7	19.5 ± 8.7	.892
Mean change	–6.2 ± 6.9	–3.9 ± 11.3	–6.0 ± 8.6	–5.8 ± 7.0	.387
PANSS Total					
N	49	51	50	50	
Baseline	67.4 ± 16.0	64.4 ± 17.9	64.9 ± 16.6	65.7 ± 14.2	.790
Mean change	–10.2 ± 11.2	–6.1 ± 20.0	–8.4 ± 14.2	–8.7 ± 11.5	.521
BPRS Positive					
N	51	51	50	50	
Baseline	5.5 ± 3.7	5.0 ± 3.3	5.3 ± 3.9	5.0 ± 2.9	.198
Mean change	–1.8 ± 2.3	–0.7 ± 3.5	–1.9 ± 3.0	–1.2 ± 2.2	.001
PANSS Negative					
N	51	51	50	50	
Baseline	19.6 ± 5.8	17.3 ± 5.8	18.6 ± 6.5	18.7 ± 5.6	.279
Mean change	–2.7 ± 3.2	–1.5 ± 5.8	–1.5 ± 4.4	–2.3 ± 4.2	.219

[a]Abbreviations: BPRS = Brief Psychiatric Rating Scale, PANSS = Positive and Negative Syndrome Scale. When a single endpoint was analyzed, the last measure after randomization was used as the last observation carried forward (LOCF).

Visitwise (observed cases). One week after randomization, the paradigm of "*gradual* APD discontinuation + *immediate* OLZ (10 mg) initiation" was superior to "*abrupt* APD discontinuation + *stepwise* OLZ initiation," according to both CGI- and PGI-Improvement (p = .005). Likewise "*gradual* APD discontinuation + *immediate* OLZ (10 mg) initiation" was superior to "*gradual* APD discontinuation + *stepwise* OLZ initiation," according to PGI-Improvement (p = .022). At 2 weeks, the paradigm of "*gradual* APD discontinuation + *immediate* OLZ (10 mg) initiation" was marginally superior to "*abrupt* APD discontinuation + *stepwise* OLZ initiation," as measured by PGI-Improvement (p = .098 overall; p = .014 pairwise). Three weeks after the initiation of the medication switch, there were no significant differences between the 4 switching paradigms in either CGI-Improvement or PGI-Improvement (Figure 2).

Figure 3 shows the percentage of patients improved, unchanged, and worsened according to CGI-Improvement scores over time. Although no significant differences were noted among these proportions at any timepoint, the numerically greatest proportion of completing patients who improved at weeks 1 and 2 were in the "*gradual* APD discontinuation + *immediate* OLZ (10 mg) initiation" group (51% and 71%, respectively). By week 3, the majority of completing patients on all 4 switching paradigms were either improved or clinically unchanged (≥ 90%). When comparing those patients who entered the study on conventional antipsychotic drug agents versus risperidone, the only significant difference between therapy groups was at week 1; those patients who were gradually discontinued from risperidone with immediate olanzapine (10 mg) initiation experienced greater improvement relative to the other switching paradigms (p = .024).

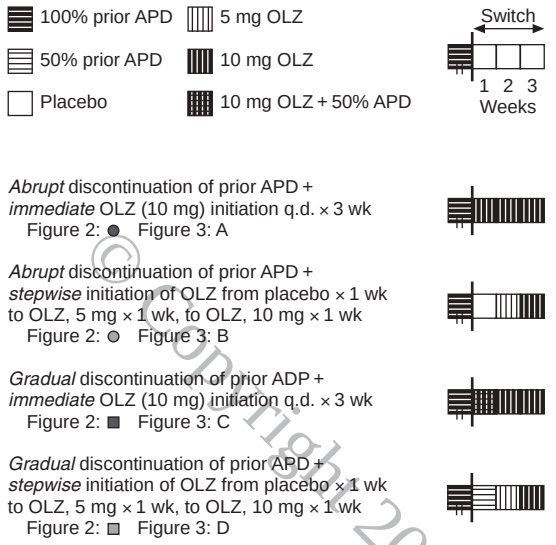
Safety

Frequencies of treatment-emergent solicited adverse events (AMDP-5) with p ≤ .10 are summarized in Table 3. Of the 4 switching paradigms, "*abrupt* APD discontinuation + *stepwise* OLZ initiation" had a significantly greater incidence of shortened sleep and difficulty falling asleep, as well as the numerically greatest incidence of interrupted sleep, early waking, and increased perspiration. Drowsiness occurred significantly most often in the "*abrupt* APD discontinuation + *immediate* OLZ (10 mg) initiation" group. There was no significant difference among the switching paradigms in any of the spontaneous, unsolicited adverse event frequencies.

Significant within-group decreases in EPS (Simpson-Angus, Barnes Akathisia, and AIMS ratings) were noted under all switching paradigms with the exception of "*abrupt* APD discontinuation + *immediate* OLZ (10 mg) initiation" in which the Barnes Akathisia and AIMS reductions did not reach statistical significance. No significant differences in EPS improvement between the switching paradigms were noted. No significant between-group differences were seen in the mean daily use of antiparkinsonian medications (p = .273) and benzodiazepines (p = .490) as described in Table 4.

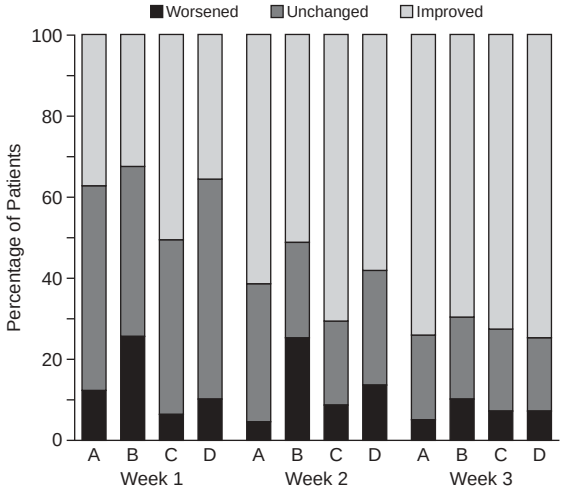
MMSE scores increased numerically for all groups but reached within-group statistical significance only in the "*gradual* APD discontinuation + *immediate* OLZ (10 mg) initiation" group (p = .025). There were no significant differences among the switching paradigms in MMSE change (p = .993).

Figure 1. Medication Switching Paradigms[a]



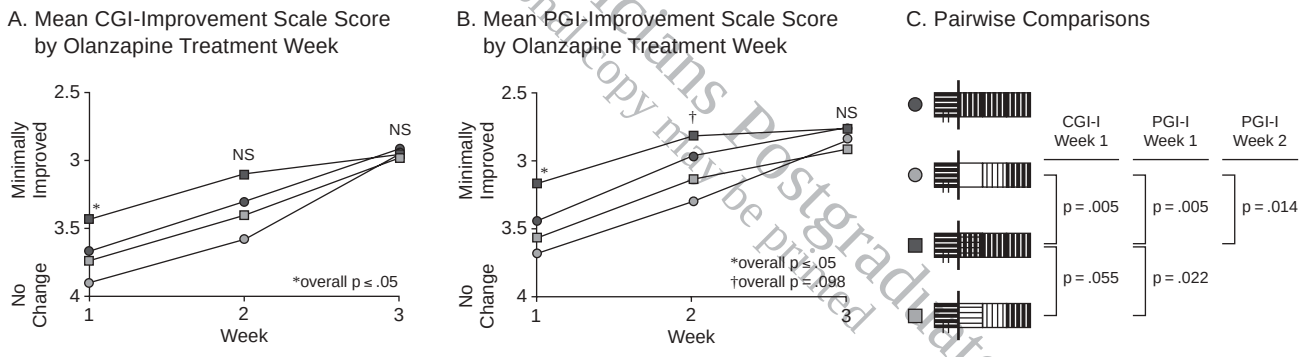
[a]Abbreviations: APD = antipsychotic drug, OLZ = olanzapine.

Figure 3. Percentage of All Patients That Improved, Were Unchanged, or Worsened Based on the CGI-Improvement Scale Score by Olanzapine Treatment Week[a]



[a]Medication switching paradigms corresponding to A–D are defined in Figure 1.

Figure 2. Mean Improvement in Scale Scores by Olanzapine Treatment Week[a]



[a]Medication switching paradigms represented by the symbols (●, ○, ■, □) are defined in Figure 1.

The proportion of patients with normal laboratory values at baseline whose values were above the upper limit or below the lower limit of normal at endpoint was not significant for any of the 33 routine laboratory analytes measured ($p \geq .097$). All groups showed a significant within-group decrease in serum prolactin concentration ($p \leq .002$).

Only 1 patient (female; baseline weight = 40.8 kg; baseline body mass index = 17; "*gradual* APD discontinuation + *immediate* OLZ (10 mg) initiation" group) gained more than 7% of her body mass, gaining 3.2 kg. No other patients gained or lost more than 7% of body mass. The mean ± SD weight increase over the 4 treatment arms at endpoint was 0.76 ± 1.83 kg ($p < .001$).

DISCUSSION

A reality of clinical pharmacotherapy is that many patients demonstrate only a partial response to antipsychotic drug therapy. Even though many such patients are considered to be clinically stable on their current medication, it is hypothesized that patients such as these could show further clinical improvement and/or a more favorable safety profile if they could be safely switched to other antipsychotic drugs. However, the comparative risks associated with different methods of antipsychotic drug discontinuation are relatively unknown.[1,21–23] Moreover, the safety and tolerability of initiating one of the newer, atypical antipsychotic drugs, such as olanzapine, at a therapeutic

dose concurrently with other antipsychotic drugs are equally unclear.

This study utilized 4 clinically relevant strategies to determine an optimal method for switching clinically stable patients with schizophrenia or schizoaffective disorder from a conventional antipsychotic drug or risperidone to olanzapine. Although the study protocol did not define a priori a "successful" switch, elements that could be considered to designate a "successful" switching paradigm would include either clinical improvement or no significant deterioration or worsening in clinical efficacy rating scale scores, a high study completion rate, low adverse event reports, and few clinically significant changes in laboratory values and vital signs.

Table 3. Number (%) of Patients With Treatment-Emergent Adverse Events Solicited From AMDP-5 (for p ≤ .10; *p < .05)[a]

	Abrupt Antipsychotic Drug Discontinuation		Gradual Antipsychotic Drug Discontinuation		
Event	Immediate Olanzapine Initiation (N = 51)	Stepwise Olanzapine Initiation (N = 52)	Immediate Olanzapine Initiation (N = 50)	Stepwise Olanzapine Initiation (N = 50)	p Value
Shortened sleep	8 (15.7)	14 (26.9)	3 (6.0)	3 (6.0)	.006*
Difficulty falling asleep	6 (11.8)	16 (30.8)	4 (8.0)	8 (16.0)	.016*
Increased perspiration	4 (7.8)	8 (15.4)	2 (4.0)	1 (2.0)	.071
Interrupted sleep	4 (7.8)	12 (23.1)	4 (8.0)	5 (10.0)	.081
Early waking	5 (9.8)	11 (21.2)	3 (6.0)	4 (8.0)	.100
Drowsiness	18 (35.3)	12 (23.1)	13 (26.0)	5 (10.0)	.022*

[a]Shaded values are the paradigms with the highest event rate row-wise.
Abbreviation: AMDP-5 = Association for Methodology and Documentation in Psychiatry.

Table 4. Mean ± SD Daily Dose of Antiparkinsonian Medications and Benzodiazepines

	Abrupt Antipsychotic Drug Discontinuation		Gradual Antipsychotic Drug Discontinuation	
Medication	Immediate Olanzapine Initiation (N = 52)	Stepwise Olanzapine Initiation (N = 53)	Immediate Olanzapine Initiation (N = 54)	Stepwise Olanzapine Initiation (N = 50)
Benzodiazepine[a] mg/day, mean ± SD	0.26 ± 0.65	0.17 ± 0.55	0.37 ± 0.91	0.22 ± 0.64
Antiparkinsonian[b] mg/day, mean ± SD	0.44 ± 0.91	0.74 ± 1.26	0.80 ± 1.15	0.87 ± 1.40

[a]Between-group differences, p = .490; diazepam equivalents.
[b]Between-group differences, p = .273; benztropine equivalents.

Switching Paradigms

According to these criteria, the most successful switching paradigm appeared to be "*gradual* APD discontinuation + *immediate* OLZ (10 mg) initiation." This paradigm was superior to the other methods in demonstrating the earliest (i.e., week 1) and greatest mean improvement in CGI- and PGI-Improvement and the greatest improvement in BPRS Positive scores. The congruence of CGI- and PGI-Improvement scores is indicative of the overall clinician/patient satisfaction with olanzapine. While the overlapping of prior antipsychotic drug with olanzapine could potentially have precipitated untoward drug-to-drug interactions, adverse event frequencies in this group were low relative to other groups. Although the possibility of "adverse behavioral syndrome," defined as a drug-drug interaction secondary to polypharmacy that produces adverse behavioral changes that are reflected in efficacy measures, was potentially greatest for this group, no evidence of decreased efficacy was seen, nor were there clinically significant changes in MMSE scores. These data suggest that for many patients a full therapeutic dose of olanzapine can be added to a patient's current treatment, while concurrently discontinuing patients from their prior antipsychotic drug without clinical worsening. In frail, elderly patients, however, clinicians may wish to consider a lower add-on dose of olanzapine, since it was noted that the only syncopal episode leading to discontinuation occurred in an 82-year-old male subject assigned to this paradigm.

The strategy of "*abrupt* APD discontinuation + *immediate* OLZ (10 mg) initiation" also provided a satisfactory switching process. While immediate cessation of prior antipsychotic drug had the potential to produce antipsychotic drug withdrawal symptoms, significant evidence (such as increased sleep disturbance) was not seen relative to other groups. However, this switching paradigm was associated with significantly greater somnolence. Thus for the majority of patients switching abruptly, these data suggest that administration of an immediate 10-mg olanzapine dose lessened the likelihood for the appearance of potential antipsychotic drug withdrawal symptoms.

The paradigm of "*gradual* APD discontinuation + *stepwise* OLZ initiation" was in some sense the most cautious switching paradigm in that the overlap of prior antipsychotic drug and olanzapine was only 1 week long with both drugs at ~50% of therapeutic levels. Although the delayed initiation of olanzapine did not offer any obvious clinical advantages in this patient population, this approach may warrant further study in more frail, physically compromised patient populations.

In the final switching paradigm, "*abrupt* APD discontinuation + *stepwise* OLZ initiation," patients experienced 1 week without active therapeutic intervention. While theoretically allowing prior antipsychotic drug adverse events (i.e., acute EPS, sedation, etc.) to wane prior to starting olanzapine, it can be argued that patients in this group were at risk of inadequate antipsychotic drug treatment and were at greatest risk to develop a possible antipsychotic drug withdrawal syndrome. After 1 week of treatment, only one half of patients in this paradigm had experienced clinical improvement, whereas two

thirds of "*gradual* APD discontinuation + *immediate* OLZ (10 mg) initiation" patients had improved. After 3 weeks of treatment, results indicate that patients had not experienced a significant clinical worsening of symptoms and had, in most respects, "caught up" to patients undergoing other switching methods. However, this group did experience the numerically lowest study completion rate. Furthermore, this switching paradigm was characterized by significantly greater incidence of sleep disturbance and autonomic instability (increased perspiration). Also, 6 of the 14 patients discontinuing due to adverse events were in this group, including the only incidences leading to discontinuation of dizziness, nausea, depression, and hallucinations. These findings lend strength to the validity of a study design that, although only 3 weeks in duration, apparently allowed sufficient time for certain withdrawal symptoms to manifest.

Other Findings

There were no clinically significant differences among the 4 paradigms in the occurrence of abnormal laboratory values. There was a significant improvement (reduction) in EPS, as measured by the Simpson-Angus Scale, after olanzapine initiation. Furthermore, there was no significant difference in the relatively low doses of antiparkinsonian medication across the 4 paradigms. These data support previous reports demonstrating that olanzapine has a comparatively superior safety profile with respect to EPS.[24] The finding that benzodiazepine dose was quite low and not different across the paradigms indicates that outcome was not influenced by differences in benzodiazepine treatment regardless of the method for switching antipsychotic drugs. Additionally, patients in this study experienced a significant reduction in prolactin levels after olanzapine initiation. Prolactin level reduction is an important observation because of the large number of patients discontinuing general antipsychotic drug therapy owing to the effects of prolactin elevations.[25]

Limitations

Several points should be considered when interpreting the results of this study. Even with a relatively generous sample size for a study of this type, since no group of patients remained on their prior antipsychotic drug throughout the study, the ability to quantify the specific therapeutic benefit of switching versus not switching was somewhat lessened. Further, the purpose of this study was neither to determine whether patients should be switched nor to determine outcome on olanzapine versus prior antipsychotic drug treatment. Rather, this study was designed to determine optimal methods for drug switching to olanzapine.

This study was performed in clinically stable patients, and, although the proposed paradigms may work equally well in other patient groups, special consideration should be taken when switching more frail or geriatric patients who may respond equally well to lower doses of olanzapine treatment. This study was purposely designed as a partly open-label study, so that a broad inclusion of prior antipsychotic drugs could be used to reflect a diverse scope of clinical practice; however, patients were randomly assigned to the method of prior antipsychotic drug discontinuation. Conversely, including a variety of prior antipsychotic drugs limits the power of the study to specifically characterize the medication transition from any particular antipsychotic drug to olanzapine. Finally, the conclusions reached regarding switching methods may not generalize to novel antipsychotic drugs other than olanzapine due to the individual pharmacology of each compound. Additional well-controlled studies of the switching process are needed to address these limitations and to confirm the findings of this study.

CONCLUSION

In clinically stable patients with schizophrenia or schizoaffective disorder among whom switching to olanzapine was indicated, the addition of a therapeutic dose of olanzapine (10 mg/day) while gradually discontinuing the patient's prior conventional medication or risperidone was the optimal medication switching strategy of those examined. Switching stable outpatients to olanzapine treatment under several different switching paradigms was accomplished in the majority of patients without an increased vulnerability to relapse or the occurrence of clinically burdensome antipsychotic withdrawal symptoms. Most patients experienced clinical improvement as a result of the medication switch.

Drug names: benztropine (Cogentin and others), clozapine (Clozaril and others), diazepam (Valium and others), haloperidol (Haldol and others), olanzapine (Zyprexa), risperidone (Risperdal).

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