Oral Ziprasidone in the Treatment of Schizophrenia: A Review of Short-Term Trials

John M. Kane, M.D.

Pharmacotherapy of schizophrenia presents a set of challenges. Ideally, antipsychotic therapy should have a rapid effect on clinical improvement, show effectiveness against symptoms in multiple domains, and possess a tolerability profile that optimizes patient adherence and overall health outcomes. The atypical antipsychotic ziprasidone has been shown in placebo- and active-comparator–controlled clinical studies to be effective in treating the positive, negative, and affective symptoms of schizophrenia. In placebo-controlled trials of 4 to 6 weeks, significant improvements in overall psychopathology and negative symptoms as early as 1 week after treatment initiation were demonstrated. In trials of 4 to 8 weeks' duration in patients with acute exacerbation of schizophrenia, ziprasidone demonstrated efficacy comparable to that of haloperidol, olanzapine, and risperidone. In a 12-week study of patients with treatment-resistant schizophrenia, ziprasidone demonstrated overall efficacy comparable to that of chlorpromazine, with superior improvement in negative symptoms. In 6-week, open-label switching studies, patients switched to ziprasidone from conventional antipsychotics, olanzapine, or risperidone because of suboptimal efficacy or tolerability experienced improvement in symptoms. Oral ziprasidone's tolerability profile includes a lower movement disorder burden than that of risperidone, a lower liability for weight gain than that of risperidone or olanzapine, and an absence of significant deleterious effects on serum lipid levels or glucose metabolism. Available clinical data support rapid titration to ≥ 120 mg/day for optimal efficacy in patients with acute exacerbation of schizophrenia. *(J Clin Psychiatry 2003;64[suppl 19]:19–25)*

Schizophrenia presents a range of therapeutic challenges. First, the relapsing/remitting nature of this disorder calls for pharmacotherapy that can rapidly improve symptoms. Second, the complex presentation of this illness, which includes positive, negative, and affective symptoms present in varying degrees in individual patients, demands effectiveness across symptom domains. Third, concerns about patient adherence and long-term health outcomes necessitate careful consideration of an antipsychotic's tolerability profile and its long-term as well as short-term implications for adherence and health outcomes.

Atypical antipsychotics have broadened our therapeutic choices and greatly changed the management of patients with schizophrenia and schizoaffective disorder. These agents share an ability both to improve the positive and negative symptoms of schizophrenia and to reduce the liability for inducing movement disorder adverse effects compared with older conventional agents.[1] The atypicals are, however, heterogeneous in other respects, including tolerability profiles.

Ziprasidone is the first and currently only atypical antipsychotic available in both oral and intramuscular formulations and thus represents a therapeutic option at all points on the treatment continuum, from control of acute exacerbation to long-term management. As described in this review, in short-term (≤ 12 weeks) trials, oral ziprasidone has demonstrated antipsychotic efficacy superior to that of placebo and comparable to that of haloperidol (with evidence of superior negative symptom efficacy) and other atypicals. Symptom improvement has been rapid (within 1 week), with benefits observed across negative, positive, and affective symptom domains. Moreover, ziprasidone has shown comparable efficacy to chlorpromazine in patients with treatment-resistant schizophrenia, as well as efficacy in patients switched from other antipsychotics because of suboptimal effectiveness or tolerability. Oral ziprasidone's tolerability profile, as demonstrated in short-term trials, includes a lower movement disorder burden than that of risperidone, a lower liability for weight gain than that of risperidone or olanzapine, and an absence of significant deleterious effects on serum lipid levels or glucose metabolism.

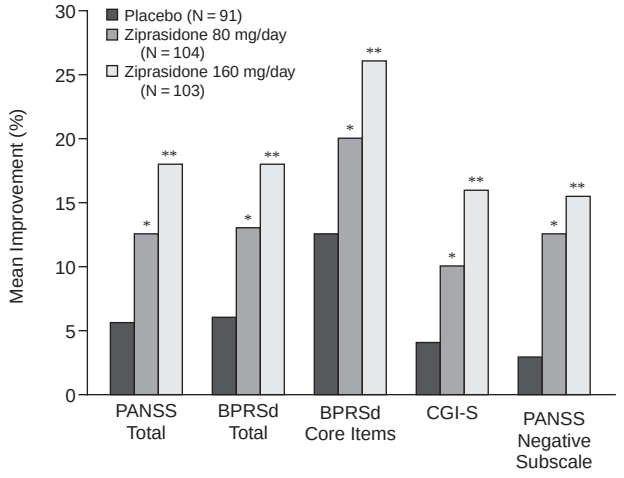
From the Department of Psychiatry, The Zucker Hillside Hospital of the North Shore Long Island Jewish Health System, Glen Oaks, N.Y.

Sponsored by Pfizer Inc, New York, N.Y.

Dr. Kane has worked as a consultant for AstraZeneca, Aventis, Bristol-Myers Squibb, Eli Lilly, Pfizer, Janssen, and Novartis.

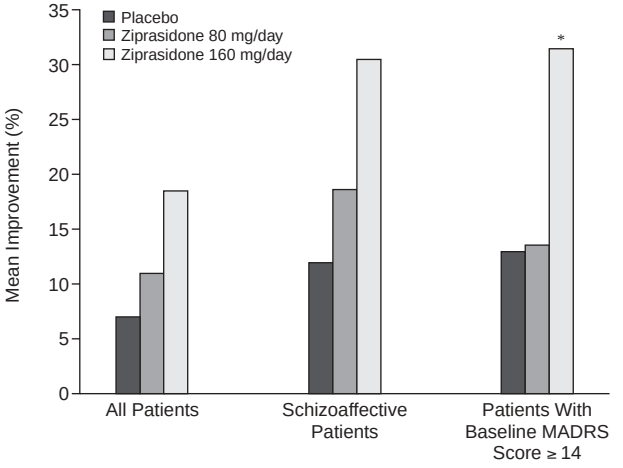
Corresponding author and reprints: John M. Kane, M.D., Chairman, Department of Psychiatry, The Zucker Hillside Hospital of the North Shore Long Island Jewish Health System, 75-59 263rd Street, Glen Oaks, NY 11004 (e-mail: psychiatry@lij.edu).

Figure 1. Mean Improvements From Baseline in Overall Psychopathology, Positive Symptoms, and Negative Symptoms (ITT, LOCF): 6-Week Study Versus Placebo[a]



[a]Reprinted with permission from Daniel et al.[2]
*p < .05 vs. placebo.
**p < .001.
Abbreviations: BPRSd = Brief Psychiatric Rating Scale (PANSS derived), CGI-S = Clinical Global Impressions-Severity of Illness scale, ITT = intent to treat, LOCF = last observation carried forward, PANSS = Positive and Negative Syndrome Scale.

Figure 2. Improvements From Baseline in Mean MADRS Total Score: 6-Week Study Versus Placebo (ITT, LOCF)[a]



[a]Reprinted with permission from Daniel et al.[2]
*p < .05 vs. placebo.
Abbreviations: ITT = intent to treat, LOCF = last observation carried forward, MADRS = Montgomery-Asberg Depression Rating Scale.

PLACEBO-CONTROLLED ACUTE-TREATMENT TRIALS

A 6-week, double-blind, placebo-controlled trial by Daniel and colleagues[2] evaluated the efficacy of fixed-dose oral ziprasidone in inpatients with acute exacerbation of schizophrenia. Following a 3- to 7-day washout period, 302 patients who had been hospitalized within the past 4 weeks were randomized to ziprasidone 80 mg/day (N = 106), 160 mg/day (N = 104), or placebo (N = 92).[2] Efficacy variables included the Positive and Negative Syndrome Scale (PANSS) total score, the PANSS negative subscale score, the Brief Psychiatric Rating Scale (BPRS) total and core items scores, and the Clinical Global Impressions-Severity of Illness scale (CGI-S) and CGI-Improvement scale (CGI-I) scores. Changes in depressive symptoms were rated using the Montgomery-Asberg Depression Rating Scale (MADRS) total score.[2] The primary analysis was by intent-to-treat, with the last observation carried forward (LOCF).

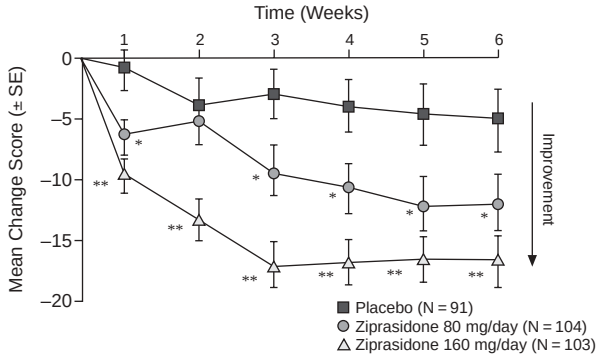
At study endpoint, both doses of ziprasidone were significantly more effective than placebo in improving mean scores across all outcome measures (Figure 1).[2] Response on PANSS total score was defined as a ≥ 30% decrease from baseline to last observation, and response on the CGI-I was defined as "very much improved" (i.e., a score of 1) or "much improved" (i.e., a score of 2) at last observation. There were significantly more PANSS responders in the ziprasidone 160 mg/day group versus the placebo group (31.1% vs. 17.6%; p < .05) and numerically more responders in the ziprasidone 80 mg/day group (28.8%; p = .09). Response rates were similar for the CGI-I, with ziprasidone 160 mg/day patients achieving a significantly greater response than placebo patients (42.7% vs. 26.1%; p < .05) and with those taking ziprasidone 80 mg/day achieving a 33% response (p = .39). In addition, statistically significant reductions in mean MADRS scores (p < .05) were observed among patients taking ziprasidone 160 mg/day who had clinically significant depressive symptoms (MADRS ≥ 14) at study baseline (Figure 2).[2]

Compared with placebo, ziprasidone 80 mg/day and 160 mg/day produced statistically superior responses (p < .05 and p < .001, respectively) in mean PANSS total (Figure 3)[2] and negative subscale scores, BPRS total and core items scores, and CGI-S score within 1 week of initiating treatment; these differences were sustained or increased over the subsequent weeks of treatment.

The overall incidence of adverse events was similar among all groups, with treatment-emergent events being of mild or moderate severity. The rate of discontinuation attributed to adverse events was similar in the ziprasidone 80 mg/day (1.8%) and placebo (1.1%) groups, whereas the rate in the ziprasidone 160 mg/day group was higher (7.7%).[2] The incidence of extrapyramidal symptoms was low (2% in the 80 mg/day group and 7% in the 160 mg/day group), and significant weight gain was not reported in either ziprasidone group.[2]

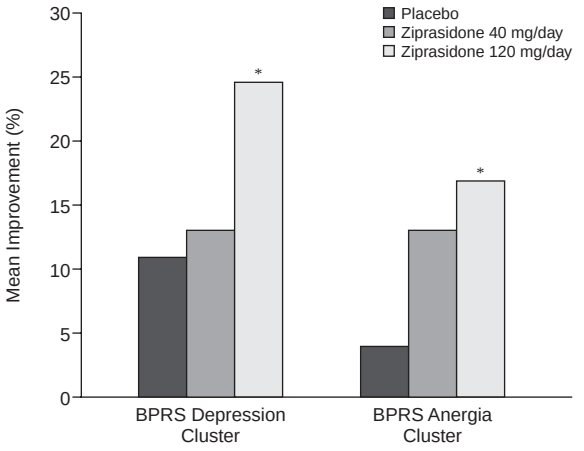
In a second fixed-dose trial, Keck and colleagues[3] evaluated the efficacy and tolerability of oral ziprasidone in acute exacerbation of schizophrenia or schizoaffective disorder. A total of 139 inpatients were randomly assigned

Figure 3. Improvement in Mean PANSS Total Scores Over Time From Baseline: 6-Week Study Versus Placebo[a]



[a]Adapted with permission from Daniel et al.[2]
*p < .05 vs. placebo.
**p < .001 vs. placebo.
Abbreviation: PANSS = Positive and Negative Syndrome Scale.

Figure 4. Mean Percentage Improvement From Baseline in BPRS Depression and Anergia Clusters Scores: 4-Week Study Versus Placebo (ITT, LOCF)[a]



[a]Adapted with permission from Keck et al.[3] BPRS depression cluster values indicate improvement in patients with baseline scores ≥ 18.
*p < .05 vs. placebo.
Abbreviations: BPRS = Brief Psychiatric Rating Scale, ITT = intent to treat, LOCF = last observation carried forward.

to 28 days of treatment with ziprasidone 40 mg/day (N = 44), 120 mg/day (N = 47), or placebo (N = 48). In addition to evaluating improvement in the 3 primary efficacy variables—BPRS total score, BPRS core items score, and CGI-S score—the investigators measured CGI-I and changes in BPRS depression cluster and anergia factor scores and Scale for the Assessment of Negative Symptoms total score, and calculated the percentage of responders (≥ 30% reduction in BPRS or CGI-I scores of 1 or 2).

An intent-to-treat LOCF analysis showed that at 4 weeks, ziprasidone 120 mg/day, but not 40 mg/day, was significantly more effective than placebo in improving mean BPRS total and CGI-S scores (both $p < .05$), with improvement in BPRS core items trending toward significance ($p < .06$).[3] Among patients with depression at baseline, significantly greater improvements in mean BPRS depression and anergia cluster scores were observed at 4 weeks with ziprasidone 120 mg/day than with placebo ($p < .05$) (Figure 4).[3] Similarly, a significant improvement in negative symptoms, as measured by the mean BPRS anergia cluster score, was observed with ziprasidone 120 mg/day ($p < .05$) but not with ziprasidone 40 mg/day or placebo. The percentage of patients classified as BPRS and CGI-I responders was significantly greater for ziprasidone 120 mg/day (48.8% and 33.3%, respectively) than for placebo (25.5% and 12.8%) ($p < .05$), but was not significantly greater with 40 mg/day.[3]

A time-course analysis showed improvement in BPRS total and core items and CGI-S scores in all 3 treatment groups after 1 week of treatment; however, no further changes were observed in the placebo group during the remaining 3 weeks. In patients receiving 40 mg/day, significantly superior improvement in CGI-S scores was noted versus placebo at week 3 ($p < .05$). In contrast, patients assigned to ziprasidone 120 mg/day experienced continued improvements in all of these parameters, with the greatest benefits observed at study endpoint.[3]

Another study by Keck and colleagues[4] analyzed the efficacy of ziprasidone in a subgroup of patients with acute exacerbation of schizoaffective disorder. Data were drawn from 2 separate double-blind trials in which 115 recently hospitalized patients with schizoaffective disorder were randomly assigned to receive 4 to 6 weeks of therapy with fixed doses of ziprasidone 40 mg/day (N = 16), 80 mg/day (N = 18), 120 mg/day (N = 22), or 160 mg/day (N = 25) or with placebo (N = 34).[4]

Analysis of pooled data showed significant, linear, dose-dependent improvements versus placebo in all primary outcome measures (mean scores for BPRS total and core items and CGI-S) with ziprasidone 160 mg/day and also in the mean BPRS manic items score, a secondary efficacy parameter (all $p < .01$).[4] An intent-to-treat LOCF analysis showed that ziprasidone 160 mg/day was significantly superior to placebo in improving overall psychopathology, as measured by improvements in mean BPRS total, core, and manic item scores and mean CGI-S scores from baseline to endpoint (all $p < .01$). Treatment with ziprasidone 120 mg/day was associated with statistically significant reductions in CGI-S scores compared with placebo changes ($p < .01$). Reductions in mean BPRS total and subscale scores were numerically, but not significantly, superior to those for placebo for all other measures and doses. The incidence of adverse effects, including movement disorders, was generally low and not dose related.

COMPARATIVE TRIALS

Ziprasidone has been shown to be comparable to haloperidol,[5] risperidone,[6] and olanzapine[7] in efficacy in short-term trials in patients with acute exacerbation of schizophrenia, while demonstrating clinically relevant differences with regard to tolerability.

Efficacy Versus Haloperidol

An exploratory, haloperidol-controlled, dose-finding study evaluated the efficacy of oral ziprasidone in patients with schizophrenia or schizoaffective disorder who had either been recently hospitalized for an acute exacerbation of illness or had resided in an intermediate treatment center for ≥ 3 months and had only partial response to antipsychotic treatment.[5]

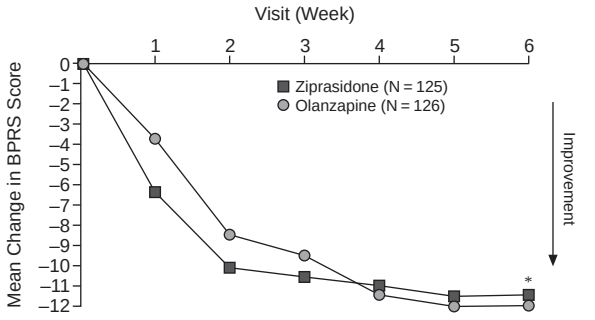
Ninety patients were randomized to 4 weeks of therapy with ziprasidone 4 mg/day (N = 19), 10 mg/day (N = 17), 40 mg/day (N = 17), or 160 mg/day (N = 20) or with haloperidol 15 mg/day (N = 17).[5] The primary efficacy parameters were mean change in BPRS total, BPRS psychosis core items, and CGI-S scores. Dose responses across ziprasidone groups on BPRS total and CGI-S scores were analyzed on the basis of linear contrast.

An intent-to-treat LOCF analysis of patients who received ≥ 1 dose of ziprasidone showed a significant ziprasidone dose response for CGI-S scores ($p < .001$) and a trend toward significance ($p = .08$) in the dose response for the BPRS total score. The ziprasidone 160 mg/day and haloperidol 15 mg/day groups had comparable reductions in BPRS total (mean change from baseline –11.9 vs. –11.6, respectively), BPRS core (–5.8 vs. –5.4, respectively), and CGI-S (–1.2 vs. –1.1, respectively) scores. BPRS responder rates were 45.0% for patients receiving ziprasidone 160 mg/day and 47.1% for patients receiving haloperidol 15 mg/day, and respective responder rates for the CGI-I were 50.0% and 41.2%. Haloperidol, but not ziprasidone, was associated with a sustained increase in serum prolactin levels. Moreover, 15% of patients receiving ziprasidone 160 mg/day were administered concomitant benztropine versus 52.9% of patients receiving haloperidol 15 mg/day.

Efficacy Versus Olanzapine

In a 6-week, double-blind, multicenter study, inpatients with acute exacerbation of schizophrenia or schizoaffective disorder were randomized to therapy with ziprasidone (40–80 mg b.i.d.; N = 136) or olanzapine (5–15 mg/day; N = 133).[7] The primary efficacy variables in this study were change in BRPS total and CGI-S scores. Other efficacy variables included changes in PANSS total and positive and negative subscale scores and in Calgary Depression Scale for Schizophrenia (CDSS) scores. Analyses were by intent-to-treat LOCF. Equivalence of the 2 treatment groups in BPRS total was demonstrated if the 2-sided 95% confidence interval (CI) of the least-squares means difference (ziprasidone minus olanzapine) included 0 and remained within a priori specified margins of ≤ 3.5 points (data on file, Pfizer Inc, New York, N.Y.).

Figure 5. Mean Change From Baseline in BPRS Total Scores With Ziprasidone and Olanzapine, All Patients (LOCF): 6-Week Trial[a]

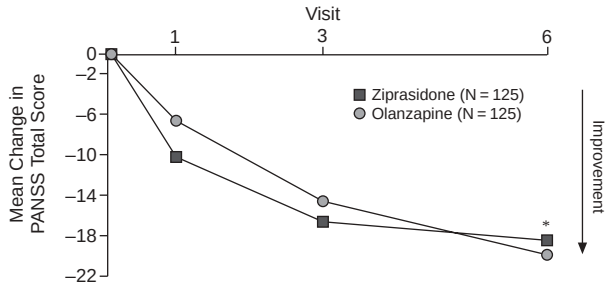


[a]Adapted with permission from Simpson et al.[7]
*p = NS; 95% confidence interval = –2.36 to 3.18.
Abbreviations: BPRS = Brief Psychiatric Rating Scale, LOCF = last observation carried forward.

The overall mean daily dose of ziprasidone was 129.9 mg (SD = 27.3) and that of olanzapine was 11.3 mg (SD = 2.8). Both groups experienced rapid and similar improvements in mean BPRS total scores (Figure 5).[7] There were no significant differences between ziprasidone and olanzapine at week 6 visit analysis or at endpoint ($p = .77$; 95% CI = –2.36 to 3.18). The CIs for differences in mean change (ziprasidone minus olanzapine) included 0 and remained within the a priori specified margin of 3.5 points, demonstrating equivalence between the 2 agents in improving mean BPRS total score. Similarly, mean CGI-S and PANSS total (Figure 6), positive, and negative subscale scores improved rapidly in both groups, with no significant differences between treatments. By study endpoint, the majority of patients in both treatment groups experienced ≥ 20% reductions in mean CDSS scores, with no significant differences between groups.

Patients treated with olanzapine experienced a 3.57-kg (7.87 lb) increase in body weight, compared with a 0.93-kg (2.05 lb) increase in patients treated with ziprasidone ($p < .0001$ vs. ziprasidone).[7] Fasting total cholesterol increased significantly by 20 mg/dL in patients receiving olanzapine but decreased by 1 mg/dL in patients receiving ziprasidone ($p < .0001$ vs. ziprasidone). Fasting low-density lipoprotein cholesterol increased significantly by 13 mg/dL in the olanzapine group, while decreasing by 1 mg/dL in the ziprasidone group ($p = .0004$ vs. ziprasidone). In addition, olanzapine, but not ziprasidone, was associated with significant ($p ≤ .0001$ vs. baseline) increases in serum insulin levels and in the homeostasis model assessment for insulin resistance.[8] One potential

Figure 6. Mean Change From Baseline in PANSS Total Scores With Ziprasidone and Olanzapine, All Patients (LOCF): 6-Week Trial[a]



[a]Adapted with permission from Simpson et al.[7]
*p = NS; 95% confidence interval = –4.44 to 5.21.
Abbreviations: LOCF = last observation carried forward, PANSS = Positive and Negative Syndrome Scale.

limitation of this study is that mean doses of both drugs were lower than what many clinicians may be currently using.

Efficacy Versus Risperidone

Addington and colleagues[6] compared the efficacy and tolerability of ziprasidone and risperidone in the treatment of acute exacerbation of schizophrenia or schizoaffective disorder. Patients were randomized to 8 weeks of flexible-dose ziprasidone 40 to 80 mg b.i.d. (N = 149) or risperidone 3 to 5 mg b.i.d. (N = 147). Mean total daily doses were 114.2 mg for ziprasidone and 7.4 mg for risperidone. Primary efficacy evaluations were changes in PANSS total and CGI-S scores; secondary measures were changes in PANSS negative symptom subscale, PANSS-derived BPRS (BPRSd) total and core items, MADRS, and Global Assessment of Functioning scores. The primary analysis population was defined a priori as evaluable patients, i.e., patients with ≥ 14 days of double-blind treatment and no protocol violations. Treatments were considered equivalent if the lower limit of the 95% CI of mean change ratio (ziprasidone/risperidone) was > 0.6.

At endpoint, ziprasidone- and risperidone-treated patients had comparable, significant mean reductions in PANSS total and CGI-S scores ($p < .001$ for each), with equivalence between the 2 groups demonstrated.[6] Similarly, significant mean improvements from baseline were observed for all secondary efficacy assessments, with equivalency between the 2 groups.[6]

This study employed the Movement Disorder Burden Score (MDBS), a prospectively defined score calculated using the incidence, duration, and severity of movement disorder adverse events; prescribed antiparkinsonian medication; and total number of days study treatment was received. Mean MDBS score was significantly ($p < .05$) lower in patients treated with ziprasidone.[6] Consistent with lower MDBS, reports of movement disorders as adverse events and the percentage of days with movement disorders were also lower in the ziprasidone group. Changes in abnormal movement scales, including the Simpson-Angus Rating Scale, Barnes Akathisia Scale, and Abnormal Involuntary Movement Scale (AIMS) were comparable for the 2 groups, although improvement in AIMS score was noted in more patients taking ziprasidone than risperidone. Mean weight gain approaching 3 lb (1.36 kg) in men and exceeding 5 lb (2.27 kg) in women was observed with risperidone during the initial treatment period, whereas a mean < 0.45-kg (1-lb) weight loss was observed in both men and women treated with ziprasidone during this period. Furthermore, at 8 weeks, median changes in prolactin levels from baseline were + 18 ng/mL for risperidone and –9 ng/mL for ziprasidone.

Notably, at the time of protocol initiation there was limited experience with optimal dosing of either ziprasidone or risperidone. In this study, it was predicted that ziprasidone 40 mg b.i.d. would be sufficient for a clinical response, and titration was also more cautious. However, subsequent experience in clinical trials suggested that some patients benefit from ziprasidone dosages of up to 80 mg b.i.d. The risperidone average total daily dose of 7.4 mg and maximum daily dose of 10 mg were higher and the titration was more rapid than current recommendations but were consistent with the recommendations at study initiation.[9,10]

EFFICACY IN TREATMENT-RESISTANT PATIENTS

Khanna and colleagues[11] carried out a 2-stage, double-blind, parallel-group trial of ziprasidone in patients with chronic schizophrenia who did not respond adequately to 6 weeks' prospective treatment with ≤ 30 mg/day of haloperidol. Treatment-refractory patients were randomized to 12 weeks of double-blind ziprasidone (80–160 mg/day; N = 153) or chlorpromazine (200–1200 mg/day; N = 154).

In the intent-to-treat population, mean improvement in PANSS negative subscale score from post-haloperidol baseline to week-12 endpoint was significantly greater in patients treated with ziprasidone (–3.4) than in those treated with chlorpromazine (–2.2) ($p < .05$). In both groups, improvements from post-haloperidol baseline were observed in BPRSd, BPRS core items, CGI-S, PANSS total, and MADRS scores, but these were not statistically significant.

EFFICACY IN PATIENTS SWITCHED FROM OTHER ANTIPSYCHOTICS

In clinical practice, patients often undergo switching of antipsychotic therapy because of inadequate symptom control, tolerability problems, or a combination thereof.

In 3 open-label, 6-week studies, Weiden and colleagues[12,13] observed improved symptoms and overall psychopathology in stable outpatients switched to ziprasidone after prior antipsychotic therapy was determined to be suboptimal in efficacy or tolerability. Patients previously treated with olanzapine (N = 104), risperidone (N = 58), or conventional antipsychotics (N = 108) were switched to ziprasidone 40 to 160 mg/day. Three switching strategies were evaluated: (1) complete discontinuation of previous treatment the day before starting ziprasidone; (2) immediate dosage reduction, with a 50% reduction in the previous antipsychotic dosage for the first week of ziprasidone, followed by complete discontinuation at the start of week 2; and (3) delayed dosage reduction, with a 50% reduction in the dosage of the previous antipsychotic on day 4 of ziprasidone treatment, followed by complete discontinuation at the start of week 2.

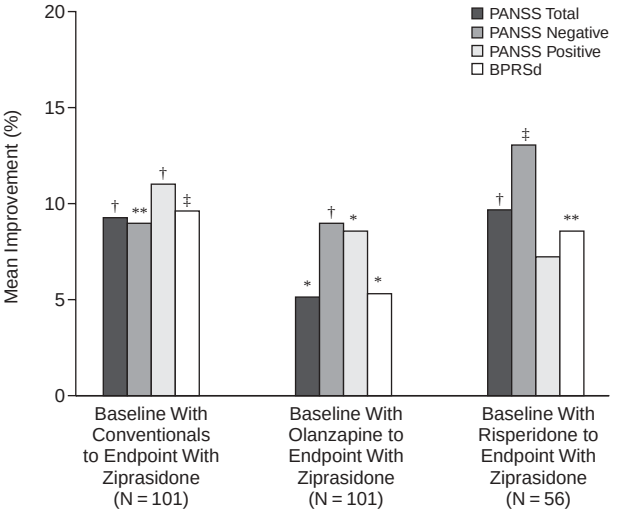
Drop-out rates did not differ significantly by switching strategy.[12] Pooled data from all switching strategies showed statistically significant improvements in mean BPRS total and PANSS total scores in patients switched to ziprasidone from risperidone, olanzapine, or conventional antipsychotics ($p < .05$) (Figure 7). Significant improvements in mean CGI-S score were observed in patients switched from conventional antipsychotics to ziprasidone ($p < .0001$).

Significant improvements in mean PANSS total score were observed as early as 1 week after the switch from olanzapine or risperidone ($p < .05$) and after 3 weeks in patients switched from conventional antipsychotics ($p \leq .001$).[12] Similarly, significant improvements in PANSS negative and positive subscale mean scores were observed by 1 to 3 weeks after patients were switched to ziprasidone ($p < .05$).

The switch to ziprasidone was generally well tolerated in these patients. Significant reductions in mean body weight were observed in patients switched from olanzapine (–3.9 lb [–1.8 kg], $p < .001$) or risperidone (–1.9 lb [–0.9 kg], $p < .05$).[12] Significant median reductions from baseline in triglyceride levels were observed in patients switched from olanzapine (–50 mg/dL; $p < .0001$) or risperidone (–29 mg/dL; $p < .01$).[13] Also seen were significant median reductions in total cholesterol levels in patients switched from olanzapine (–17 mg/dL; $p < .0001$) or risperidone (–12 mg/dL; $p < .005$).[13] Mean score on a measure of movement disorders (Simpson-Angus Scale) improved significantly in patients switched from conventional agents or risperidone to ziprasidone ($p < .01$ for each).[12] Median prolactin level decreased in those switched from risperidone ($p < .0001$) or conventional agents ($p = .05$).[13]

Notwithstanding the inherent limitations of uncontrolled switch studies, these findings are encouraging, suggesting that ziprasidone can be helpful in patients who have not experienced an optimum response with other agents.

Figure 7. Mean Percentage Improvement in Measures of Antipsychotic Efficacy in Patients Switched From Conventional Antipsychotics, Olanzapine, or Risperidone to Ziprasidone: 6-Week Open-Label Studies[a]



[a]Reprinted from Weiden et al.[12]
*$p < .05$ vs. baseline.
**$p < .01$ vs. baseline.
†$p < .005$ vs. baseline.
‡$p < .0001$ vs. baseline.
Abbreviations: BPRSd = Brief Psychiatric Rating Scale (PANSS derived), PANSS = Positive and Negative Syndrome Scale.

OPTIMAL DOSING

Using pooled data from four 4- to 6-week (short-term), fixed-dose, placebo-controlled trials and three 6- to 8-week flexible-dose, active-comparator trials, Murray and colleagues[14] investigated the optimal dosing of oral ziprasidone. A total of 569 patients were enrolled in the short-term trials (ziprasidone 40–160 mg/day), and 706 patients were enrolled in the flexible-dose trials (up to 160 mg/day).

In a pooled analysis of the placebo-controlled short-term trials, statistically significant improvement in mean BPRS total score was observed at weeks 2 through 6 in patients treated with ziprasidone 120 mg/day and at weeks 1 through 6 in patients taking the 160-mg/day dose.[14] In contrast, statistically significant improvement with the 80 mg/day dose was observed only during the final 2 weeks of treatment. The 120-mg/day and 160-mg/day doses of ziprasidone also had greater placebo-corrected treatment effects on mean BPRS total score at the final visit than did the 40-mg/day and 80-mg/day doses. Time-course analysis revealed ongoing improvement with doses of < 120 mg/day; however, doses ≥ 120 mg/day achieved efficacy by week 1.

Patients treated with ziprasidone 120 or 160 mg/day had lower rates of discontinuation due to inadequate clini-

cal response during the first 2 weeks of treatment compared with those given lower doses.[14]

Among patients enrolled in the flexible-dose active-comparator studies, mean daily doses of ziprasidone were consistently > 80 mg/day.[14] More than 80% of patients enrolled in these studies required mean doses ≥ 80 mg/day for optimal therapeutic effect, and between 48% and 80% required ziprasidone daily doses ≥ 120 mg/day.

Importantly, the incidence of treatment-emergent, treatment-related side effects and of treatment-related serious adverse events was comparable across the total daily dose ranges.[14]

These data indicate that higher ziprasidone doses are associated with a more rapid favorable response in overall psychopathology and a lower discontinuation rate due to inadequate clinical response.[14] The higher ziprasidone doses (≥ 80 mg/day) used in these studies were well tolerated and support the use of rapid titration to ≥ 120 mg/day in patients with acute schizophrenia and for the prevention of relapse.

DISCUSSION

In the management of patients with schizophrenia, clinicians face myriad situations that prompt choices about antipsychotic therapy: the patient with exacerbation of illness who requires rapid symptom improvement, the patient whose chronic treatment resistance must be overcome, and the stable patient whose treatment is inadequately effective or presents tolerability problems. In these situations, new options, when supported by data from clinical trials, are most welcome.

The trials reviewed here demonstrate that in short-term treatment ziprasidone possesses antipsychotic efficacy comparable to that of existing agents and superior to that of placebo and indicate that this agent offers important tolerability advantages, particularly with regard to weight and metabolic indices. These trials provide sound evidence of oral ziprasidone's clinical utility in the management of patients with schizophrenia.

Drug names: chlorpromazine (Thorazine, Sonazine, and others), haloperidol (Haldol and others), olanzapine (Zyprexa), risperidone (Risperdal), ziprasidone (Geodon).

REFERENCES

1. Beaumont G. Antipsychotics: the future of schizophrenia treatment. Curr Med Res Opin 2000;16:37–42
2. Daniel DG, Zimbroff DL, Potkin SG, et al. 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
3. 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
4. Keck PE Jr, Reeves KR, Harrigan EP, et al. Ziprasidone in the short-term treatment of patients with schizoaffective disorder: results from two double-blind, placebo-controlled, multicenter studies. J Clin Psychopharmacol 2001;21:27–35
5. 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
6. Addington D, Pantelis C, Dineen M, et al. Ziprasidone vs risperidone in schizophrenia: 52 weeks' comparative data [poster]. Presented at the 156th annual meeting of the American Psychiatric Association; May 17–22, 2003; San Francisco, Calif
7. Simpson GM, Romano SJ, Horne RL, et al. Ziprasidone vs olanzapine in schizophrenia: results of a double-blind trial [poster]. Presented at the 154th annual meeting of the American Psychiatric Association; May 5–10, 2001; New Orleans, La
8. Glick ID, Romano SJ, Simpson G, et al. Insulin resistance in olanzapine- and ziprasidone-treated patients: results of a double-blind, controlled 6-week trial [poster]. Presented at the 154th annual meeting of the American Psychiatric Association; May 5–10, 2001; New Orleans, La
9. Risperdal (risperidone). Physicians' Desk Reference. Montvale, NJ: Medical Economics; 2002:1796-1800
10. Williams R. Optimal dosing with risperidone: updated recommendations. J Clin Psychiatry 2001;62:282–289
11. Khanna S, Kane J, Rajadhyaksha S, et al. Ziprasidone vs chlorpromazine in treatment-refractory schizophrenia [poster]. Presented at the International Congress on Schizophrenia Research (ICOSR); March 29–April 2, 2003; Colorado Springs, Colo
12. Weiden PJ, Simpson GM, Potkin SG, et al. Effectiveness of switching to ziprasidone for stable but symptomatic outpatients with schizophrenia. J Clin Psychiatry 2003;64:580–588
13. Weiden PJ, Daniel DG, Simpson G, et al. Improvement in indices of health status in outpatients with schizophrenia switched to ziprasidone. J Clin Psychopharmacol 2003;23:595–600
14. Murray S, Siu CO, Romano SJ. Optimal dosing of oral ziprasidone: analysis of clinical trial data [poster]. Presented at the 156th annual meeting of the American Psychiatric Association; May 17–22, 2003; San Francisco, Calif