Effectiveness of Switching to Ziprasidone for Stable but Symptomatic Outpatients With Schizophrenia

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Background: Many outpatients with schizophrenia experience persistent symptoms or side effects on their current antipsychotic regimen. Few studies have prospectively examined the effects of the prior medication or switching method on the safety and efficacy of a newly available antipsychotic. Efficacy and tolerability of ziprasidone were evaluated in patients with DSM-IV schizophrenia or schizoaffective disorder who were switched from conventional or atypical antipsychotics in three 6-week, multicenter, randomized, open-label, parallel-group trials.

Method: Stable outpatients with persistent symptoms or troublesome side effects on (1) conventional antipsychotic (N = 108), (2) olanzapine (N = 104), or (3) risperidone (N = 58) therapy were switched to an open-label, 6-week, flexible-dose trial of ziprasidone (40–160 mg/day). Patients were randomly assigned at baseline to 1 of 3 switching schedules during the first week of ziprasidone therapy. Baseline and outcome assessments included Positive and Negative Syndrome Scale (PANSS) and Clinical Global Impressions of Severity (CGI-S) ratings.

Results: All 3 switching strategies were well tolerated for all 3 patient groups. After 6 weeks on ziprasidone therapy, significant (p < .05) improvements were observed on all major symptom measures and almost all subscales for all switched subgroups.

Conclusion: Switching stable but symptomatic outpatients from their previous antipsychotic to ziprasidone was generally well tolerated and was associated with symptom improvements 6 weeks later. Improvements occurred in patients recently on other first-line atypical antipsychotic, as well as in those on conventional antipsychotic, treatment. While limitations of switching study designs do not permit interpretation of comparative efficacy, these studies suggest that outpatients who partially respond to conventional antipsychotics, risperidone, or olanzapine may experience improved control of psychotic symptoms following a switch to ziprasidone.

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Formerly, most stable outpatients with schizophrenia would remain on the same antipsychotic for years. Residual symptoms of schizophrenia would usually be treated with dosage adjustments and persistent extrapyramidal symptoms (EPS) with adjunctive antiparkinsonian agents. The recent introduction of a new class of antipsychotic medications has dramatically increased the therapeutic options in the treatment of schizophrenia. Patients and clinicians are looking for better and healthier outcomes above and beyond relapse prevention. This change in outlook has altered the willingness and readiness of clinicians to change antipsychotic medications for patients who are "stable" but not "well." Nowadays, "stable" outpatients with persistent symptoms or distressing side effects are much more likely to try changing their antipsychotic medication. Pharmacoepidemiologic studies have shown that the 1-year switch rates now range from 25% to 50%.[1]

Relative to older antipsychotics, the class of newer atypical agents offers a wider range of symptom benefits and an overall reduction in burden of side effects, especially EPS, and reduced risk of tardive dyskinesia. It is not surprising that some of the more common reasons to switch from a conventional antipsychotic to a first-line atypical antipsychotic include persistent positive symptoms, negative symptoms, and affective symptoms and the need to reduce the risk of tardive dyskinesia and reduce ongoing EPS side effects.[2,3] Because of these poten-

tial benefits, most patients in the United States are being treated with 1 of the first-line atypical antipsychotics.

In the last few years, another trend has emerged. Many patients continue to have problems on the newer medications that may be indications for switching antipsychotics. They may continue to have persistent positive, negative, or cognitive symptoms or experience distressing side effects (e.g., residual EPS, weight gain) from the newer antipsychotic medications. Given this state of flux, there are many unanswered questions related to switching antipsychotics when another first-line atypical antipsychotic becomes available. Are patients already taking a first-line atypical antipsychotic likely to benefit from a switch to a more recently available first-line atypical antipsychotic? Are there clinically relevant differences in the number or severity of side effects after switching to a newer medication with hypothetical side effect advantages?

These questions are asked by clinicians whenever a new antipsychotic becomes available. Most recently these questions have been asked of ziprasidone. Ziprasidone is the fifth atypical antipsychotic introduced in the United States, following clozapine, risperidone, olanzapine, and quetiapine. Clinical trials have demonstrated that ziprasidone's antipsychotic efficacy is comparable to that of the conventional antipsychotic haloperidol and the atypical antipsychotic olanzapine for the treatment of patients with acute exacerbation of schizophrenia and schizoaffective disorder.[4–7] In addition to improving positive and negative symptoms, ziprasidone has been shown to improve comorbid depressive symptoms[4,5] and some aspects of cognitive dysfunction.[8] In clinical trials, ziprasidone has exhibited low liability for EPS[4–6,9] and weight gain.[4,5,9] In a recently reported trial, significantly less weight gain was observed after 6 weeks of treatment with ziprasidone than with olanzapine.[7] These clinical data suggest that ziprasidone may offer advantages in some patients who cannot tolerate or do not respond well to conventional and other atypical antipsychotic agents.

As with previously introduced atypical medications, major issues for clinicians considering switching an outpatient to ziprasidone include the optimal switching technique, as well as its side effect profile and effectiveness for common indications. These concerns are not directly addressed by random-assignment, double-blind trials using parallel groups. On the other hand, pre- and post-switching studies are better able to characterize the specific medication status prior to switching, as well as provide useful information on crossover methods. Therefore, to further explore these clinical questions, we examined the safety and tolerability of switching to ziprasidone using 3 distinct switching strategies and clearly identifying 3 different medication groups entering into the ziprasidone switch. We evaluated the impact of a 6-week ziprasidone trial on persistent symptoms and common side effects. The 3 studies differed in the patients' maintenance

antipsychotic medication status just prior to the ziprasidone switch. One group had been taking a conventional antipsychotic, another group, risperidone, and the third, olanzapine. The study design used an effectiveness orientation, in that study physicians prescribed open-label ziprasidone using flexible doses and only enrolled patients when there was a clear clinical indication to change antipsychotic medications.

METHOD

Objective

The primary objective was to compare the effectiveness of 3 ways to switch stable but symptomatic outpatients from their previous antipsychotic to ziprasidone. Data were pooled from 3 individual studies with the same basic design—the studies differed only in terms of patients' prior antipsychotic regimen. In each of the 3 studies, clinical improvement from baseline to endpoint in the entire study population (with switching groups pooled) was also evaluated.

Design

All 3 studies were 6-week, open-label, multicenter, parallel-group trials enrolling stable outpatients. The studies differed only with regard to patients' baseline antipsychotic treatment, which consisted of a stable dosage regimen of monotherapy with either (1) conventional antipsychotic, (2) risperidone, or (3) olanzapine.

For the crossover to ziprasidone, all groups were started on open-label oral ziprasidone at 80 mg/day (given as 40 mg b.i.d.) for 2 days, followed by flexible dosing between 40 and 160 mg/day (given in divided, twice-daily doses). The patients' prior antipsychotic regimen was discontinued in 1 of 3 randomly assigned ways: (A) complete discontinuation of the previous antipsychotic the day before starting ziprasidone; (B) immediate dose reduction, with a 50% reduction in the dosage of the previous antipsychotic for the first week of ziprasidone, followed by discontinuation starting week 2; and (C) delayed dose reduction, during which the previous antipsychotic drug was reduced by 50% on the fourth day of open-label ziprasidone and then discontinued by the second week of ziprasidone treatment. For patients to be eligible for the study, their prior medication had to be a monotherapy regimen within an accepted dosage range. Regardless of switching technique, all patients were on ziprasidone monotherapy after the first week of the ziprasidone crossover.

Eligibility and Screening

Participants were men and women with a DSM-IV diagnosis of schizophrenia or schizoaffective disorder who were between 18 and 55 years of age and had at least an eighth grade reading level and the capacity to provide

written, informed consent (which was subsequently obtained). At screening, participants were required to have been outpatients taking a stable oral monotherapy regimen of one of the relevant antipsychotics within the recommended daily dose, which was defined as ± 25% of the range given by the medication's package insert. Patients had to be at least partially responsive to their current regimen, but be judged to be candidates for changing their antipsychotic on the basis of either persistent symptoms or continued side effects. Patients with active substance abuse, medication nonadherence, or treatment-refractory positive symptoms were excluded, as were those with active depressive or suicidal symptoms (i.e., Montgomery-Asberg Depression Rating Scale score ≥ 16).

Efficacy Assessments

The primary measures of psychopathology were the Positive and Negative Syndrome Scale (PANSS; Total and Positive and Negative subscales),[10] the Brief Psychiatric Rating Scale derived from the PANSS (BPRSd), and the Clinical Global Impressions-Severity (CGI-S) and CGI-Improvement (CGI-I) scales.[11] Raters blinded to the patients' crossover group assignments administered these evaluations. The assessments were performed at baseline, before the switch to ziprasidone, and weekly through week 6 or at early termination.

Tolerability and Safety Assessments

Movement disorders (e.g., parkinsonism, tardive dyskinesia, akathisia) were evaluated at baseline and at 6 weeks or early termination by Simpson-Angus,[12] Barnes Akathisia,[13] and Abnormal Involuntary Movement Scale (AIMS)[14] rating instruments. In addition to physical and psychiatric examinations, assessments conducted at baseline and 6 weeks or early termination included an electrocardiogram (ECG), laboratory tests, and measurements of vital signs and body weight.

All observed or volunteered adverse events (AEs) were recorded at each visit, along with the date of onset, duration, the investigator's assessments of severity and the possible causative relationship to study drug, and whether an intervention (e.g., change of the ziprasidone dose or withdrawal from treatment) was required. Adverse events included treatment-emergent illnesses, exacerbation of preexisting illnesses, adverse drug reactions, and any adverse objective test findings that resulted in a change in study drug. Adverse events were reported using COSTART terminology.[15]

Statistical Analysis

For switching-schedule comparisons, efficacy variables within each study were analyzed pairwise across switching strategies at baseline and after the first and second weeks of ziprasidone treatment. Adverse events were compared among strategies within each study. The pri-

Table 1. Demographic and Baseline Characteristics in 270 Patients With DSM-IV Schizophrenia or Schizoaffective Disorder

Characteristic	Conventional Antipsychotics (N = 108)	Olanzapine (N = 104)	Risperidone (N = 58)
Men, %	70	63	67
Age, y			
Mean	39.3	36.0	37.2
Range	18–61	19–57	18–61
With schizophrenia, %	75	69	83
Weight, lb			
Mean	196.9	205.3	192.1
Range	121.0–305.8	110.0–349.8	114.4–308.0
PANSS Total score, mean ± SD	67.5 ± 16.3	65.6 ± 16.7	71.0 ± 18.7
PANSS Positive score, mean ± SD	15.8 ± 5.5	15.4 ± 5.7	16.4 ± 6.6
PANSS Negative score, mean ± SD	19.0 ± 6.4	18.8 ± 6.4	20.0 ± 6.9

Abbreviation: PANSS = Positive and Negative Syndrome Scale.

mary efficacy variables were PANSS Total score, BPRSd, CGI-S, and CGI-I. No formal a priori sample-size power calculation was performed in these studies.

Changes from baseline in psychopathology and global severity scores, Simpson-Angus scores, and weight were analyzed separately for each of the 3 antipsychotic groups. Changes from baseline were analyzed by analysis of covariance (ANCOVA) using last observation carried forward (LOCF) to endpoint (week 6 or study termination) in all patients; analyses of completers were also performed. The p values for comparisons of strategies were based on an ANCOVA model with baseline value as covariate and fixed-effect terms for center and treatment. The significance threshold was .05. Switching methods were not analyzed as covariates in the efficacy analyses because of the lack of significant effects of switching method. For occasions when the results of the crossover method of the 3 studies were the same, samples were pooled and the data reported as a single study. Post hoc chi-square testing was conducted to evaluate differences in discontinuation rates by switching strategy (both within and across studies) and by prior medication (i.e., by study).

RESULTS

Demographic and Baseline Characteristics

Of the 270 patients enrolled in these switching studies, 108 were taking conventional antipsychotics, 104 were taking olanzapine, and 58 were taking risperidone prior to switching to ziprasidone. Baseline demographics and symptoms were similar in these 3 groups (Table 1).

Discontinuations

Comparison of switching strategies. A potential proxy marker for the effectiveness and tolerability of switching antipsychotics is the overall rate of study discontinuation.

Discontinuation rates did not differ significantly by switching strategy, either within each study or when results were pooled across studies (p = NS). Rates of discontinuation deemed related to the study drug, whether due to adverse events or inadequate clinical response, were 11.4% for strategy A (complete discontinuation), 12.8% for strategy B (immediate dose reduction), and 2.9% for strategy C (delayed dose reduction) in the conventional antipsychotic study. In the olanzapine study, discontinuation rates were 11.8% for strategy A, 2.8% for strategy B, and 2.9% for strategy C. In the risperidone study, there were no discontinuations possibly related to the study drug for strategy A, and rates of 5% for strategy B and 9.5% for strategy C.

Patients pooled across switching strategies. The majority of study patients started on ziprasidone were able to complete 6 weeks of ziprasidone therapy. The studies were completed by 72%, 79%, and 79% of patients who switched to ziprasidone from conventional antipsychotics, olanzapine, or risperidone, respectively. Discontinuations due to inadequate clinical response occurred in 3.7%, 3.8%, and 1.7% of patients in the 3 groups, respectively. Discontinuations due to adverse events occurred in 11.1%, 6.7%, and 8.6% of patients in the 3 groups, respectively. Discontinuation rates also did not differ by prior medication status (p = .44), suggesting that the ability to complete crossover to ziprasidone was relatively independent of the specific first-line (non-clozapine) antipsychotic. Because of the concern that there may be differences in patterns of early adverse events depending on prior medication, we evaluated the frequency and reasons for discontinuation during the first 2 weeks of the study period. Eight (7.4%) patients switched from conventional antipsychotics discontinued treatment because of adverse events, whereas 2 (1.9%) patients switched from olanzapine and 2 (3.4%) patients switched from risperidone discontinued due to adverse events during the first 2 weeks.

Ziprasidone Dosing

Mean daily ziprasidone doses for the duration of treatment (i.e., the mean of the mean daily dose at each weekly visit) were similar in the 3 studies, and within each study they were similar among the 3 switching strategies. In the conventional antipsychotic study, the mean (SD) daily ziprasidone dose was 91 mg (± 26 mg) and the median 80 mg. For the olanzapine group, the mean was 90 mg (± 23 mg) and the median 84 mg; and for the risperidone group, the mean was 92 mg (± 24 mg) and the median 86 mg. Given the flexible-dose nature of the protocol, with permissible ziprasidone dose ranges between 40 and 160 mg/day, this study suggests that many of the investigators judged that a target daily dose in the 80- to 100-mg range is appropriate when switching stable outpatients with schizophrenia.

To determine whether there was any association between dose and discontinuation, we calculated mean and median daily doses of ziprasidone on the day before study completion or treatment discontinuation for completers of the study and discontinuing patients. The last day before completion or discontinuation was used to calculate dose to avoid coding errors from discontinuing patients taking only the morning dose on their last treatment day.

We found a pattern that both completers and discontinuing patients were within acceptable therapeutic dosing range, but that completers were taking somewhat higher doses than those who discontinued. In each of the 3 studies, the median daily dose was 120 mg for completers and 80 mg for patients discontinuing treatment. The mean daily dose was 109 mg for patients in the conventional antipsychotic group who completed the 6 weeks and 97 mg for patients who discontinued treatment. In the olanzapine switching study, the mean daily dose was 107 mg for completers and 89 mg for discontinuing patients. Among patients switched from risperidone, the mean daily dose was 106 mg for completers and 95 mg for discontinuing patients.

Use of Concomitant Medication

Lorazepam was administered to 26.9% of patients switched from conventional antipsychotics, 39.4% of patients switched from olanzapine, and 22.4% of those switched from risperidone, compared with baseline usage rates of 12.0%, 18.3%, and 13.8%, respectively. In all 3 groups, these rates reflected use during the first week of switching, after which use of lorazepam tended to decline steadily. By the end of the study, most patients who once received lorazepam were no longer taking it. At week 6, only 5.6% of patients switched from conventional antipsychotics, 8.7% of patients switched from olanzapine, and 10.3% of patients switched from risperidone were still receiving adjunctive lorazepam.

Zolpidem was used by 11.1% of those switched from conventional antipsychotics, 12.5% of those switched from olanzapine, and 15.5% of those switched from risperidone, versus respective baseline usage rates of 12.0%, 1.9%, and 6.9%. The pattern of zolpidem prescribing was similar to that of lorazepam, with most patterns reflecting use during the first week of switching, and declines in use thereafter. At the end of the 6 weeks, only 5.6% of patients switched from conventional antipsychotics, 1.9% of patients switched from olanzapine, and 5.2% of patients switched from risperidone were still receiving zolpidem. Of note is that the incidence of insomnia as an adverse event (Table 2) was higher in the olanzapine group (42.3%) than it was in the groups switched from conventional antipsychotics (21.3%) or risperidone (27.6%); these differential rates of insomnia may explain the higher usage rates of lorazepam and zolpidem in the olanzapine switch group.

Table 2. Summary of Discontinuations Due to Adverse Events and Most Frequently Reported Treatment-Emergent Adverse Events (incidence > 10% in any study)

Variable	Switched to Ziprasidone From Conventionals (N = 108)		Switched to Ziprasidone From Olanzapine (N = 104)		Switched to Ziprasidone From Risperidone (N = 58)	
	N	%	N	%	N	%
Discontinuations due to any adverse event	12	11.1	7	6.7	5	8.6
Adverse event > 10% in any study						
Insomnia	23	21.3	44	42.3	16	27.6
Somnolence	25	23.1	14	13.5	15	25.9
Nausea	16	14.8	17	16.3	6	10.3
Anxiety	20	18.5	22	21.2	5	8.6
Dizziness	17	15.7	16	15.4	3	5.2
Headache	12	11.1	14	13.5	4	6.9

Figure 1. Mean Percentage Improvement in Overall Efficacy Variables From Baseline (before the switch to ziprasidone) to Endpoint (week 6 after the switch to ziprasidone) for All Patients (LOCF)
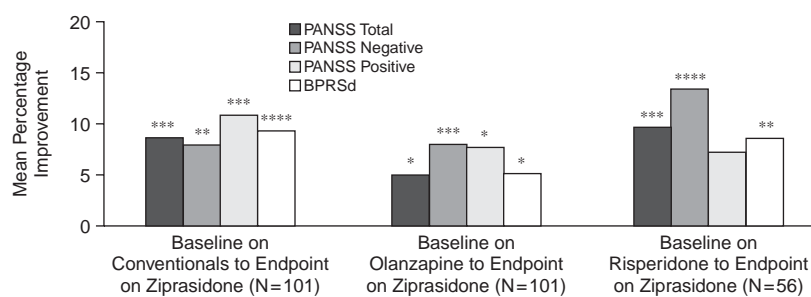
*p < .05 vs. baseline, **p < .01 vs. baseline, ***p < .005 vs. baseline, ****p < .0001 vs. baseline.
Abbreviations: BPRSd = Brief Psychiatric Rating Scale derived from the PANSS, LOCF = last observation carried forward, PANSS = Positive and Negative Syndrome Scale.

Changes in Symptoms and Global Illness Severity

Comparison of switching strategies. Among all patients (LOCF) in each of the 3 studies, there were no significant pairwise differences between any 2 switching strategies in change from baseline to endpoint PANSS Total, BPRSd, PANSS Negative subscale, PANSS Positive subscale, CGI-S, or CGI-I scores at endpoint. Analysis of study completers yielded similar results. Consequently, we report detailed results on changes in symptoms and global illness severity from patients pooled across switching strategies in each study.

Patients pooled across switching strategies. All patients (LOCF). Statistically significant improvements in overall psychopathology (all p < .05, PANSS Total score; all p < .05, BPRSd Total score) were observed for patients switched from conventional antipsychotics, olanzapine, or risperidone to ziprasidone (Figure 1). Improved psychopathology was also evident from the PANSS subscales analyzed. Positive symptoms significantly improved (p < .05) for patients switched from either conventional antipsychotics or olanzapine. Positive symptom

improvement in the risperidone group trended toward improvement but did not reach statistical significance (p = .08). Negative symptoms improved significantly (p < .005) in all 3 switch groups (Figure 1).

The mean CGI-S score improved significantly (p < .0001) at endpoint for patients switched from conventional antipsychotics to ziprasidone. There was no significant improvement (or worsening) of CGI-S scores for patients switched from either risperidone or olanzapine to ziprasidone. Mean CGI-I score was 3.3 in patients switched from conventional antipsychotics, 3.5 in patients switched from olanzapine, and 3.3 in patients switched from risperidone.

We examined the time course of symptom change. Significant improvement in PANSS Total score was observed as early as 1 week after the switch to ziprasidone from either olanzapine or risperidone (p < .05), and by 3 weeks after the switch from conventional antipsychotics to ziprasidone (p ≤ .001, Figure 2A). Improvement in negative symptoms followed a similar time course, with the changes observed after the switch from risperidone to ziprasidone evident by week 1 (p < .05) and from olanzapine to ziprasidone by week 2 (p < .05, Figure 2C). A significant improvement in positive symptoms was evident by weeks 2 and 3, respectively, in patients switched to ziprasidone from conventional antipsychotics or olanzapine (p < .01, Figure 2B). All statistically significant improvements were maintained or increased until endpoint.

Completers. From an effectiveness viewpoint, a completers' analysis addresses the question, "What is the response, should the patient actually receive a full trial of medication?" For the subgroup of patients who completed the studies (78, 82, and 46 patients switched from conventional antipsychotics, olanzapine, and risperidone to ziprasidone, respectively), statistically significant im-

Figure 2. Mean PANSS Total (A), Positive Subscale (B), and Negative Subscale (C) Scores by Week After the Switch to Ziprasidone From Conventional Antipsychotics, Olanzapine, or Risperidone for All Patients (LOCF)
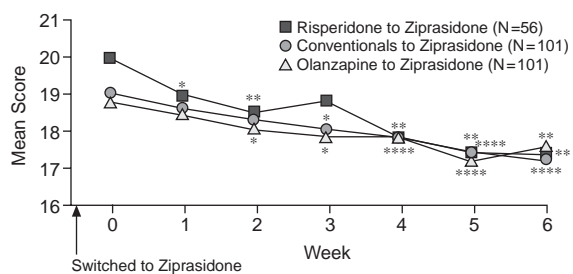

A. PANSS Total
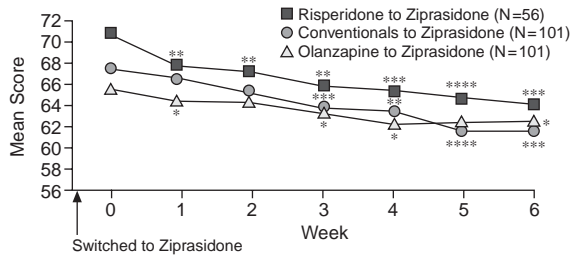
B. PANSS Positive subscale
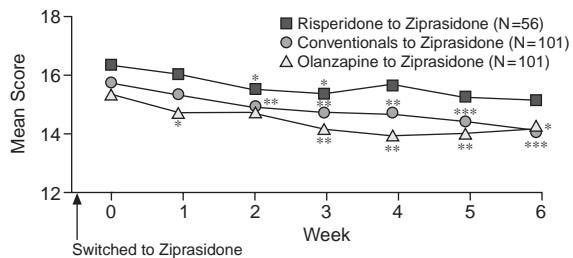
C. PANSS Negative subscale

*p < .05 vs. baseline, **p ≤ .01 vs. baseline, ***p ≤ .001 vs. baseline, ****p ≤ .0001 vs. baseline.
Abbreviations: LOCF = last observation carried forward, PANSS = Positive and Negative Syndrome Scale.

provements were observed both in PANSS Total (p < .003 in all studies) and in BPRSd Total score (p < .002 in all studies). In addition, there were significant improvements in all 3 studies in PANSS Positive (p < .002 in all studies) and PANSS Negative scores (p < .001 in all studies). For CGI-S, completers' results were similar to those of all patients (LOCF), with significant improvement from baseline in all 3 studies (p < .05).

Tolerability and Safety

Ziprasidone was generally well tolerated, with a safety profile consistent with that seen in other ziprasidone clinical trials. A summary of the most frequently reported adverse events and the discontinuation rates due to treatment-related adverse events is presented in Table 2.

In all 3 studies, few patients discontinued treatment because of adverse events during the first 2 weeks of treatment. In the switch from conventional antipsychotics study, 8 such withdrawals occurred: 3 with strategy A (complete discontinuation), 4 with strategy B (immediate dose reduction), and 1 with strategy C (delayed dose reduction). In the switch from olanzapine study, discontinuations numbered 2, 0, and 0, respectively; in the switch from risperidone study, they numbered 0, 2, and 0, respectively. A common clinical concern during crossover is the possibility of a symptom flare-up. The COSTART term *psychosis* could be considered to be a proxy marker for exacerbation of psychotic symptoms; the highest rate of psychosis as an adverse event was 8.8%, in patients switched from conventional antipsychotics through strategy C.

Data on both baseline and endpoint weight were available for 103 patients switched from conventional antipsychotics, 101 patients switched from olanzapine, and 56 patients switched from risperidone. For patients switched from olanzapine, a significant reduction in mean body weight (baseline 205.5 lb [93.4 kg], endpoint 201.5 lb [91.6 kg]; mean change –3.9 lb [–1.8 kg], p < .001) was observed. A lesser, but still significant, decline in mean body weight was seen in patients switched from risperidone (baseline 192.1 lb [87.3 kg], endpoint 190.3 lb [86.5 kg]; mean change –1.9 lb [–0.9 kg], p < .05). Patients switched from conventional antipsychotics exhibited no significant change in mean weight (baseline 197.6 lb [89.8 kg], endpoint 198.2 lb [90.1 kg]; mean change 0.6 lb [0.3 kg], p > .1). There was no significant correlation in any of the studies between baseline weight and change in weight at endpoint (p > .1).

Movement disorders were infrequent after ziprasidone therapy commenced, with mean Simpson-Angus scores improving significantly after the switch from conventional antipsychotics (baseline 2.5, endpoint 1.2; mean change –1.2 [52%]) or risperidone (baseline 1.6, endpoint 0.9; mean change –0.7 [44%]; p < .01). No significant change in mean Simpson-Angus scores occurred in patients switched from olanzapine (baseline 1.4, endpoint 1.5; mean change 0.1 [5.2%], p = .74). The highest incidence of dystonia, which occurred among patients switched from conventional antipsychotics, was 1.9%.

These 3 studies did not reveal any pattern of laboratory abnormalities associated with the switch to ziprasidone, nor were there any clinically relevant ECG alterations. In patients switched from conventional antipsychotics to ziprasidone, an increase in mean corrected QT interval (QTc) over baseline (387.3 ± 20.8 msec) of 3.9 ± 21.3 msec was observed at endpoint (391.2 ± 22.7; median = 388.6 msec). Among those switched from olanzapine, a mean increase of 4.4 ± 22.3 msec from baseline (387.4 ± 20.2 msec) was noted at endpoint (391.8 ± 19.6; median = 388.3 msec). Among patients switched from

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risperidone, there was a mean increase of 4.9 ± 20.6 msec from baseline (383.6 ± 22.9 msec) to endpoint (388.5 ± 21.8 msec; median = 386.8 msec). No patient exhibited QTc interval ≥ 500 msec while receiving ziprasidone.

DISCUSSION

Our results indicate that switching to ziprasidone reduced positive and negative symptoms and overall psychopathology in stable outpatients experiencing persistent symptoms or side effects on their current antipsychotic regimen. The magnitude of symptom response did not seem to be related to the specific class of antipsychotic used prior to the switch to ziprasidone. In other words, the degree and time course of response seemed similar for patients switched from a conventional antipsychotic, olanzapine, or risperidone.

In all of these studies, PANSS Total scores, BPRSd scores, and Positive and Negative subscale scores improved after the switch to ziprasidone. Significant improvement on the CGI-S was also observed for patients switched from conventional antipsychotics and olanzapine to ziprasidone.

Ziprasidone was well tolerated by these patients, as indicated by low discontinuation rates and by assessment of adverse events, vital signs, ECG, and clinical laboratory test results. More detailed data on changes in EPS and indices of health status are to be presented in a companion paper. In all 3 studies, the number of patients discontinuing treatment because of adverse events during the first 2 weeks of treatment was low, although it was somewhat higher among patients switched from conventional antipsychotics. It is possible that adverse events associated with the previous antipsychotic among patients switched because of poor tolerability account for this difference, although this cannot be determined from our data. One finding that may be clinically relevant is the higher reported rate of insomnia among patients switching from olanzapine compared with risperidone or conventional antipsychotics. It may be that insomnia is more likely to be reported when patients are switched from a sedating antipsychotic.

The specific crossover technique used during the first week of ziprasidone therapy did not seem to influence the outcome at 6 weeks. No significant differences in PANSS Total scores or Positive or Negative subscale scores, BPRSd Total scores, or CGI-S scores were observed between any of the strategies in any of the studies. Similarly, tolerability was comparable between switching strategies within each study. Of note is that the switching method did not seem to affect the efficacy response seen at endpoint or at 6 weeks. The subgroup of patients who completed the entire 6 weeks of ziprasidone treatment had a more robust response than the entire LOCF analysis

group. There is the unsurprising observation that study completers do the best, and the somewhat surprising observation that the switching method does not affect the likelihood of completing the trial or the robustness of the clinical response. It might be concluded from these observations that as long as the patient receives therapeutic antipsychotic doses, the exact switching technique is less important than completing a full therapeutic trial of the new antipsychotic.

Although switching of therapy is common in the treatment of patients with schizophrenia, and clinical considerations for this practice have been suggested,[1,2] there are only limited empiric data on the course and outcomes of switching. Malla et al.[3] reported results from a retrospective study of 31 outpatients who had been switched from a conventional antipsychotic to risperidone owing to lack of efficacy or poor tolerability. They found that 71% and 81% of the patients respectively, exhibited a positive response to the change in treatment, as measured by a 30% reduction in psychotic and disorganization symptoms. In addition, switching therapy resulted in significant declines in service utilization, level of psychotic disorganization, negative symptoms, and use of anticholinergic drugs.

Prospective data on switching are few. Kirov et al.[16] switched patients to risperidone after immediate discontinuation of prior antipsychotic therapy and a taper of anticholinergic agents. They reported that 23 (61%) of 38 patients switched successfully (i.e., completed the study with no consistent worsening in any rating scales). In an observational study of 130 patients switched from depot antipsychotics to risperidone, improvement was observed in PANSS scores, Global Assessment of Function, and indices of EPS after 3 months of treatment with risperidone.[17] More recently, Kinon et al.[18] have reported a 3-week open study in which 209 patients on conventional antipsychotics or risperidone were switched to olanzapine through 1 of 4 strategies. The results of this study were qualitatively similar to the results here: patients showed reductions in symptoms and side effects after completing 6 weeks of olanzapine, and switching technique did not affect the final outcome, except in the group that had a complete medication washout.

Our results suggest that stable but symptomatic outpatients being treated with a conventional antipsychotic, olanzapine, or risperidone may experience further improvement by switching to ziprasidone. This finding should be interpreted cautiously, however. Our studies employed an open-label design, which might bias efficacy findings in favor of ziprasidone, and other nonpharmacologic factors unrelated to the medication switch (e.g., regression to the mean) may have contributed to the symptom improvements seen. Also, patients in these studies were followed more closely (i.e., weekly) and more intensively tested for symptom improvement than might be done in clinical practice.

A switching design cannot be used to directly compare efficacy between antipsychotic medications, so it cannot be inferred from the improvements observed after 6 weeks of ziprasidone that ziprasidone has greater efficacy than the prior antipsychotic medications. Patients in these studies were screened specifically for not doing well on their current regimen, in terms of either symptoms or side effects. This kind of selection bias will skew the baseline ratings against the prior medication and possibly in favor of any subsequent switch medication (in this case, ziprasidone).

The apparent lack of difference in efficacy or tolerability between any of the 3 switching strategies also needs to be interpreted with caution, especially given the close monitoring received by patients in clinical trials. Expert consensus guidelines on switching, as well as clinical experience, indicate that the preferred switching method is to overlap the old and the new antipsychotic for several weeks.[19] The longest overlap period in these studies was 1 week. A 1-week crossover time frame is still much shorter than is commonly used in clinical practice. A more cautious conclusion from these studies is that a fast switching technique can be used safely when needed, assuming adequate clinical monitoring.

These results, however, provide the clinician with an empiric rationale and data on the strategy and results of switching to this new atypical antipsychotic. The orientation of these studies was more consistent with effectiveness research in attempting to guide clinical practice under real-world conditions once ziprasidone became available. The low dropout rate suggests that the clinical responses seen were pharmacologic and sustainable, as does the fact that many of these subjects continued on ziprasidone therapy for several years after the 6-week trial.

These findings might be interpreted to support differential efficacy between first-line atypical antipsychotics on the level of individual patients.[20] Available data from controlled, double-blind, random-assignment comparison studies indicate that ziprasidone has, on average, comparable efficacy to conventional antipsychotics and first-line atypical antipsychotics.[4–7] The results from these switching studies are consistent with a hypothesis of differential efficacy among atypical antipsychotics. This hypothesis, if true, would explain why there were comparable efficacy benefits from switching to ziprasidone even if the patient's last treatment had been a conventional antipsychotic or another first-line atypical antipsychotic. The data from these studies support the use of ziprasidone as a treatment option for stable outpatients with schizophrenia who continue to have symptoms from their current (non-clozapine) antipsychotic regimen.

In conclusion, the results from these 3 open-label studies suggest that patients can be successfully switched to ziprasidone from conventional or first-line atypical antipsychotics, and in a relatively short period, using any of 3 switching strategies commonly employed in clinical practice. The 3 switching strategies were equally well tolerated. In addition, many patients switched to ziprasidone may experience enhanced control of positive or negative symptoms or both.

REFERENCES

1. Weiden P, Mackell J. Differing side-effect burdens with newer antipsychotics. Presented at the 39th annual meeting of the New Clinical Drug Evaluation Unit (NCDEU) (sponsored by the National Institutes of Health); June 1–4, 1999; Boca Raton, Fla

2. Masand PS, Berry SL. Switching antipsychotic therapies. Ann Pharmacother 2000;34:200–207

3. 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

4. Daniel DG, Zimbroff DL, Potkin SG, et al, and the Ziprasidone Study Group. Ziprasidone 80 mg/day and 160 mg/day in the acute exacerbation of schizophrenia and schizoaffective disorder: a 6-week placebo-controlled trial. Neuropsychopharmacology 1999;20:491–505

5. Keck P Jr, Buffenstein A, Ferguson J, et al. Ziprasidone 40 and 120 mg/day in the acute exacerbation of schizophrenia and schizoaffective disorder: a 4-week placebo-controlled trial. Psychopharmacology (Berl) 1998;140:173–184

6. Goff DC, Posever T, Herz L, et al. An exploratory haloperidol-controlled dose-finding study of ziprasidone in hospitalized patients with schizophrenia or schizoaffective disorder. J Clin Psychopharmacol 1998;18:296–304

7. Simpson GM, O'Sullivan RL, Siu C. Ziprasidone versus olanzapine in schizophrenia: results of a double-blind trial. In: New Research Program and Abstracts of the 154th Annual Meeting of the American Psychiatric Association; May 5–10, 2001; New Orleans, La. NR252:68–69

8. Hagger C, Mitchell D, Wise AL, et al. Effects of oral ziprasidone and risperidone on cognitive function in patients with schizophrenia or

schizoaffective disorder. Eur Neuropsychopharmacol 1997;7(suppl 2): S219

9. Arato M, O'Connor R, Bradbury JE, et al. Ziprasidone in the long-term treatment of negative symptoms and prevention of exacerbation of schizophrenia. Int Clin Psychopharmacol 2002;17:207–215

10. Kay S, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Schizophr Bull 1987;13:261–276

11. Clinical Global Impressions. In: Guy W. ECDEU Assessment Manual for Psychopharmacology. US Dept of Health, Education, and Welfare publication ADM 76-338. Rockville, Md: National Institute of Mental Health; 1976:218–222

12. Simpson GM, Angus JWS. A rating scale for extrapyramidal side effects. Acta Psychiatr Scand 1970;45(suppl 212):11–19

13. Barnes TRE. A rating scale for drug-induced akathisia. Br J Psychiatry 1989;154:672–676

14. The Abnormal Involuntary Movement Scale. In: Guy W, ed. ECDEU Assessment Manual for Psychopharmacology. US Dept of Health, Education, and Welfare publication ADM 76-338. Rockville, Md: National Institute of Mental Health; 1976:534–537

15. United States Food and Drug Administration. National Adverse Drug Reaction Directory: COSTART (Coding Symbols for Thesaurus of Adverse Reaction Terms). Rockville, Md: FDA; 1970

16. Kirov GK, Murray RM, Seth RV, et al, and the Risperidone Switching Study Group. Observations on switching patients with schizophrenia to risperidone treatment. Acta Psychiatr Scand 1997;95:439–443

17. Desai NM, Huq Z, Martin SD, et al. The Schizophrenia Treatment and Assessment Group. Switching from depot antipsychotics to risperidone: results of a study of chronic schizophrenia. Adv Ther 1999;16:78–88

18. 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

19. McEvoy J, Scheifler P, Frances A. Expert Consensus Guideline Series: Treatment of Schizophrenia 1999. J Clin Psychiatry 1999;60(suppl 11): 1–80

20. Weiden PJ, Aquila R, Dalheim L, et al. Switching antipsychotic medications. J Clin Psychiatry 1997;58(suppl 10):63–72