Maintaining Symptom Control: Review of Ziprasidone Long-Term Efficacy Data

Nina R. Schooler, Ph.D.

Reducing the risk of relapse and maintaining symptom control are core goals in the long-term treatment of patients with schizophrenia or schizoaffective disorder because symptom control can allow patients and clinicians to focus on functional improvement. The atypical antipsychotic agents have gained widespread acceptance in this setting because they are at least as effective as the conventional antipsychotic agents, may offer an advantage in relapse prevention, and offer safety advantages, primarily a reduced liability for movement disorders. However, there are differences among the atypical agents that may affect both clinician choice and patient adherence to long-term therapy. Ziprasidone has shown long-term antipsychotic efficacy in comparisons with haloperidol, olanzapine, and risperidone, as well as efficacy in patients switched from another antipsychotic agent. This review examines symptom efficacy data for ziprasidone in long-term trials that lasted between 28 and 52 weeks. Antipsychotic medication is the foundation of long-term treatment of schizophrenia. Optimization of treatment for the individual patient requires consideration of symptom control, prevention of relapse, and possible long-term health consequences. Clinical trial data on ziprasidone's long-term efficacy provide a firm basis for selection of this agent. *(J Clin Psychiatry 2003;64[suppl 19]:26–32)*

It has long been established that maintenance treatment with antipsychotics significantly reduces the risk of schizophrenic relapse and maintains symptom control.[1,2] Maintenance therapy with conventional antipsychotic agents, however, puts patients at significant risk for tardive dyskinesia, whereas the atypical antipsychotics have clear safety advantages with regard to movement disorders.[3,4] Furthermore, evidence suggests that maintenance therapy with atypical agents is at least as effective as that with conventional neuroleptics in reducing the risk of relapse of schizophrenia.[5] A recent meta-analysis by Leucht and colleagues[6] found a significant advantage of atypical agents in prevention of relapse.

These advantages notwithstanding, the emergence of atypical antipsychotic agents has been accompanied by new tolerability and safety concerns unrelated to movement disorders, with implications for long-term therapeutic adherence and medical outcomes. Clozapine, olanzapine, and risperidone have been associated with weight gain.[7] Olanzapine and clozapine have been associated with alterations in lipid profile, most notably increases in triglycerides.[8] New-onset diabetes has been reported in patients receiving olanzapine.[9] Thus, additional options for maintenance treatment of schizophrenia are welcome.

Ziprasidone is a novel atypical antipsychotic agent with a unique pharmacologic profile that has been shown to improve positive, negative, and affective symptoms in short-term trials of patients with schizophrenia or schizoaffective disorder.[10,11] The long-term antipsychotic efficacy of ziprasidone in the maintenance treatment of patients with schizophrenia and schizoaffective disorder has been studied in controlled trials versus haloperidol, risperidone, olanzapine, and placebo. This review focuses on the efficacy results from these trials.

DATA SELECTION AND DATA SYNTHESIS

One-Year Placebo-Controlled Trial

In a 1-year, randomized, double-blind, placebo-controlled trial (the Ziprasidone Extended Use in Schizophrenia [ZEUS] study), 278 stable inpatients with chronic schizophrenia received daily ziprasidone, 40 mg (N = 72), 80 mg (N = 68), or 160 mg (N = 67) in 2 divided doses, or placebo (N = 71).[12] Efficacy variables included Positive and Negative Syndrome Scale (PANSS) total and negative subscale scores, Global Assessment of Functioning (GAF) scores, and Clinical Global Impressions-Severity of Illness (CGI-S) scale scores. Patients were withdrawn if deemed at risk of impending relapse, defined as a Clinical

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Global Impressions-Improvement (CGI-I) score of ≥ 6 (very much worse), or scores of ≥ 6 (severe) on PANSS hostility (P7) or uncooperativeness R(G8) items that persisted for 2 successive days. Kaplan-Meier survival curves estimated the probability of remaining relapse-free. Efficacy analyses included patients with ≥ 1 assessment before relapse (last observation carried forward [LOCF] analysis).

The total numbers of patients withdrawn from the study were 61 (86%), 42 (58%), 39 (57%), and 37 (55%) for the placebo and ziprasidone, 40 mg/day, 80 mg/day, and 160 mg/day groups, respectively.[12] The numbers of patients withdrawn due to adverse events were 11 (15%), 7 (10%), 7 (10%), and 5 (7%), for the same treatment groups, respectively. All dosages of ziprasidone were substantially more effective than placebo in preventing impending relapse. Kaplan-Meier analysis showed that the probability of relapse at 1 year was significantly lower for ziprasidone-treated patients than for placebo-treated patients— i.e., ziprasidone, 40 mg/day (43%), 80 mg/day (35%), 160 mg/day (36%), versus placebo (77%) (p = .002, p < .001, p < .001 vs. placebo, respectively) (Figure 1). Among the subgroup of patients who remained in treatment for ≥ 6 months, only 9% (10/110) in the ziprasidone groups versus 42% (8/19) in the placebo group subsequently relapsed (p = .001).

Mean scores on all efficacy scales worsened in the placebo group, but scores remained stable in all ziprasidone groups (Table 1).[12] In addition, all 3 ziprasidone treatment groups showed progressive improvement in negative symptoms throughout the study, with significant differences from placebo observed from week 16 onward. Changes in PANSS negative subscale scores from baseline to endpoint (LOCF) were 1.4 in the placebo group versus –1.9, –1.0, and –2.8 in the ziprasidone, 40 mg/day, 80 mg/day, and 160 mg/day treatment groups, respectively (p < .001 for 40 mg/day and 160 mg/day vs. placebo; p = .011 for 80 mg/day vs. placebo).

Although patients received ziprasidone twice as long as placebo, the tolerability profiles of ziprasidone and placebo were similar as was discontinuation due to adverse events, which was rare in all groups.[12] There were small mean reductions in body weight, reductions in median prolactin levels, and small mean improvements in Simpson-Angus Scale (Simpson-Angus), Barnes Akathisia Scale (BAS), and Abnormal Involuntary Movement Scale (AIMS) scores in all groups. Ziprasidone was not associated with clinically significant effects on QTc intervals compared with placebo, with no intervals > 500 ms.

Exploratory analyses of results from the ZEUS study using the penultimate observation carried forward (POCF) approach have been reported.[13] In POCF analysis, the second-to-last assessments of patients who discontinued prematurely are included and those at point of discontinuation are excluded, allowing long-term changes in symp-

Figure 1. Kaplan-Meier Estimate of Time to Relapse in the ZEUS Study, a 1-Year, Placebo-Controlled Trial of Ziprasidone[a,b]
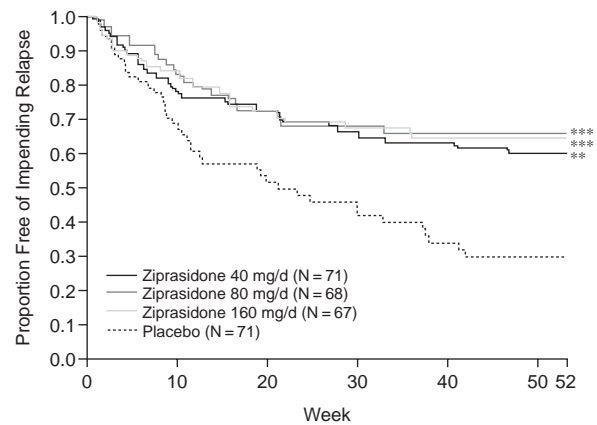
[a]Reproduced with permission from Arató et al.[12]
[b]The probability of relapse was significantly lower in patients treated with ziprasidone than in patients treated with placebo (p = .0001, overall log-rank value).
**p < .01 vs. placebo.
***p < .001 vs. placebo.
Abbreviation: ZEUS = Ziprasidone Extended Use in Schizophrenia.

toms to be assessed while the confounding effects of impending relapse (emergent positive symptoms) are minimized. The POCF approach was used to compare mean changes in PANSS total scores over time in treatment groups to elucidate the pattern of long-term symptom change during the nonrelapsing treatment period.[13] There was a small early improvement in the mean PANSS total score in all groups, perhaps due to a reduction in extrapyramidal symptoms or negative symptoms associated with discontinuation of previous neuroleptic treatment. Thereafter, there was little change in the placebo group, but continuing improvement in the ziprasidone group for the duration of the 1-year study (Figure 2).

In the POCF analysis of the PANSS negative subscale scores, mean baseline-to-endpoint reductions were statistically significantly greater in the ziprasidone, 40 mg/day and 160 mg/day groups, compared with placebo (–3.8 and –4.0 vs. –2.0, respectively; p ≤ .003 for both ziprasidone groups vs. placebo) (H. Y. Meltzer, M.D.; M. Arato, M.D.; N. R. Schooler, Ph.D., unpublished data, 2003). In addition, there were significantly more negative symptom responders (defined as a ≥ 30% reduction from baseline on the PANSS negative subscale score) in the ziprasidone, 160 mg/day group (23.4%), than in the placebo group (6.7%; p = .012). The proportions of responders in the ziprasidone, 40 mg/day and 80 mg/day groups, were 19.7% (p = .058 vs. placebo) and 15.5% (p = .15 vs. placebo), respectively.

Path analysis was performed to assess the proportion of negative symptom improvement attributable to direct

Table 1. Mean Baseline and Endpoint Efficacy Variables (ITT LOCF) in the ZEUS Study[a]

Variable	Treatment Dosage (mg/d)	N	Baseline Mean	Baseline SD	Endpoint Mean	Endpoint SD	Mean Change	Least Squares Mean Difference Versus Placebo	p Value[b]
PANSS total	Placebo	71	88.4	10.0	104.0	27.1	15.6	…	…
	Ziprasidone 40	71	84.2	18.4	87.1	27.6	2.9	−13.1	.001
	Ziprasidone 80	68	86.2	18.6	88.0	30.8	1.9	−12.7	.001
	Ziprasidone 160	67	84.5	18.3	83.2	25.8	−1.3	−16.8	< .001
PANSS negative subscale	Placebo	71	25.8	5.1	27.1	7.2	1.4	…	…
	Ziprasidone 40	71	24.8	6.3	22.9	7.4	−1.9	−3.5	< .001
	Ziprasidone 80	68	24.8	5.4	23.7	7.4	−1.0	−2.4	.011
	Ziprasidone 160	67	25.1	5.9	22.3	7.0	−2.8	−4.2	< .001
PANSS positive subscale	Placebo	71	18.0	6.2	24.2	9.0	6.2	…	…
	Ziprasidone 40	71	17.3	5.7	20.3	9.0	3.0	−3.3	.008
	Ziprasidone 80	68	17.9	5.8	19.0	9.0	1.2	−4.7	< .001
	Ziprasidone 160	67	16.7	5.4	18.5	8.5	1.8	−4.3	.001
CGI-S	Placebo	71	4.1	0.8	5.0	1.2	1.0	…	…
	Ziprasidone 40	71	4.0	0.7	4.5	1.3	0.4	−0.6	.002
	Ziprasidone 80	68	4.0	0.6	4.2	1.4	0.2	−0.8	< .001
	Ziprasidone 160	67	4.0	0.7	4.2	1.4	0.1	−0.8	< .001
GAF	Placebo	70	46.9	12.8	36.7	15.1	−10.2	…	…
	Ziprasidone 40	71	48.0	11.7	44.0	18.7	−4.0	6.9	.005
	Ziprasidone 80	68	46.9	12.0	45.9	19.6	−1.0	8.5	.001
	Ziprasidone 160	66	47.6	11.8	46.7	19.6	−0.9	9.1	< .001

[a]Adapted with permission from Arató et al.[12]
[b]Versus placebo for change from baseline (analysis of covariance).
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, GAF = Global Assessment of Functioning, ITT = intention-to-treat, LOCF = last observation carried forward, PANSS = Positive and Negative Syndrome Scale.

medication effects versus indirect effects (e.g., changes in positive symptoms, depressive symptoms, and extrapyramidal symptoms) (H. Y. Meltzer, M.D.; M. Arato, M.D.; N. R. Schooler, Ph.D., unpublished data, 2003). Analysis of all 3 ziprasidone dosage groups revealed that ziprasidone had a statistically significant direct effect on negative symptoms (p < .05), whereas the contribution of indirect effects to negative symptom improvement was not statistically significant.

Trials Versus Other Antipsychotics

Ziprasidone versus haloperidol. Ziprasidone was compared with haloperidol in a 28-week, double-blind, multicenter, parallel-group trial in 301 outpatients with stable chronic or subchronic schizophrenia.[14] Patients received flexible-dose ziprasidone, 80–160 mg/day (N = 148), or haloperidol, 5–15 mg/day (N = 153). Primary efficacy variables included PANSS total and PANSS negative subscale scores; additional variables examined included Montgomery-Asberg Depression Rating Scale (MADRS), the CGI-S scale, and the PANSS derived Brief Psychiatric Rating Scale (BPRSd) core items. Patients who completed at least 14 days of medication were considered evaluable and were included in efficacy analyses if they had ≥ 1 postbaseline assessment.

A total of 66 patients (45%) in the ziprasidone group and 64 patients (42%) in the haloperidol group completed 28 weeks of treatment. Among evaluable patients, the rate of discontinuation due to insufficient clinical response was 18% in both the ziprasidone-treated (N = 20/110) and haloperidol-treated (N = 21/117) groups.[14] Compa-

rable improvements from baseline in all efficacy variables were observed with ziprasidone and haloperidol (Figure 3). The proportion of negative symptom responders (≥ 20% decrease in the PANSS negative subscale score) was significantly higher with ziprasidone (48%) than with haloperidol (33%; p < .05). The rate of discontinuations due to treatment-related adverse events was 8% for ziprasidone versus 16% for haloperidol. Patients treated with haloperidol exhibited increases in mean Simpson-Angus, BAS, and AIMS scores, whereas patients treated with ziprasidone had decreases in mean Simpson-Angus and AIMS scores and no change in BAS scores.[14]

Ziprasidone versus olanzapine. Simpson and colleagues[15] compared ziprasidone and olanzapine in a 26-week, blinded, multicenter, continuation study of 133 outpatients with schizophrenia or schizoaffective disorder who had completed 6 weeks of double-blind treatment with a satisfactory clinical response (defined as ≥ 20% decrease in PANSS total score or CGI-I score ≤ 2 [much improved]). Patients received ziprasidone (N = 62), 40 mg, 60 mg, or 80 mg b.i.d., or olanzapine (N = 71), 5 mg, 10 mg, or 15 mg q.d. Efficacy assessments included the BPRS, PANSS, Calgary Depression Scale for Schizophrenia (CDSS), and CGI-S.

A total of 43 ziprasidone-treated patients (69.4%) and 50 olanzapine-treated patients (70.4%) discontinued treatment, with the majority of discontinuations judged unrelated to study drugs.[15] Mean daily dosages for the study were 136.9 mg for ziprasidone and 12.2 mg for olanzapine. Ziprasidone and olanzapine were associated

Figure 2. Mean Change in PANSS Total Scores in the ZEUS Study, a 1-Year, Placebo-Controlled Trial of Ziprasidone (using LOCF and POCF analyses)[a]
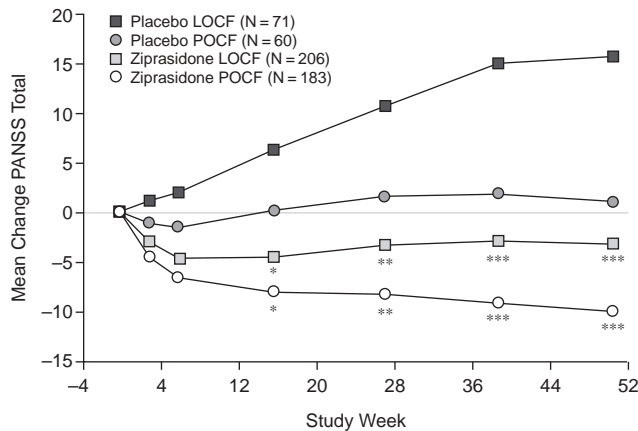
[a]Reproduced with permission from O'Connor and Schooler.[13]
*p < .05 versus placebo.
**p < .01 versus placebo.
***p ≤ .001 versus placebo.
Abbreviations: LOCF = last observation carried forward,
  PANSS = Positive and Negative Syndrome Scale,
  POCF = penultimate observation carried forward,
  ZEUS = Ziprasidone Extended Use in Schizophrenia.

Figure 3. Mean Percentage Improvement in Efficacy Variables From Baseline at Week 28 (evaluable patients, LOCF) in Trial of Ziprasidone Versus Haloperidol[a]
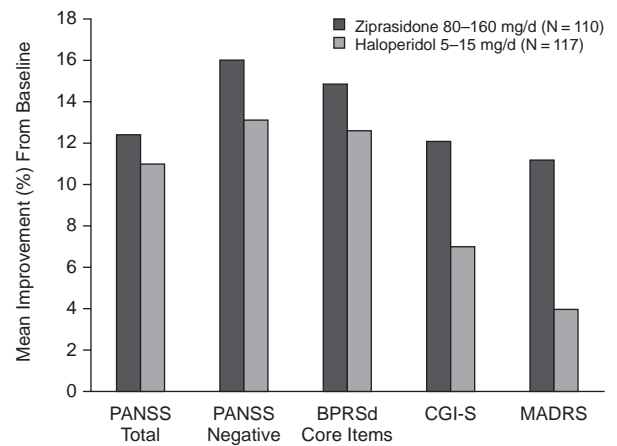
[a]Reproduced with permission from Hirsch et al.[14]
Abbreviations: BPRSd = Brief Psychiatric Rating Scale derived from the PANSS (Positive and Negative Syndrome Scale),
  CGI-S = Clinical Global Impressions-Severity of Illness scale,
  LOCF = last observation carried forward,
  MADRS = Montgomery-Asberg Depression Rating Scale.

with comparable, sustained improvements in BPRS total scores, CGI-S scores, and PANSS total scores from baseline of the 6-week study to endpoint of the 6-month study (LOCF) (Figure 4).

In addition, the treatments were associated with comparable long-term improvements from baseline in PANSS positive and negative subscale scores (positive subscale mean change of –9.2 and –10.0 for ziprasidone and olanzapine, respectively; negative subscale mean change of –7.7 and –8.0 for ziprasidone and olanzapine, respectively) (p = nonsignificant for between-group difference).[15] The majority of ziprasidone- and olanzapine-treated patients also exhibited comparable, sustained improvements in mood-related symptoms, as reflected by nonsignificant reductions in CDSS total scores (mean change of –2.0 for the ziprasidone group and –2.9 for the olanzapine group). In terms of adverse effects, ziprasidone was associated with favorable or neutral effects on weight and metabolic variables (i.e., fasting insulin, plasma glucose, and serum lipids). In contrast, significant weight gain and adverse changes in these metabolic parameters were seen in the olanzapine group.

More recently, Kane and colleagues[16] reported a 28-week double-blind trial comparing ziprasidone and olanzapine. Inpatients and outpatients with schizophrenia—entry criteria included an initial score of ≥ 42 on PANSS derived BPRS and ≥ 4 on 1 of the PANSS positive items as well as a score of ≥ 4 on the CGI-S scale—were randomized to olanzapine, 10–20 mg/day (N = 277), or ziprasidone, 80–160 mg/day (N = 271). The primary efficacy measure was PANSS total score; secondary measures included PANSS subscales, CGI-S, and CGI-I.

Mean modal dosages in this study were 15.1 mg/day for olanzapine and 114.8 mg/day for ziprasidone. At 28 weeks, patients receiving olanzapine had significantly greater improvement in PANSS total (p < .001), positive (p < .001), negative (p = .003), general pathology (p < .001), and cognitive (p < .001) scores than patients receiving ziprasidone. Olanzapine-treated patients had significantly greater improvement in CGI-S scores (p < .001) and CGI-I scores (p = .006). Among patients with PANSS total response (≥ 30% improvement at 8 weeks), those treated with olanzapine maintained response significantly longer than those treated with ziprasidone (p = .004).

In tolerability assessments, mean changes from baseline to maximum (not endpoint) in movement disorder rating scales (Simpson-Angus, BAS, AIMS) were significantly higher for ziprasidone (p < .03). However, there was a significant (p < .001) difference in mean weight change (+3.06 kg [6.7 lb] for olanzapine, –1.12 kg [2.5 lb] for ziprasidone). There were also significant (p ≤ .005) between-group mean changes in total cholesterol, low-density lipoprotein cholesterol, and triglycerides, which increased in the olanzapine group but decreased in the ziprasidone group, and in high-density lipoprotein cholesterol, which increased with ziprasidone but decreased with olanzapine. Mean changes in fasting glucose did not differ significantly; measurements of fasting insulin or insulin resistance were not reported.

Figure 4. Mean Change After 6 Months of Treatment With Ziprasidone or Olanzapine[a]

BPRS[b]

CGI-S[b]

PANSS Total Score
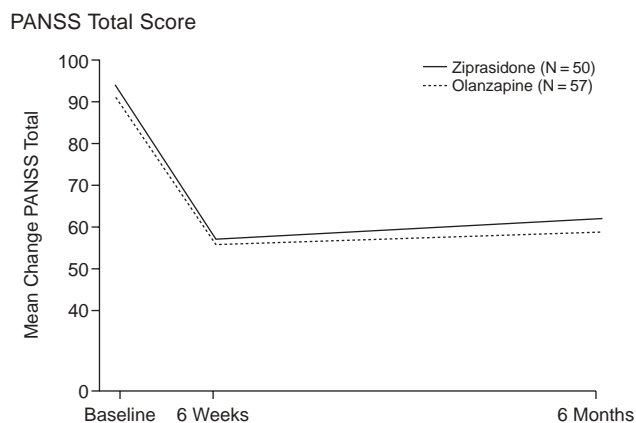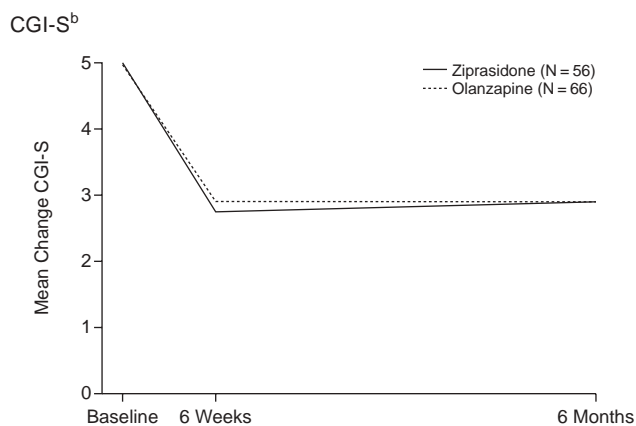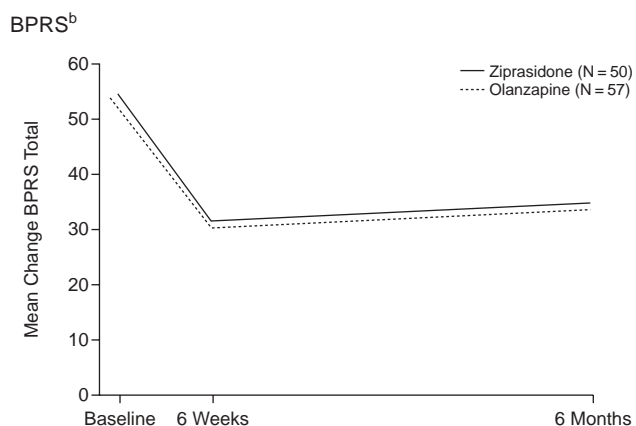
[a]Reproduced with permission from Simpson et al.[15]
[b]All patients, LOCF.
Abbreviations: BPRS = Brief Psychiatric Rating Scale,
  CGI-S = Clinical Global Impressions-Severity of Illness scale,
  LOCF = last observation carried forward, PANSS = Positive and
  Negative Syndrome Scale.

Table 2. Mean Change From Baseline to Last Visit in Efficacy Variables in a 52-Week Ziprasidone Versus Risperidone Comparison (all patients, LOCF)[a]

Efficacy Variable	Change With Ziprasidone (N)*	Change With Risperidone (N)*	Between-Group Difference (p Value)
PANSS total	−26.66 (59)	−32.43 (75)	NS
PANSS negative subscale	−7.53 (59)	−7.52 (75)	NS
BPRSd total	−14.25 (59)	−18.56 (75)	NS
BPRSd core items	−5.44 (59)	−6.97 (75)	NS
CGI-S	−1.14 (59)	−1.51 (76)	NS
GAF	14.98 (59)	20.81 (72)	NS
MADRS	−5.43 (58)	−4.63 (76)	NS

[a]Reproduced with permission from Addington et al.[17]
*p < .001 for all patients from the 8-week core study baseline to the 44-week continuation study endpoint.
Abbreviations: BPRSd = Brief Psychiatric Rating Scale (derived), CGI-S = Clinical Global Impressions-Severity of Illness scale, GAF = Global Assessment of Functioning, LOCF = last observation carried forward, MADRS = Montgomery-Asberg Depression Rating Scale, NS = not significant, PANSS = Positive and Negative Syndrome Scale.

Ziprasidone versus risperidone. Ziprasidone has also been compared with risperidone in patients with schizophrenia or schizoaffective disorder in a randomized, double-blind, parallel-group, multicenter study.[17] The trial included an 8-week comparison of ziprasidone and risperidone (core study) and a 44-week continuation study in treatment responders (defined as ≥ 20% decrease in PANSS total score and CGI-I score of 1 or 2 [very much or much improved] at last observation in the core study). Patients received flexible-dose ziprasidone, 40 mg, 60 mg, or 80 mg b.i.d. (N = 149), or flexible-dose risperidone, 3 mg, 4 mg, or 5 mg b.i.d. (N = 147). A total of 62 ziprasidone-treated patients and 77 risperidone-treated patients entered the continuation study. Of these, 21 ziprasidone-treated patients (33.9%) and 32 risperidone-treated patients (41.6%) completed 44 weeks of treatment.

Treatment-related discontinuations were comparable in the 2 groups, with 25.8% and 19.5% of ziprasidone- and risperidone-treated patients, respectively, withdrawn from treatment due to insufficient clinical response.[17] Both treatment groups experienced significant (p < .001) and comparable sustained improvements in all efficacy variables from the 8-week core study baseline to the 44-week continuation study endpoint (Table 2).

A notable finding in this study involved mean change in MADRS score.[17] Among all patients in the study and those with a baseline score of ≥ 14, mean change from baseline to endpoint in MADRS score was comparable for the 2 groups. But among completers, approximately 70% of ziprasidone-treated patients (N = 21) had ≥ 50% improvement in mean MADRS score at 52 weeks, compared with approximately 40% of risperidone-treated patients (N = 31) (p < .05 ziprasidone vs. risperidone) (data on file, Pfizer Inc, New York, N.Y.). Of note, ziprasidone was associated with less weight gain, less prolactin elevation, and a lower movement disorder burden than risperidone.[17]

Figure 5. Mean Changes in PANSS Negative Subscale Scores From Baseline of 6-Week Core Study to End of Extension Study in Patients Switched to Ziprasidone From Olanzapine, Risperidone, or Conventionals (LOCF)[a]
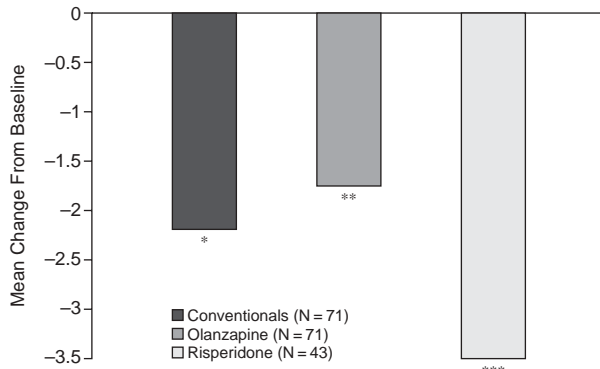
[a]Reproduced with permission from Schooler et al.[19]
*p < .01 versus baseline.
**p < .05 versus baseline.
***p < .001 versus baseline.
Abbreviations: LOCF = last observation carried forward,
    PANSS = Positive and Negative Syndrome Scale.

Long-Term Efficacy in Patients Switched From Other Antipsychotics

In 3 identical, open-label switch trials, stable outpatients with schizophrenia or schizoaffective disorder and persistent symptoms or troublesome side effects on conventional antipsychotics (N = 108), olanzapine (N = 104), or risperidone (N = 58) therapy were switched to flexible-dose oral ziprasidone, 40–160 mg/day.[18] At the end of the 6-week studies, patients with a CGI-I score ≤ 4 were enrolled in extensions, which lasted ≥ 31 weeks.[19] In each of the extension studies, patients had significantly improved PANSS negative subscale scores compared with the 6-week core study baseline (Figure 5). In addition, PANSS total score improved significantly (p = .009) in patients switched from a conventional agent (data on file, Pfizer Inc, New York, N.Y.).

DISCUSSION

In studies of up to 52 weeks' duration, patients with schizophrenia or schizoaffective disorder treated with ziprasidone demonstrated reduced risk of relapse, maintained positive symptom control, and improved negative symptoms. The long-term efficacy of ziprasidone was comparable to that of risperidone in the only study that compared the 2 agents.[17] Ziprasidone was comparable to olanzapine in 1 study[15] and less effective in the other.[16] The discrepancy in efficacy results between the Kane et al. 28-week study[16] and the 6-month study reported by Simpson and colleagues[15] may be accounted for by differences in dosing or design. The mean modal dose for olanzapine in the 28-week study was higher than the mean

daily dose in the 6-month trial, and the mean modal dose for ziprasidone in the 28-week study was lower than the mean modal dose in the 6-month study. A recent analysis of ziprasidone clinical trial data indicated that dosages of at least 120 mg/day achieved superior response relative to lower dosages in short-term fixed-dose trials, without an excess of treatment-related events, and that mean daily doses typically exceeded 120 mg/day during flexible dosing.[20] Furthermore, the study designs differed. The Simpson et al. study[15] was limited to patients who had already shown an initial clinical response to treatment, whereas the Kane et al. study[16] randomized patients who were symptomatic.

Ziprasidone was superior to haloperidol in terms of rate of negative symptom response. In addition, ziprasidone was associated with significant sustained improvement in negative symptoms in comparison with placebo and in patients switched from haloperidol, risperidone, and olanzapine.

Ziprasidone's efficacy in improving negative symptoms, in particular, has substantial clinical implications. A study by Ho and colleagues[21] found negative symptoms, more so than psychotic or disorganized symptoms, to be predictive of occupational impairment, financial dependence, impaired social relationships, impaired ability to enjoy recreational activities, and poor functioning in first-episode patients. Moller and colleagues[22] found during a 15-year follow-up that negative symptoms were more frequent and prominent in patients with schizophrenia, and the course and outcome of disease was more deleterious than in patients with affective and schizoaffective disorders. In a study that assessed the relationship of cognitive functioning and negative symptoms to functional outcome across severity of negative symptoms, McGurk and colleagues[23] found that among 208 geriatric poor-outcome schizophrenics, negative symptoms and cognitive functioning had the strongest relationships to functional status, regardless of negative symptom severity. Thus, across the life course of schizophrenic illnesses, the persistence of negative symptoms has an impact on outcome.

The effect of tolerability on adherence is also a consideration in treatment selection. Ziprasidone's safety and tolerability in long-term treatment are well characterized and are discussed in detail elsewhere in this issue. In the studies presented here, ziprasidone was well tolerated. In the 1-year ZEUS study, the tolerability profiles of ziprasidone and placebo were similar, with small mean reductions in body weight, reductions in median prolactin levels, and small mean improvements in movement disorder scores seen in both treatment groups. Ziprasidone was not associated with clinically significant effects on QTc interval compared with placebo, with no intervals > 500 ms. Ziprasidone and olanzapine were both associated with low rates of movement disorders. However, ziprasidone was associated with favorable/neutral effects on weight and

metabolic variables (i.e., fasting insulin, plasma glucose, and serum lipids) compared with olanzapine, which was associated with significant weight gain and adverse changes in these metabolic parameters. In comparison with risperidone, ziprasidone was associated with less weight gain, less prolactin elevation, and a lower movement disorder burden.

Antipsychotic medication is the foundation of long-term treatment of schizophrenia. In deciding which antipsychotic will be optimal for an individual patient, the clinician must take into account symptom control, prevention of relapse, and possible long-term health consequences. Clinical trial data on ziprasidone's long-term efficacy provide a firm basis for selection of this agent.

Drug names: clozapine (Clozaril and others), haloperidol (Haldol and others), olanzapine (Zyprexa), risperidone (Risperdal), ziprasidone (Geodon).

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