Efficacy and tolerability of switching to ziprasidone from olanzapine, risperidone or haloperidol: an international, multicenter study

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To compare the effectiveness of a switch from haloperidol (N=99), olanzapine (N=82), or risperidone (N=104) to 12 weeks of treatment with 80–160 mg/day ziprasidone in patients with stable schizophrenia or schizoaffective disorder. Stable outpatients with persistent symptoms or troublesome side effects were switched using one of three 1-week taper/switch strategies as determined by the investigator. Efficacy was assessed using the Brief Psychiatric Rating Scale score, Clinical Global Impression, Positive and Negative Symptom Scale, Montgomery–Åsberg Depression Rating Scale, and the Global Assessment of Functioning Scale, and tolerability by using standard measures of weight change, extrapyramidal symptoms, and laboratory findings. Suboptimal efficacy was the primary reason for switching. The preferred switch strategy was immediate discontinuation, and the preferred dosing regimen was 120 mg/day. Completer rates were 68, 60, and 86% in the haloperidol, risperidone, and olanzapine pre-switch groups, respectively. At week 12, a switch to ziprasidone resulted in statistically significant improvement from baseline on the Brief Psychiatric Rating Scale score, Clinical Global Impression-Improvement, Positive and Negative Symptom Scale, and Global Assessment of Functioning scales, reduction in extrapyramidal symptoms and a neutral impact on metabolic parameters. Switch from olanzapine and risperidone resulted in weight reduction and from haloperidol in some weight increase. In conclusion, oral ziprasidone of 80–160 mg/day with food was a clinically valuable treatment option for stable patients with schizophrenia or schizoaffective disorder experiencing suboptimal efficacy or poor tolerability with haloperidol, olanzapine, or risperidone. Int Clin Psychopharmacol 24:229–238 © 2009 Wolters Kluwer Health | Lippincott Williams & Wilkins.

Keywords: antipsychotics, haloperidol, olanzapine, risperidone, schizophrenia, switch, ziprasidone

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Introduction

Switching antipsychotic medication in patients with schizophrenia is a common clinical practice across a variety of treatment settings (Essock et al., 2006; Weiden, 2006). It is estimated that switching because of suboptimal antipsychotic efficacy or tolerability occurs in 30–50% of patients a year in outpatient clinics (Weiden, 2006). The results of the CATIE study concur with these findings (Stroup et al., 2006): of the 1493 patients, 1052 (70.4%) patients discontinued phase 1 and entered phase 2 of the trial. Among these patients, 51% underwent an antipsychotic medication switch, 99 patients (9%) because of suboptimal efficacy and 444 patients (42%) because of suboptimal tolerability.

Despite the frequency of switching in patients with schizophrenia, little is known about the optimal clinical strategies for switching, and the specific reasons for switching antipsychotic medication. For example, one study identified weight gain as the primary reason for switching from olanzapine to risperidone (Ganguli et al., 2008), whereas another study evaluated the effects of switching from risperidone to olanzapine in patients with hyperprolactinemia and related reproductive adverse events (AEs) (Kinon et al., 2006).

The effectiveness of switching to atypical antipsychotic ziprasidone was studied in several formal switch studies in stable patients with schizophrenia, and suboptimal efficacy or tolerability under past antipsychotic treatment (Weiden et al., 2003a; Bartkó et al., 2006; Rossi et al., 2008). A recent study by Lublin et al. (2008) compared the effectiveness of switching to 12 weeks of treatment with either 80–160 mg/day ziprasidone or one of the comparator drugs (i.e. olanzapine, risperidone, or haloperidol) in patients with chronic schizophrenia. Other studies

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examined the effects of switching to ziprasidone on metabolic parameters (Garman et al., 2003; Weiden et al., 2003b; Montes et al., 2007; Weiden et al., 2008) or cognition (Harvey et al., 2004).

Given the frequency and importance of antipsychotic switching in patients with schizophrenia, there is a need for additional data to further elucidate the reasons for switching in an individual patient and the implementation of switching strategies that meet the individual needs and expectations of patients (Remington et al., 2005; Scheifler and Weiden, 2006; Weiden et al., 2006; Davis and Leucht, 2008). This study was designed with the aim to better understand the clinical effects of switching to ziprasidone from other antipsychotics. The specific objective was to compare the effectiveness of 12 weeks of treatment with ziprasidone after a switch from haloperidol, olanzapine, or risperidone in patients with schizophrenia or schizoaffective disorder from nine countries across the Middle East, Africa, and Europe.

Materials and methods

Study design and dosing

This study was carried out between November 2004 and April 2006. It was a 12-week, open-label, non-randomized, baseline-controlled, single-treatment, flexible-dose study of oral ziprasidone (80–160 mg/day) in the treatment of stable patients with schizophrenia or schizoaffective disorder with suboptimal efficacy or intolerable side effects. It was carried out across 30 centers in nine countries across the Middle East (Jordan, Lebanon, Kuwait, UAE, and Saudi Arabia), Africa (South Africa and Egypt), and Southern Europe (Greece and Turkey). The study comprised seven visits: baseline, day 3, weeks 1, 2, 4, and 8 (±3 days), and week 12/early termination. All patients received open-label ziprasidone of 80 mg/day with food on days 1 to 2, 120 mg/day on days 3–8 and flexible dosing of 80–160 mg/day for 11 weeks. Downward titration to less than 120 mg/day was allowed for safety and/or tolerability reasons. Patients were switched from their past antipsychotic treatment during the first week using one of the following strategies on the basis of the preference of the treating psychiatrist:

1. **Immediate switch**: discontinuation of past antipsychotic on the day before initiating ziprasidone and the initiation of ziprasidone 80 mg/day on day 1.
2. **A 50 to 0% taper**: a dose of antipsychotic equivalent/closed to 50% of the baseline dose was administered on day 1, maintained for the first 7 days, and then discontinued. Ziprasidone (80 mg/day) was initiated on day 1.
3. **A 1-week taper**: 100% of the original antipsychotic dose was maintained on days 1–3, reduced to 50% on days 4–7, and then discontinued. Ziprasidone (80 mg/day) was initiated on day 1.

**Inclusion and exclusion criteria**

Male and female outpatients aged 18–65 years treated with haloperidol, olanzapine or risperidone within ±25% of the recommended daily dose as per package insert for ≥3 months before baseline and with a primary *Diagnostic and Statistical Manual of Mental Disorders* (fourth edition) diagnosis of schizophrenia or schizoaffective disorder were eligible for participation. The eligible patients should have had a history of at least partial beneficial response to antipsychotic(s) during the current episode, with a Clinical Global Impression (CGI)-Improvement Score (CGI-I, Guy, 1976) of 1–4 at screening. In patients with a CGI-I = 1 (very much improved) or CGI-I = 2 (much improved) at screening, the presence of troublesome side effects attributed to the current medication was required to justify a switch to ziprasidone. Pregnant or lactating women, or women of childbearing potential not using an acceptable method of contraception; patients with moderate depressive symptoms (a score ≥16 on the Montgomery–Åsberg Depression Rating Scale (MADRS; Montgomery and Åsberg, 1979); those who met the full *Diagnostic and Statistical Manual of Mental Disorders* (fourth edition) criteria for major depression; those who had donated blood or blood products for transfusion or participated in any other clinical trial involving investigational or marketed products concomitantly during the 30 days before initiation of ziprasidone; or those who were deemed resistant to conventional antipsychotic drugs were not eligible. Furthermore, patients were not eligible if they had received treatment with antiepileptics, antipsychotics, antidepressants, or mood stabilizers, which might have interfereed with the evaluation of the study drug during the study; with antipsychotic agents other than olanzapine, risperidone, or haloperidol at the start of treatment regimen within 12 h before the first dose of the study drug; with clozapine ≤3 months before baseline; with depot antipsychotic medication within a period of 2 weeks or one treatment cycle from baseline; or with antidepressants or mood stabilizers within 2 weeks (for fluoxetine 5 weeks) before baseline. Treatment with medications that prolong the QTc interval; presence of psychiatric or medical conditions that would interfere with the study assessments; immediate risk of harming self or others; or history of suicide attempts in the year before the screening precluded inclusion in the study. The patients unable/unlikely to comprehend/follow the protocol; having participated in this trial in the past or in any other clinical trial with ziprasidone; having been treated in the past with ziprasidone or with a history of intolerance/hypersensitivity to ziprasidone; with confirmed clinically significant abnormal laboratory values or any other abnormal baseline laboratory findings considered by the treating psychiatrists to be indicative of conditions that might affect the study results were not eligible for participation.
Concomitant medication
When considered clinically necessary, anticholinergic agents or propranolol may have been administered for akathisia at the discretion of the treating psychiatrist, but not prophylactically. Throughout the study, lorazepam (1 to 2 mg every 6 h for a maximum of 6 mg/day) may have been used to control agitation and anxiety; and zolpidem 10 mg for insomnia. Benzodiazepines may have been administered as per the discretion of the treating psychiatrist and according to the package insert.

Outcome variables
The primary endpoint variable was change from baseline in total Brief Psychiatric Rating Scale score (BPRS; Overall and Gorham, 1962) used at weeks 1, 2, 4, and 8, whereas at baseline and at the end of week 12/early termination it was derived from the 18 items of the Positive and Negative Symptom Scale [PANSS; Kay et al., 1987 (items P2-P7, N1, N2, and G1-G10)]. To ensure interrater reliability of the primary outcome measure across countries, study raters were trained on the PANSS until they achieved a $\kappa$ of 0.876. Substandard raters received additional training until adequate proficiency was attained before recruiting any patients. The secondary variables were change from baseline in the CGI-Severity score (CGI-S; Guy, 1976) and CGI-I scores (Guy, 1976) assessed on each visit; PANSS, MADRS, Global Assessment of Functioning (GAF; American Psychiatric Association, 1987), and Drug Attitude Inventory (Hogan et al., 1983) scores assessed at baseline and week 12 early termination. All observed or volunteered AEs were recorded at each visit. Laboratory tests were carried out at baseline and at week 12/early termination; body weight was measured at all visits. Modified Simpson–Angus Scale (m-SAS; Simpson and Angus, 1970; where the Head Rotation item substituted the original item Head Dropping), Barnes Akathisia Scale (BAS; Barnes, 1989), and Abnormal Involuntary Movement Scale (AIMS; Guy, 1976) were used at baseline and week 12/early termination to assess Parkinsonian symptoms, akathisia, and tardive dyskinesia, respectively. Physical examination, vital signs measurements, and ECG were carried out at baseline and at the end of week 12/early termination.

Statistical analysis
A sample size of 294 patients, 98 in each treatment group, allowed for a 20% dropout rate. Power considerations were based on testing for noninferiority of ziprasidone to each of the three switched medications using a 1-sided $t$-test and change from baseline at week 12 in the BPRS score. Ziprasidone was considered to be noninferior to a switched medication if the mean change in the BPRS score was $\leq 3.5$, with positive change indicating worsening. The same standard deviation (SD) estimate of 9.3 was used for BPRS score change with all three switched medications. An overall type I error rate of 0.025 (analogous to 0.05 in two-sided tests) was used. As three tests were carried out, each test used $z = 0.025/3 = 0.0083$, with the required power of $\geq 80\%$. The calculated sample size also provided 80% power to detect a 1.2 kg ($\pm 0.2$ kg) weight change at week 12 for each treatment group, using a one-sided test at the same $z$ of $0.025/3 = 0.0083$ or a two-sided test at 0.05/3. For this study, an $z$ of 0.05 was proposed for all secondary endpoints using two-sided tests.

This study included a safety population and two efficacy analysis populations: the intent-to-treat population and the efficacy evaluable population. All efficacy variables were analyzed using the both populations. Noninferiority hypothesis testing was carried out to determine whether ziprasidone was noninferior to antipsychotic medications (haloperidol, olanzapine, or risperidone) with respect to change in BPRS from baseline to week 12. If noninferiority was established, testing for a significant change in BPRS from baseline was carried out. Statistical inference was achieved by the construction of two-sided confidence intervals (CIs) based on $t$-tests. As there were three groups, 98.3% CIs were used to account for multiple tests. A noninferiority limit of 3.5 was prespecified; if the upper limit of the 98.5% CI was less than 3.5, then noninferiority would be inferred. Moreover, if the upper CI was less than 0, then an improvement from baseline in BPRS would also be inferred. The overall $t$ error rate remained at 0.025. Hypothesis testing for the secondary outcomes was formulated to test whether change from baseline was significant, and was only performed at week 12. The $P$ values were not adjusted for multiple endpoints or multiple groups, and a $P$ value of less than 0.05 was considered significant. Descriptive statistics appropriate for the data type (continuous or categorical) were presented. For analyses of efficacy variables and weight, missing values were imputed using the last observation carried forward method; however, baseline values were not carried forward. Therefore, for an endpoint measured only at baseline and final visit, any missing values at final visit were not computed. All AEs reported in this study were clinically reviewed and coded using Pfizer coding dictionary conventions (Pfizer Inc., New York, USA). Summaries of the number and percentage of AEs, by relationship to study medication (all causality and treatment-related), by severity, and by whether or not it led to discontinuation, are tabulated.

Body weight change and categorized weight change by visit based on 7% cut-off value are tabulated. Descriptive statistics for laboratory parameters were not generated, because no central laboratory was used in this study and local laboratories were not standardized. The post-hoc analysis was performed on the metabolic parameters (lipids, HgA1c, and prolactin levels) at baseline and at the end of study for all three switch groups, using the
median as a measure of location because it is less sensitive to extreme values frequently observed with laboratory data. Preferred switching and dosing/titration patterns, and the baseline clinical correlates were described. All analyses were performed using Statistical Analysis Systems (SAS software, version 8.2, SAS Institute Inc., Cary, North Carolina, USA).

**Ethical aspects**

This study was conducted in compliance with the ethical principles originating/derived from the Declaration of Helsinki, in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines, and all local regulatory requirements. The final protocol, amendments, and informed consent were reviewed and approved by the Institutional Review Board(s) and/or Independent Ethics Committee(s) at each of the investigational centers. Written informed consent was obtained from each patient before initiation of any protocol-specified procedures.

**Results**

**Demographic and baseline characteristics**

A total of 319 patients from 30 centers in nine countries were screened for entry; with 32 screen failures, 287 patients were assigned to treatment, and 80 patients prematurely discontinued the study. More patients were switched from risperidone ($n = 104$) than haloperidol ($n = 99$) or olanzapine ($n = 82$). A greater proportion of patients discontinued in the olanzapine pre-switch group ($40\%, n = 33$) than in the haloperidol ($32\%, n = 32$) or risperidone ($14\%, n = 15$) groups, with AEs being the principal reason for discontinuation in all three pre-switch groups, and lack of efficacy in only one patient in the haloperidol group, with no patients in the other two groups. Patients’ disposition is summarized in Fig. 1.

At week 12, completer rates were 68, 60, and 86% in the haloperidol, olanzapine and risperidone pre-switch groups, respectively.

Baseline characteristics of the treatment groups are presented in Table 1. Except for the higher mean age of female haloperidol pre-treated patients, and a higher baseline mean weight for both male and female olanzapine pre-treated patients, other baseline characteristics or rating scale scores were similar across the treatment groups.

**Reasons for switching, dosing, and compliance**

Suboptimal efficacy was a primary reason for switching in 61, 56, and 53% of patients in the haloperidol, olanzapine, and risperidone groups, respectively.
and risperidone pre-switch groups, respectively; and suboptimal tolerability in 39, 44, and 47% of patients, respectively. The largest proportions of all patients were assigned to immediate discontinuation of their current antipsychotic switch strategy (66% in each group), followed by a 1-week taper strategy (in 21, 20, and 20% of haloperidol-treated, olanzapine-treated, and risperidone-treated patients, respectively). Immediate discontinuation was also the preferred switch strategy among patients switched for efficacy (in 70, 76, and 69% of haloperidol-treated, olanzapine-treated, and risperidone-treated patients, respectively) or tolerability (in 59, 53, and 63%, respectively) reasons.

Although many dosing patterns were observed, the most commonly used dosing regimen was 120 mg daily throughout the study, assigned to 46, 27, and 40% of patients in the haloperidol, olanzapine, and risperidone pre-switch groups, respectively. Similar mean doses were observed in allpatient and completer groups, with lower doses in the noncomplerter group (Table 1). In the treating psychiatrists’ judgment, treatment compliance was high ⟨≥ 94%⟩ throughout the study for all groups.

**Efficacy**
Noninferiority of ziprasidone over all three switch medications was observed on the primary efficacy variable, BPRS, at week 12; the upper limit of the 98.3% CI was less than 3.5. Moreover, significant improvements in the BPRS total score were observed with ziprasidone treatment at week 12 (Fig. 2), with the largest magnitude of change occurring during the first 2 weeks of ziprasidone treatment. Patients who were switched from haloperidol and risperidone experienced greater improvements than patients switched from olanzapine. The BPRS results from the evaluable population were similar to and supportive of the intent-to-treat results, with significant improvements from baseline over all three switch medications at week 12 (data not shown).

Significant improvements from baseline at week 12 were also observed on the CGI-S, PANSS Total, Positive and Negative, and MADRS in all three groups switched to ziprasidone, except for the olanzapine switch group on the MADRS (Table 2). On the CGI-I, 65–71% of patients were rated as at least improved (Table 2).

Significant improvements with ziprasidone treatment were observed on the GAF (P ≤ 0.002) at week 12 in all three pre-switch groups, and on the Drug Attitude Inventory in the haloperidol and risperidone pre-switch groups (P < 0.05), but not in the olanzapine pre-switch group. The greatest magnitude of improvement was observed in the haloperidol and risperidone pre-switch groups on all efficacy variables used in this study.

**Safety and tolerability**
In total, 148 (52.1%) patients had treatment-emergent AEs during this study, whereas serious AEs were reported in seven patients. Forty-five (15.8%) patients prematurely discontinued the study because of AEs. Treatment-emergent AEs with frequency of ⟨≥ 5%⟩ in any treatment group are presented in Table 3.

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**Table 1** Group characteristics and rating scale scores at baseline; mean doses of study medication throughout the study

<table>
<thead>
<tr>
<th>Pre-switch medication</th>
<th>Haloperidol, N=99</th>
<th>Olanzapine, N=82</th>
<th>Risperidone, N=104</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (SD)</td>
<td>Male (n=64)</td>
<td>Female (n=35)</td>
<td>Male (n=51)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td>White</td>
<td>Black</td>
<td>Asian</td>
</tr>
<tr>
<td>Male (n=64)</td>
<td>Female (n=35)</td>
<td>Male (n=51)</td>
<td>Female (n=31)</td>
</tr>
<tr>
<td>Mean duration (range) of illness, years</td>
<td>10.6 (3.3–32.2)</td>
<td>84</td>
<td>15</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td>White</td>
<td>Black</td>
<td>Asian</td>
</tr>
<tr>
<td>Mean duration (range) of illness, years</td>
<td>10.6 (3.3–32.2)</td>
<td>84</td>
<td>15</td>
</tr>
<tr>
<td>BPRS score (SD)</td>
<td>44.3 (14.80)</td>
<td>41.8 (12.49)</td>
<td>3.9 (1.15)</td>
</tr>
<tr>
<td>PANSS total (SD)</td>
<td>78.6 (23.97)</td>
<td>74.6 (22.32)</td>
<td>77.5 (19.67)</td>
</tr>
<tr>
<td>CGI-S (SD)</td>
<td>3.9 (1.15)</td>
<td>3.9 (0.93)</td>
<td>3.9 (0.93)</td>
</tr>
<tr>
<td>MADRS (SD)</td>
<td>8.6 (4.74)</td>
<td>9.2 (4.53)</td>
<td>9.3 (3.92)</td>
</tr>
<tr>
<td>Mean dose</td>
<td>118.6</td>
<td>118.6</td>
<td>119.1</td>
</tr>
<tr>
<td>All patients</td>
<td>118.7</td>
<td>119.0</td>
<td>119.3</td>
</tr>
<tr>
<td>Completers</td>
<td>Noncompleters</td>
<td>Mean dose</td>
<td>All patients</td>
</tr>
<tr>
<td>BPRS, Brief Psychiatric Rating Scale score; CGI-S, Clinical Global Impression-Severity; MADRS, Montgomery–Åsberg Depression Rating Scale; PANSS, Positive and Negative Symptom Scale.</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Majority of patients were Egyptians.
Similar proportions of patients in each group temporarily discontinued or had their dose reduced as a result of one or more AEs: 14% (n = 14), 15% (n = 12), and 19% (n = 20) for the haloperidol, olanzapine and risperidone pre-switch groups, respectively, with somnolence being the most commonly reported reason, followed by dizziness.

The highest baseline score on all three extrapyramidal symptoms (EPS) rating scales was in the haloperidol pre-switch group, followed by the risperidone and olanzapine groups (Table 4). Improvements from baseline in EPS assessed by m-SAS, BAS, and AIMS scales at week 12 were observed across all three groups, irrespective of the level of baseline symptomatology, with statistically significant improvements from baseline observed after switching from haloperidol or risperidone, but not from olanzapine (Table 4).

Significant mean weight loss (SD) of 2 kg (4.0 kg) (P < 0.001) was observed in the olanzapine pre-switch group at week 12. Nonsignificant mean reduction (SD) in body weight of 0.6 kg (3.2 kg) was observed in the risperidone pre-switch group, and a mean increase (SD) of 0.4 kg (4.0 kg) in the haloperidol pre-switch group. At week 12, four (4%) , 13 (16%), and seven (7%) patients lost ≥ 7%, and nine (9.5%), two (2.4%), and seven (6.9%) gained ≥ 7% of their baseline body weight in the haloperidol, olanzapine and risperidone pre-switch groups, respectively. Switching to ziprasidone had a neutral effect on metabolic parameters and prolactin (Table 5).
Concomitant medication

The proportion of patients who used anti-Parkinsonian medication at baseline varied among the pre-switch groups, with the lowest use in the olanzapine pre-switch group (6.1%), followed by the haloperidol (42.4%) and risperidone (44.2%) pre-switch groups. During the course of the study, in the majority of patients there was no change in usage and dosage of baseline anti-Parkinsonian medication (in 74.2, 89.2, and 69.0% of haloperidol-treated, olanzapine-treated, and risperidone-treated patients, respectively). In the haloperidol and risperidone pre-switch groups, which displayed the highest burden of EPS at baseline, anti-Parkinsonian medication dosage was reduced in 22.5 and 25.0% of patients, respectively, and increased/startedin 3.3 and 6.0% of patients, respectively. In the olanzapine group, dosage was reduced in 1.4% of patients, and increased/startedin 9.5% of patients. Hypnotics and anxiolytics were concomitantly used by 8.1, 15.9, and 6.7% of the patients in the haloperidol, olanzapine, and risperidone pre-switch groups, respectively.

Discussion

In this study, stable patients with schizophrenia or schizoaffective disorder were switched to 12 weeks of treatment with ziprasidone (80–160 mg/day) because of suboptimal efficacy or tolerability with past antipsychotic treatment. They experienced statistically significant improvements from baseline assessed by changes in the BPRS, CGI-S, PANSS Total, Positive and Negative scales, with a majority of patients rated at least as improved on the CGI-I. Switching from haloperidol or risperidone was associated with statistically significant improvements in the EPS, and from olanzapine in a statistically significant reduction in body weight. Ziprasidone displayed a neutral effect on metabolic parameters measured in this study across individual centers. In the majority of patients, concomitant anti-Parkinsonian medications use either remained unchanged or dosage was reduced during the study. The treating psychiatrists preferred an immediate switch strategy, the most frequently used drug regimen was 120 mg/day throughout the study.

Our efficacy, safety, and tolerability results fully concur with earlier published results of the ziprasidone switch studies, despite some differences in study design and patient population (Weiden et al., 2000b, 2003a; Bartko et al., 2006; Lublin et al., 2008; Rossi et al., 2008). In this study, ziprasidone was associated with a significant improvement from baseline on the primary and secondary efficacy outcome variables (BPRS, PANSS Total, Positive and Negative scales, and CGI-S). This is consistent with the results of all other above-cited switch studies of ziprasidone, regardless of their duration (i.e. 6 vs. 12 weeks), patient samples in terms of diagnosis (i.e.
mixed stable schizophrenia spectrum disorder samples vs. chronic patients with schizophrenia), or geographical location of the studies (USA, Europe). Although the studies used both fixed and flexible ziprasidone dosing regimens, it seems that dosing of ≥ 120 mg/day may be associated with an improved outcome after the switch (Weiden et al., 2000b, 2003a), which concurs with the results of the PET study showing that the optimal dose of ziprasidone is at least 120 mg/day (Mamo et al., 2004). In our study, the preferred dosing was 120 mg/day throughout the study, with similar mean doses across all patient and completer groups, and lower mean doses across noncompleter groups. These results support switching to ziprasidone in optimal oral daily doses of 80–160 mg with food as a treatment strategy in stable but still symptomatic patients with schizophrenia, and show that treatment benefits in efficacy can be gained. In addition to these efficacy benefits, statistically significant improvements were observed in general functioning in this study, as well as in subjective well-being or cognitive functioning in other ziprasidone switch studies (Harvey et al., 2004; Rossi et al., 2008).

Similar to the Rossi et al.’s (2008) study (72%), in our study the principal reason for switching was suboptimal efficacy, in 60.6, 56.1, and 52.9% of patients in the haloperidol, olanzapine, and risperidone pre-switch groups, respectively. Reasons for the switch were not reported by Weiden et al. (2000b, 2003a), while poor tolerability was the principal reason in the Bartkó et al. (2006) study. In the Lublin et al.’s (2008) study, where the treating psychiatrists could indicate multiple reasons for the switch, in ≥ 50% of patients combined suboptimal efficacy and poor tolerability was a reason for switching from the earlier antipsychotic medication. On the basis of the results of the more recent studies, suboptimal antipsychotic efficacy is being accepted as a valid reason for switching. This may indicate that psychiatrists now better understand antipsychotic switch as a therapeutic strategy that can also be successfully applied to achieve attainable efficacy gains in appropriately selected candidate patients (Weiden et al., 2006; Weiden, 2007a, 2007b).

Switching remains an important treatment strategy in patients presenting with tolerability problems under current antipsychotic treatment, particularly in those with weight gain, significant changes in metabolic parameters, or with concomitant somatic disease such as diabetes mellitus or cardiovascular disease (Weiden et al., 2006; Weiden, 2007a, 2007b). For example, weight gain was a reason for switching in more than 40% in ziprasidone and combined groups in the Lublin et al.’s study (2008). In our study, individual AEs leading to the switch were not collected, but a higher baseline weight of the olanzapine pre-switch group compared with the other two groups may indicate that weight gain might have led to switching in a number of patients. As the presence of systemic somatic disease or abnormal laboratory parameters at baseline represented exclusion criteria for this study, those patients were not selected for participation, and therefore we cannot speculate what the effects of switching to ziprasidone would be in such a population.

In this study, treating psychiatrists could choose among three switch strategies. Irrespective of whether the reason for switching was suboptimal efficacy or tolerability, the preferred strategy was immediate switch (in two of three of patients), followed by a 1-week taper (in up to one-fifth of patients). The psychiatrists’ choice may indicate their confidence in switching as an important treatment strategy, based on the knowledge of the antipsychotics they are using in everyday practice. In addition, the choice of an immediate switch strategy may also reflect the patients’ and caregivers’ hopes and expectations for a quick resolution of the problems they experienced under the earlier treatment.

In agreement with other switch studies, ziprasidone displayed a good tolerability profile across all pre-switch groups. Ziprasidone-related AEs were the reason for premature discontinuation in 14.1, 19.5, and 9.6% of patients in the haloperidol, olanzapine, and risperidone pre-switch groups, respectively. Somnolence was the most commonly reported treatment-emergent AE. At baseline, EPS symptoms assessed by m-SAS, BAS, and AIMS scores were most prominent in the haloperidol and risperidone pre-switch groups. However, irrespective of the EPS symptom burden, treatment with ziprasidone was associated with improvements from baseline in all three groups, reaching statistical significance in the haloperidol and risperidone pre-switch groups. This improvement was also reflected in the dosage of concomitant anti-Parkinsonian medication, which was reduced during the study in 22.5% patients in the haloperidol and 25.0% in the risperidone pre-switch groups.

Switching from olanzapine resulted in a significant reduction of baseline body weight (SD) of 2 kg (4.0 kg). In all three pre-switch groups, ziprasidone displayed a neutral effect on metabolic factors. These effects of switching to ziprasidone were also consistently reported in other switch studies (Weiden et al., 2000b, 2003a; Bartkó et al., 2006; Lublin et al., 2008; Rossi et al., 2008). Specific favorable effects on lipid profiles were additionally shown by Garman et al. (2003), and on metabolic disturbances by Montes et al. (2007).

There were several limitations to this study. First, it was an open-label, nonrandomized study, in which both patients and treating psychiatrists were aware of the
treatment assignment, thereby increasing the possibility of biased efficacy findings toward ziprasidone. Furthermore, the noncomparative nature of the study prevented any direct comparisons among the three groups. Exclusion of patients with contraindication for treatment with ziprasidone according to prescribing information (i.e., clinically significant ECG abnormalities, particularly prolongation of the QTc interval (>500 ms), concomitant treatment with QTc prolonging drugs, and hypersensitivity to ziprasidone) may have resulted in a selection bias by including patients potentially less likely to have AEs associated with ziprasidone treatment. However, the current lack of data on prevalence rates of chronic symptomatic patients with schizophrenia screened for inclusion in clinical trials, and excluded because of the above criteria, prevents any conclusion on how such exclusion could affect the results. Moreover, currently it is not known whether treatment duration beyond 12 weeks could have resulted in more beneficial outcomes, whether the gains remain sustained over long-term treatment, and what would be the net effect of discontinuation rates known to increase with prolonged treatment (Weiden, 2007a, 2007b). Finally, usage of a central laboratory or standardized local laboratories could have rendered more reliable laboratory results. However, the Garman et al. (2003) study based on retrospective patient chart data from US Veterans Administration-Information Systems and Technology Architecture and no central/standardized laboratory also found that switching from olanzapine to ziprasidone resulted in a significant decrease of LDL-cholesterol and triglyceride levels. The noninferiority design chosen for this study is recognized as having some limitations: it may only be able to establish noninferiority, but not superiority and some may disagree with the selected, prespecified noninferiority margin. In this design, only if noninferiority is initially established (in this study, based on change from baseline in the BPRS scores), tests for superiority are used. As in this study superiority (i.e., significant change from baseline in the BPRS scores) was established for all pre-switch groups, the use of noninferiority design could not influence the robustness of the results.

As many patients with schizophrenia are stable but still present with residual symptoms or troublesome side effects, elective switching of antipsychotic medication is one of the treatment strategies that can improve treatment outcome in individual patients (Weiden et al., 2006). However, the decision to switch has to take into consideration whether the target goals are amenable to change, whether the patient and family/caregivers are capable of handling the logistics and anxiety of switching, what will be the adherence with the new antipsychotic, and whether the patient is generally treatment-resistant (Weiden et al., 2007). Other factors, such as type and phase of the illness, type and dosage of current antipsychotic medication, adjunctive medications, age, sex, and ethnicity, should also be evaluated before switching (Weiden et al., 2007). Our results may provide treating psychiatrists with valuable practical information as to which stable patients with schizophrenia may benefit the most from switching to oral 80–160 mg/day ziprasidone administered with food. On the basis of our results, further clinical improvement may be achieved in patients with suboptimal efficacy during treatment with haloperidol, olanzapine, or risperidone after switching to ziprasidone. In patients treated with either haloperidol or risperidone, presenting with EPS symptoms and concomitantly treated with anti-Parkinsonian medication, switching to ziprasidone may lead to a reduction of EPS and/or concomitant medication. In patients treated with olanzapine and displaying weight gain, switching to ziprasidone may lead to a significant body weight reduction.

In conclusion, the results of this study confirm the effectiveness of oral 80–160 mg/day ziprasidone with food as an appropriate switch option for stable patients with schizophrenia or schizoaffective disorder experiencing suboptimal efficacy or poor tolerability with haloperidol, olanzapine, or risperidone.

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