Ziprasidone in Treatment-Resistant Schizophrenia: A 52-Week, Open-Label Continuation Study

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Objective: To evaluate the efficacy, safety, and tolerability of long-term ziprasidone therapy in treatment-resistant schizophrenia.

Method: This prospective, 1-year, open-label study of ziprasidone (40–160 mg/day) was conducted in subjects who had participated in a previous randomized 12-week comparison of ziprasidone and chlorpromazine in treatment-resistant schizophrenia (DSM-III-R criteria). The clinical response of 62 subjects was evaluated (32 subjects had been on ziprasidone treatment and 30 had been on chlorpromazine treatment prior to enrollment in the continuation study). Assessments included the Positive and Negative Syndrome Scale total and subscale scores, movement disorder scales, body weight, and laboratory measures. This study was conducted from May 2000 to April 2002.

Results: Thirty-three subjects (53%) completed 1 year of open-label ziprasidone therapy. Ziprasidone maintained clinical improvement (no significant symptom exacerbation) in 30 of 41 subjects (73%) who responded to the initial 12-week double-blind treatment with either ziprasidone or chlorpromazine. Ziprasidone did not increase body weight and was associated with a favorable metabolic profile during the continuation study period. There were no significant changes in standard movement disorder measures from the core study baseline during long-term ziprasidone treatment.

Conclusion: Ziprasidone was effective and well tolerated in the long-term therapy of patients with treatment-resistant schizophrenia.

(J Clin Psychiatry 2007;68:1333–1338)

Received Oct. 16, 2006; accepted June 18, 2007. From Pfizer Inc, New York, N.Y. (Drs. Loebel, Rajadhyaksha, and Giller); the Department of Psychiatry, National Institute of Mental Health and Neurosciences, Bangalore, India (Dr. Khanna); Data Power (DP), Inc., Ringoes, N.J. (Dr. Siu); and the Department of Psychiatry and Human Behavior, University of California, Irvine (Dr. Potkin).

This study was supported by Pfizer Inc.

The study was presented in poster form at the 158th annual meeting of the American Psychiatric Association, May 21–26, 2005, Atlanta, Ga.

Financial disclosure appears at the end of this article.

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The treatment of resistant schizophrenia continues to be a substantial clinical challenge. While the prevalence of treatment-resistant schizophrenia is definition-dependent, estimates have ranged from 15% to over 40%.[1] Such patients can require long-term institutional care, experience significant social and functional disabilities, and contribute disproportionately to the high costs associated with schizophrenic illness.[2]

Current treatment options for treatment-resistant schizophrenia are limited. Clozapine, a second-generation (atypical) antipsychotic agent, has been shown to have superior efficacy and a reduced risk of certain side effects, such as extrapyramidal symptoms (EPS), compared with conventional antipsychotics in treating refractory schizophrenia.[2,3] However, the use of clozapine has been severely curtailed in part by the increased risk of life-threatening leukopenia and agranulocytosis, which necessitates routine blood monitoring,[4,5] as well as other adverse effects such as weight gain, dyslipidemia, hyperglycemia, cardiomyopathy, and seizures.

Other second-generation agents have not consistently demonstrated superior efficacy over conventional antipsychotics in the treatment of this patient population.[6,7] In a randomized, double-blind, 14-week study of patients with a history of suboptimal response to treatment, clozapine and olanzapine (but not risperidone) demonstrated a statistically significant but clinically modest effect on total and negative symptom scores when compared with haloperidol.[6] The efficacy differences among treatments were, however, small, and clozapine and olanzapine were associated with greater weight gain.[6] Conley et al.[8] found no advantage for olanzapine over chlorpromazine in a double-blind, 8-week study of treatment-resistant schizophrenia. In contrast, Breier and Hamilton[9] found olanzapine to have superior efficacy over haloperidol in a subgroup of patients meeting treatment-resistant criteria, in a 6-week, double-blind study in which 50% of subjects were outpatients at the time of study entry. Given these data, the search for effective short- and long-term therapies for patients with treatment-resistant schizophrenia remains an urgent priority.

In the 12-week, comparative trial that preceded the current continuation study, ziprasidone showed significantly

greater improvement than chlorpromazine in negative symptoms while producing comparable efficacy in overall psychotic symptoms and global illness severity.[10]

We report here on a cohort of treatment-resistant schizophrenic patients who received up to 1 year of open-label ziprasidone treatment after participating in a 12-week, double-blind trial comparing ziprasidone and chlorpromazine.[10] This is the first report, to our knowledge, on the use of ziprasidone in the long-term, maintenance therapy of treatment-resistant schizophrenia.

METHOD

This was a prospective, 1-year, single-arm, open-label trial of ziprasidone (40–160 mg/day) in 129 subjects who had previously participated in a randomized, 12-week, double-blind study (conducted from April 1997 to February 2001) comparing ziprasidone (80–160 mg/day) and chlorpromazine (100–1200 mg/day) in treatment-resistant schizophrenia. The design of the core study has been described elsewhere and is summarized below.[10] The continuation study was conducted in India from May 2000 to April 2002; all patients provided written informed consent prior to study enrollment. The protocol was reviewed and approved by institutional review boards at the investigational sites.

Patient Eligibility

Before starting the core study, all eligible subjects were required to meet both retrospective criteria for treatment resistance (failure to respond to at least three 6-week treatment periods within the past 5 years, with at least 2 different neuroleptic agents)[2] and prospective criteria for resistance (failure to respond to 6 weeks of prospective, open-label haloperidol up to 30 mg/day in the screening period prior to randomization). The core study excluded subjects who met response criteria, defined as a ≥ 20% decrease in the total Brief Psychiatric Rating Scale (BPRSd)[11] derived from the Positive and Negative Syndrome Scale (PANSS)[12] score, plus either a posttreatment Clinical Global Impressions-Severity of Illness scale (CGI-S)[13] score of ≤ 3 or a posttreatment BPRSd score of ≤ 35, after the prospective haloperidol treatment period. Eligible subjects were men and women 18 years or older with a primary diagnosis of chronic or subchronic schizophrenia as defined by DSM-III-R. All subjects who had participated in the core study (whether or not they had responded to or completed treatment) were eligible to receive open-label ziprasidone therapy in the continuation study. Subjects were also required to have had no clinically significant adverse event, no imminent risk of suicide, and normal laboratory and electrocardiogram (ECG) findings at study entry.

During the 1-year open-label extension study, subjects were discontinued from ziprasidone treatment if (1) clinically important adverse events or serious laboratory or ECG abnormalities occurred, (2) the subject showed consistent signs of nonresponse in the investigator's opinion, (3) the subject significantly failed to comply with the protocol, or (4) in the investigator's judgment, continuation in the study would be detrimental to the subject's condition.

All 129 subjects entering the 1-year continuation trial (including those previously randomly assigned to chlorpromazine) received open-label treatment with ziprasidone (40–160 mg/day). The starting dose was 40 mg/day, with subsequent adjustments (up to a maximum of 160 mg/day) permissible after the first 2 days to optimize efficacy and tolerability. A total of 82 men (64%) and 47 women (36%) were enrolled. The mean age was 34.7 years (range, 19–63 years). Due to administrative delays regarding regulatory approval of the continuation study, 67 subjects (3 subjects did not complete the core phase) entered the continuation trial after some delay (median duration of time lapse between the core study and continuation trial was 43 days; range, 33–1134 days). Efficacy results of these delayed subjects are noted separately and excluded from the primary analyses in this report. The remaining 62 subjects who entered the continuation study directly (within 10 days of last dose in the core study) were considered evaluable for the current efficacy and tolerability analyses.

Treatment

Among the 62 evaluable subjects, 41 (66%) were male, and the mean age was 34.9 years (SD = 8.8). Of these, 32 had received ziprasidone (80–160 mg/day) and 30 had received chlorpromazine (100–1200 mg/day) for the 12 weeks of the core study. During the continuation trial, anticholinergic drugs were permitted to treat EPS and β-blockers were permitted for akathisia, but these were not to be prescribed prophylactically. Benzodiazepines, such as lorazepam (intramuscular or oral), could be used for agitation or insomnia. Flurazepam, up to a maximum of 30 mg/day, was permissible for insomnia. Chronic use of certain medications (hormones, antihypertensives, diuretics, H_2 blockers, and oral hypoglycemics) was permitted, if these had been taken for at least 2 months prior to study entry and the involved subject's condition was stable. No psychoactive drugs, other than those noted above, were permitted.

Outcome Assessments

Primary efficacy measures included the PANSS and the CGI-S. EPS were assessed using the Simpson-Angus Rating Scale,[14] akathisia using the Barnes Akathisia Scale,[15] and tardive dyskinesia using the Abnormal Involuntary Movement Scale (AIMS).[16] Safety assessments were based on all data collected from the first dose of ziprasidone through last observation in the continuation

study. Key safety assessments included vital signs, body weight, clinical laboratory tests, treatment-related adverse events, and ECGs. Efficacy assessments were administered at the core study baseline, end of the 12-week core study, and weeks 1, 3, 6, 9, 12, 24, and 52 (or at discontinuation) and were rated within 48 hours of the last dose of ziprasidone in the continuation study. Laboratory tests, a serum pregnancy test (in females), and 12-lead ECG evaluations were performed at the core study baseline, end of the core study, and at weeks 3, 24, and 52 (or at discontinuation).

Statistical Methods

We conducted post hoc analyses for the primary efficacy and tolerability measures, based on the 62 evaluable subjects who had completed the core phase and entered the continuation study directly. Descriptive efficacy data for the 64 nonevaluable (delayed) subjects who completed the core phase and had efficacy assessments during the continuation phase are also provided. Safety data are presented for all 129 subjects.

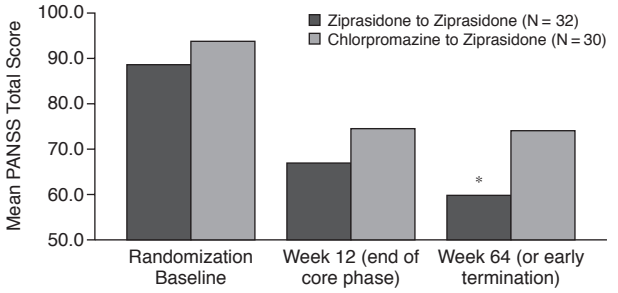
For the purpose of evaluating long-term improvement, mean changes in PANSS and CGI-S scores were derived from the initiation of study treatment in the core double-blind trial through the end of the open-label continuation phase (up to 64 weeks). For the purpose of evaluating maintenance efficacy with ziprasidone treatment, entry into the open-label continuation phase was used as the baseline reference for the analysis of the response maintenance rate. Inferential analyses were based on the comparison of PANSS and CGI-S scores (last-observation-carried-forward [LOCF] endpoint) between the 2 groups of subjects who were initially treated with ziprasidone or chlorpromazine in the 12-week core phase, after adjusting for the baseline scores using the analysis of covariance (ANCOVA) method. A paired t test with mean and 95% confidence interval (CI) was applied to evaluate the significance of within-group improvement from the specified baseline.

Subjects shown to have responded at 12 weeks and continued past week 12 were included in the response maintenance analysis. A responder at 12 weeks was defined as having shown improvement in the PANSS total score of ≥ 20% from the core study baseline. The proportion of subjects not exhibiting significant symptom exacerbation after meeting response criteria at week 12 (end of the double-blind core study) was evaluated using a χ^2 test. Significant symptom exacerbation was defined as ≥ 20% worsening in the PANSS total score and a CGI-S score ≥ 3.[17]

RESULTS

Discontinuation rates for all causes during the 1-year continuation period were comparable for the total sample (47.3%, 61/129) and evaluable subjects (46.8%, 29/62). Insufficient clinical response led to discontinuation in 10.9% of subjects, and adverse events in 7%. The median treatment duration on open-label ziprasidone treatment (continuation phase) was 52 weeks. The modal dose of ziprasidone was 160 mg/day; 82% of subjects received 160 mg/day during the continuation trial.

Figure 1. Positive and Negative Syndrome Scale (PANSS) Total Score for Evaluable Subjects (N = 62)



*p = .01 for between-group comparisons (ziprasidone-to-ziprasidone vs. chlorpromazine-to-ziprasidone) in change scores from the core study baseline through the last study visit (up to 64 weeks).

During open-label continuation therapy of ziprasidone, 30 (73%) of the 41 evaluable subjects who had responded to the initial 12-week, double-blind treatment with ziprasidone or chlorpromazine maintained symptom control (did not experience significant symptom exacerbation) at endpoint (LOCF). These included 17 of 23 (74%) from the initial ziprasidone group and 13 of 18 (72%) from the chlorpromazine group (p = .9, χ^2 test). Ziprasidone was effective in maintaining the mean improvement in PANSS total score achieved in the initial 12-week core study for subjects initially treated with ziprasidone or chlorpromazine (Figure 1).

Mean PANSS and CGI-S scores at the core study baseline, start of the continuation trial, and long-term endpoint (LOCF) are provided in Table 1. These results suggest that much of the long-term improvement from the core study baseline occurred during the initial 12-week core study, with sustained improvement observed thereafter. Of interest is that at endpoint (up to 64 weeks), mean PANSS total score (p = .01, ANCOVA) improvement from the core study baseline was greater in subjects who had started and continued on treatment with ziprasidone than in those initially treated with chlorpromazine, with a similar trend observed for CGI-S (p = .058, ANCOVA). Consistent numeric improvement (from the start of the continuation trial) was also observed in all efficacy measures among the nonevaluable subjects excluded from the present analyses.

Nine subjects did not show a 20% improvement in PANSS total score (from the mean of 85.2 at core base-

Table 1. Mean PANSS and CGI-S Scores: 12-Week Double-Blind Ziprasidone or Chlorpromazine Treatment Followed by 1-Year Open-Label Ziprasidone Continuation Period

	Evaluable Subjects (no delay in start of continuation study)									
	Ziprasidone to Ziprasidone (N = 32)			Chlorpromazine to Ziprasidone (N = 30)			Nonevaluable Subjects (excluded due to delay in enrollment in the continuation study; N = 64)			
Scale	Core Study Baseline	Week 12[a]	Week 64/ last visit	Core Study Baseline	Week 12[a]	Week 64/ last visit	Core Study Baseline	Week 12[a]	Open-Label Study Baseline[b]	Week 64/ last visit
PANSS										
Total	88.7	67.0	59.6[c]	93.9	74.7	74.3	84.2	72.3	77.3	68.6
Positive	21.6	15.4	14.7	23.5	16.4	17.8	22.3	17.9	20.6	16.8
Negative	24.1	18.6	16.2	24.9	22.4	20.9	22.0	19.5	21.0	18.7
CGI-S	4.4	3.5	3.3[c]	4.8	3.8	4.1	4.8	4.0	4.2	3.8

[a]Week 12 is the start of the continuation study (evaluable subjects) or last visit in the core study.
[b]Median duration of time lapse between week 12 (last visit in the core study) and open-label study baseline (the start of 1-year, open-label ziprasidone) was 43 days (range, 33–1134 days).
[c]p = .01 for PANSS total score and p = .058 for CGI-S between-group comparisons (ziprasidone-to-ziprasidone vs. chlorpromazine-to-ziprasidone) for change from the core study baseline through the last study visit (up to 64 weeks or early termination).
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, LOCF = last observation carried forward, PANSS = Positive and Negative Syndrome Scale.

line visit) during the 12-week core study and subsequently agreed to continue on ziprasidone in the continuation phase. These 9 subjects showed significant improvement in PANSS total score (mean change = –25.7) from week 12 (mean score = 84.8) to endpoint in the extension phase ($p < .01$, LOCF). These data suggest that a lack of formal response at 12 weeks in treatment-resistant schizophrenia may not preclude subsequent improvement.

For the 32 ziprasidone subjects continuing on ziprasidone treatment (up to 64 weeks), long-term mean change in body weight from the core study baseline to last visit was minimal (0.55-lb increase from a mean baseline weight of 125.3 lb, SD = 9.77 lb, p = .77, paired t test). Median reductions in nonfasting cholesterol and triglycerides, from the core study baseline through long-term continuation therapy (up to 64 weeks), were –3 mg/dL (p = .25) and –45.5 mg/dL (p = .0002), respectively. No worsening from the core study baseline was observed in the Simpson-Angus Rating Scale (–0.97, SD = 3.45, p = .14), AIMS (–0.39, SD = 2.30, p = .37), or Barnes Akathisia Scale (–0.17, SD = 0.54, p = .10) scores.

Among the 129 subjects participating in the 1-year continuation phase, 4 subjects discontinued due to adverse events related to the study drug; 5 discontinued due to adverse events deemed unrelated to the study drug. The ziprasidone dose for 7 subjects was decreased due to adverse events, primarily somnolence (5 subjects). The majority of adverse events were mild or moderate in severity. The most frequently reported (> 10%) treatment-related adverse events during continuation therapy were EPS (39.5%), insomnia (20.2%), tardive dyskinesia (18.6%), somnolence (14.7%), and anorexia (10.9%). The rate of observed EPS was consistent with that observed in the 12-week core study (32.2%).[10] Most EPS events were judged to be mild (71%, 36/51) or moderate (27%, 14/51) in severity. Fifty-nine patients (45.7%) received concomitant medication for movement disorders. No subject was discontinued due to EPS, and no EPS event was considered to be serious. Median QTc interval change was 3.5 msec (median baseline QTc was 402.8 msec) from time of first dose of ziprasidone through last observation (up to 64 weeks). No subject had a QTc interval ≥ 500 msec.

DISCUSSION

The current findings indicate that ziprasidone, at a modal dose of 160 mg/day, was effective in maintaining symptom control over a 1-year continuation study period in subjects with treatment-resistant schizophrenia. The response maintenance rate associated with 1-year ziprasidone continuation therapy was similar in subjects who were treated with either ziprasidone (74%) or chlorpromazine (72%) in the initial core phase. The demonstration of ziprasidone's maintenance efficacy in the subgroup of patients initially treated with chlorpromazine suggests that the results are not limited to an enriched sample composed only of ziprasidone responders, and hence may broaden the generalizability of these findings. Response maintenance rates observed in this study are consistent with those reported in previous studies using the same definition of relapse.[17,18] Tran et al.[17] reported results in similar ranges, with 87.9% of olanzapine subjects versus 67.7% of risperidone subjects not experiencing relapse in a 28-week schizophrenia study. Likewise, Simpson et al.[18] reported that 85.5% of ziprasidone-treated subjects versus 84.5% of olanzapine-treated subjects did not experience relapse during a 6-month, double-blind schizophrenia study.

The adverse event rates for EPS associated with ziprasidone in the core and continuation studies were similar and were higher than those previously reported for non-Asian subjects receiving oral ziprasidone in phase 2/3 schizophrenia trials (14% vs. 8% for placebo).[19] The higher incidence of EPS in this study is consistent with

clinical observations that Asians may be more sensitive to movement disorders associated with antipsychotic treatment.[10,20] However, objective movement disorder scales did not show significant changes.

During the 1-year, open-label study period, ziprasidone showed a neutral effect on weight and was associated with a favorable metabolic profile. Given that obesity and metabolic disturbances have significant health implications, results of this study are important in confirming the low propensity of ziprasidone to cause weight gain and dyslipidemia in the long-term treatment of schizophrenia. These metabolic results are consistent with previous ziprasidone studies in fasting[18,21,22] and nonfasting[23] subjects. Our findings suggest that ziprasidone may offer the potential for improved health outcomes in a population that has a high prevalence of obesity and related comorbidities.

Adverse effects such as weight gain, sexual dysfunction, and EPS can contribute to the high rates of noncompliance and discontinuation of medication noted during antipsychotic treatment.[24] Ziprasidone's ability to maintain treatment response with generally limited effects on weight, EPS severity, and sedation may have had a favorable impact on the treatment adherence rate. In this 1-year continuation study of ziprasidone, we observed a discontinuation rate of 47%; this compares with the 42% discontinuation rate in a much shorter 14-week study of chronic schizophrenia in patients with a history of suboptimal treatment response[6] and the 74% discontinuation rate observed in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) phase 1 trial (up to 18 months).[21]

There is increasing evidence that ziprasidone is associated with a dose-response trend that may be most evident in acutely ill patients[25] as well as in patients who have partially or not responded to a lower dose.[26] The ziprasidone modal dose of 160 mg/day in this study (82% of patients received this dose during the continuation period) may have contributed to the favorable overall outcomes observed in the study.

The current study is subject to certain limitations inherent to all open-label, uncontrolled designs. The lack of a randomized, control group may have introduced bias in the estimation of treatment effects. However, the naturalistic design of this continuation study facilitated evaluation of the long-term effectiveness of ziprasidone in a setting approximating real-world clinical practice. The sample size in the continuation phase is relatively small, representing a subgroup of all eligible patients from the core study. Subjects with a delay ≥ 10 days in continuation study enrollment were excluded from the primary efficacy analyses. Nevertheless, robust and consistent results are demonstrated in analyses both with and without the delayed subjects. While results of this study should be viewed as preliminary, they are consistent with the efficacy and tolerability of ziprasidone reported previously in short- and long-term randomized, controlled trials on other schizophrenia populations.[18,22,27,28]

In summary, these results suggest that ziprasidone is effective for the long-term maintenance therapy of patients with treatment-resistant schizophrenia. Over 1 year of continuous treatment, ziprasidone was well tolerated, with a relatively low rate of discontinuation, and was associated with favorable effects on weight and metabolic parameters. Further investigation of ziprasidone therapy in treatment-resistant schizophrenia is warranted to confirm the preliminary findings reported here.

Drug names: chlorpromazine (Thorazine, Sonazine, and others), clozapine (FazaClo, Clozaril, and others), flurazepam (Dalmane and others), lorazepam (Ativan and others), olanzapine (Zyprexa), risperidone (Risperdal), ziprasidone (Geodon).

Financial disclosure: Drs. Loebel, Rajadhyaksha, and Giller are employees of Pfizer, and Dr. Giller is a major stock shareholder in Pfizer. Dr. Siu is a consultant for Pfizer and Organon. Dr. Potkin has received grants/funding from AstraZeneca, Bristol-Myers Squibb, Dainippon-Sumitomo, Forest, Fujisawa, Janssen, Merck, Novartis, Ono, Organon, Otsuka, Pfizer, Solvay, Roche, National Institutes of Health, Harvard Massachusetts General Hospital, Brigham and Women's Hospital, and Wyeth; is a consultant for, is a member of the advisory board for, or has received honoraria from the American Psychiatric Association, AstraZeneca, Bristol-Myers Squibb, Janssen, Novartis, Organon, Otsuka, Pfizer, and Praecis; and is a member of the speakers bureaus of AstraZeneca, Bristol-Myers Squibb, the International Society for CNS Clinical Trials and Methodology (ISCTM), Novartis, and Pfizer. Dr. Khanna reports no additional financial or other relationship relevant to the subject of this article.

REFERENCES

1. Conley RR, Kelly DL. Management of treatment resistance in schizophrenia. Biol Psychiatry 2001;50:898–911
2. Kane J, Honigfeld G, Singer J, et al. Clozaril Collaborative Study Group. Clozapine for the treatment-resistant schizophrenic: a double-blind comparison with chlorpromazine. Arch Gen Psychiatry 1988;45:789–796
3. Lieberman JA, Safferman AZ, Pollack S, et al. Clinical effects of clozapine in chronic schizophrenia: response to treatment and predictors of outcome. Am J Psychiatry 1994;151:1744–1752
4. Alvir JM, Lieberman JA, Safferman AZ, et al. Clozapine-induced agranulocytosis. N Engl J Med 1993;329:162–167
5. Lieberman JA, Johns CA, Kane JM, et al. Clozapine-induced agranulocytosis: non–cross-reactivity with other psychotropic drugs. J Clin Psychiatry 1988;49:271–277
6. Volavka J, Czobor P, Sheitman B, et al. Clozapine, olanzapine, risperidone, and haloperidol in the treatment of patients with chronic schizophrenia and schizoaffective disorder. Am J Psychiatry 2002;159:255–262
7. Chakos M, Lieberman J, Hoffman J, et al. Effectiveness of second-generation antipsychotics in patients with treatment-resistant schizophrenia: a review and meta-analysis of randomized trials. Am J Psychiatry 2001;158:518–526
8. Conley RR, Tamminga CA, Bartko JJ, et al. Olanzapine compared with chlorpromazine in treatment-resistant schizophrenia. Am J Psychiatry 1998;155:914–920
9. Breier A, Hamilton S. Comparative efficacy of olanzapine and haloperidol for patients with treatment-resistant schizophrenia. Biol Psychiatry 1999;45:403–411
10. Kane JM, Khanna S, Rajadhyaksha S, et al. Efficacy and tolerability of ziprasidone in patients with treatment-resistant schizophrenia. Int Clin Psychopharmacol 2006;21:21–28
11. Overall JE, Gorham DR. The Brief Psychiatric Rating Scale. Psychol Rep 1962;10:799–812
12. Kay SR, Opler LA, Fiszbein A. The Positive and Negative Syndrome Scale (PANSS) Manual. North Tonawanda, NY:

Multi-Health System; 1986
13. Guy W. ECDEU Assessment Manual for Psychopharmacology. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976:218–222
14. Simpson GM, Angus JWS. A rating scale for extrapyramidal side effects. Acta Psychiatr Scand 1970;45(suppl 212):11–19
15. Barnes TRE. A rating scale for drug-induced akathisia. Br J Psychiatry 1989;154:672–676
16. Psychopharmacology Research Branch, National Institute of Mental Health. Abnormal Involuntary Movement Scale (AIMS). In: Guy W, ed. ECDEU Assessment Manual for Psychopharmacology, Revised. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976:534–537
17. Tran PV, Hamilton SH, Kuntz AJ, et al. Double-blind comparison of olanzapine versus risperidone in the treatment of schizophrenia and other psychotic disorders. J Clin Psychopharmacol 1997;17:407–418
18. Simpson GM, Weiden P, Pigott T, et al. Six-month, blinded, multicenter continuation study of ziprasidone versus olanzapine in schizophrenia. Am J Psychiatry 2005;162:1535–1538
19. Geodon [package insert]. New York, NY: Pfizer; 2006
20. Dhavale HS, Pinto C, Dass J, et al. Prophylaxis of antipsychotic-induced extrapyramidal side effects in east Indians: cultural practice or biological necessity? J Psychiatr Pract 2004;10:200–202
21. Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Eng J Med 2005;353:1209–1223
22. Simpson GM, Glick ID, Weiden PJ, et al. Randomized, controlled, double-blind multicenter comparison of the efficacy and tolerability of ziprasidone versus olanzapine in acutely ill inpatients with schizophrenia or schizoaffective disorder. Am J Psychiatry 2004;161:1837–1847
23. 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
24. Meltzer HY. Putting metabolic side effects into perspective: risks versus benefits of atypical antipsychotics. J Clin Psychiatry 2001;62(suppl 27): 35–39
25. Nemeroff CB, Lieberman JA, Weiden PJ, et al. From clinical research to clinical practice: a 4-year review of ziprasidone. CNS Spectr 2005;10: S1–S20
26. Deutschman DA, Deutschman DH. High-dose ziprasidone: efficacy and tolerability in clinical practice. Presented at the 157th annual meeting of the American Psychiatric Association; May 1–6, 2004; New York, NY
27. Arato M, O'Connor R, Meltzer H. The Ziprasidone Extended Use in Schizophrenia (ZEUS) study: a double-blind, placebo-controlled, 1-year clinical trial. Int Clin Psychopharmacol 2002;17:207–215
28. Hirsch S, Kissling W, Bauml J, et al. A 28-week comparison of ziprasidone and haloperidol in outpatients with stable schizophrenia. J Clin Psychiatry 2002;63:516–523

