Effectiveness and Tolerability of Oral Ziprasidone in Psychiatric Inpatients With an Acute Exacerbation of Schizophrenia or Schizoaffective Disorder: A Multicenter, Prospective, and Naturalistic Study

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Objective: This prospective, uncontrolled, and naturalistic study aimed to evaluate the effectiveness and tolerability of oral ziprasidone in psychiatric inpatients with an acute exacerbation of schizophrenia or schizoaffective disorder treated in the clinical practice setting.

Method: Patients had to be at least 18 years old and meet DSM-IV-TR criteria for acute exacerbation of schizophrenia or schizoaffective disorder. Patients were followed until discharge and were evaluated with the Brief Psychiatric Rating Scale (BPRS), Clinical Global Impressions (CGI) scale, Drug Attitude Inventory, and the Scale to Assess Unawareness of Mental Disorder. Ziprasidone dose requirements, dose escalation, discontinuation of treatment, and the use of any concomitant medication including cotreatment with other antipsychotics were established individually according to the clinical judgment of each investigator. The study was conducted from February 2005 to June 2007.

Results: We included a total of 196 patients (intent-to-treat population), 9 (5%) of whom discontinued treatment with ziprasidone (3 because of side effects). The mean (SD) length of stay was 23.4 (34.2) days. The mean (SD) dose at discharge was 186.3 (67.6) mg/day, and the median dose was 160 mg/day (interquartile range, 120–240 mg/day). Response rates at the endpoint, according to BPRS and CGI criteria, were 74% (95% CI = 68% to 80%) and 67% (95% CI = 61% to 74%), respectively. Progressive and statistically significant improvements in all BPRS scores and CGI-Severity of Illness scores were observed from the first week through discharge. All changes from baseline to the study endpoint for BPRS and CGI scores were clinically relevant, with effect sizes greater than 0.80. The insight into illness and the attitude toward medication also improved significantly over the course of the study. Ziprasidone was well tolerated.

Conclusion: Although our results should be interpreted with caution because of the uncontrolled design of our study, they suggest that, in acutely ill inpatients with schizophrenia or schizoaffective disorder, the use of ziprasidone under routine clinical conditions is associated with a rapid and progressive improvement in psychopathologic symptoms and a clinically relevant improvement in insight into their illness.

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Second-generation antipsychotics are considered a first-line treatment in the acute management of initial episodes and exacerbations of schizophrenia in hospitalized patients.[1–3] Ziprasidone is a novel second-generation antipsychotic that has been licensed in the United States for the treatment of schizophrenia and bipolar mania.[4] Intramuscular ziprasidone (20 mg) has been shown to be effective in the treatment of acute agitation in patients with schizophrenia.[5] In short-term clinical trials in patients with schizophrenia or schizoaffective disorders, oral ziprasidone demonstrated superior antipsychotic efficacy to placebo[6,7] and comparable antipsychotic efficacy to haloperidol.[8] Furthermore, oral ziprasidone has shown some limited clinical advantages over first-generation antipsychotics in improving negative symptoms.[4] However, a meta-analysis has shown that, in contrast to risperidone and olanzapine, the remaining second-generation antipsychotics, including ziprasidone, are not significantly different from first-generation antipsychotics in improving overall psychotic symptoms.[9]

Ziprasidone has been compared with other second-generation antipsychotics in several randomized trials in patients with schizophrenia,[10–14] including a large pragmatic trial.[15,16] Compared with olanzapine, ziprasidone has been shown to be equally effective in a short-term trial.[11] However, long-term trials demonstrated superior efficacy of olanzapine over ziprasidone as evaluated by

treatment retention variables.[13,14,16] In short-term randomized clinical trials, ziprasidone has proved as effective as risperidone[10] and aripiprazole.[12] The most frequent adverse effects in short-term studies with ziprasidone were somnolence, gastrointestinal effects, akathisia, dizziness, and respiratory disorders.[17] In addition to its very low liability to induce movement disorders and hyperprolactinemia,[18] ziprasidone appears to have a minimal effect on plasma lipids and glucose levels, and minor impact on weight.[15,19,20] This effectiveness and tolerability profile has also been shown in outpatients with schizophrenia who are treated with ziprasidone in routine clinical practice.[21,22]

Published data on the use of ziprasidone in hospitalized patients, however, are limited to a 6-week randomized clinical trial comparing flexible doses of ziprasidone and olanzapine in acutely ill inpatients with schizophrenia or schizoaffective disorders, in which both drugs demonstrated comparable antipsychotic efficacy.[11] In addition, 2 short-term randomized clinical trials have compared ziprasidone with placebo[7] or aripiprazole[12] in acutely ill patients with schizophrenia or schizoaffective disorders who had to be hospitalized for at least 2 weeks after randomization. In these latter trials, ziprasidone was more effective than placebo and similar to aripiprazole in improving psychotic symptoms, both at the study endpoint and at week 2.[7,12]

Although there are randomized clinical trials in hospitalized patients with acute exacerbations of schizophrenia with all second-generation antipsychotics, including ziprasidone,[7,11,12] they are difficult to generalize to daily clinical practice. From an efficacy point of view, the need to recruit a homogeneous sample implies the use of very restrictive selection criteria,[23] which generally exclude patients with concomitant disorders (e.g., patients with substance abuse or with severe medical conditions) or difficult-to-treat patients, such as those refractory to previous treatments or at risk of suicide.[24,25] These exclusions have also been imposed in trials of ziprasidone in acutely ill patients.[7,10,18] As such, the subjects entering clinical trials are not particularly representative of patients in short-term units who do not enter the studies.[26] From a tolerability point of view, antipsychotic polypharmacy and excessive dosing are frequently observed in psychiatric practice[27–30] and may compromise the tolerability of antipsychotics. For these reasons, once the efficacy and safety of a specific treatment has been established in randomized clinical trials and the treatment has been introduced in clinical practice, epidemiologic studies help to answer unresolved questions, completing the information gained from the clinical trials.[31,32]

The objective of the present study was to evaluate the effectiveness and tolerability of oral ziprasidone in psychiatric inpatients with an acute exacerbation of schizophrenia or schizoaffective disorder treated in the clinical practice setting.

METHOD

Patients

For inclusion in the study, patients had to be at least 18 years old and meet DSM-IV-TR criteria for acute exacerbation of schizophrenia or schizoaffective disorder. Patients were excluded if they were hospitalized for a cause other than an acute exacerbation, had any serious medical condition, were pregnant or lactating women, or were women of reproductive age not using adequate contraception.

Design

This prospective, uncontrolled, and observational study in inpatients was carried out at 16 short-term inpatient units in Spain from February 2005 to June 2007.

All patients who met the selection criteria were included in the study. They received nonblinded treatment with oral ziprasidone and were followed up during their hospitalization until discharge or withdrawal. Dose requirements, dose escalation, discontinuation of treatment, and the use of any concomitant medication were established individually according to the clinical judgment of each investigator.

The study was approved by the Ethics Committee of the Hospital Clínico Universitario of Madrid (Spain). The study was carried out in accordance with the principles contained in the Declaration of Helsinki. All patients gave informed consent before taking part in this study.

Assessments

Patients were evaluated at baseline, at weeks 1 and 2, and at discharge. Psychopathology was evaluated at each study visit with the Brief Psychiatric Rating Scale (BPRS) and the Clinical Global Impressions-Severity of Illness (CGI-S) scale. In addition, the CGI-Improvement (CGI-I) scale was administered at the 3 follow-up visits. The BPRS, which consists of 18 items separately rated on a 7-point scale of severity (1 = not present to 7 = extremely severe), measures major psychotic and nonpsychotic symptoms.[33] Its focus is primarily inpatient psychopathology; it provides a rapid and efficient evaluation of treatment response in both clinical trials and routine clinical practice.[34] In patients with schizophrenia, a factor structure has been described that consists of 5 factors: anxiety/depression, anergia, thought disturbance, activation, and hostile/suspiciousness.[34] The CGI scale is a clinician-rated instrument consisting of 3 subscales assessing overall severity of illness, clinical outcome (improvement), and therapeutic effect[35]; of these, only the first 2 subscales were used in this study.

The subjective response to medication and insight were evaluated with the Drug Attitude Inventory (DAI-30) and the Scale to Assess Unawareness of Mental Disorder (SUMD), respectively. The DAI-30 is a 30-item

self-report instrument assessing the subjective response to medication in patients with schizophrenia,[36] focusing on the negative and unpleasant aspects associated with the side effects of antipsychotics. The Spanish version of the DAI-30 was used, which has similar psychometric properties to the original version[37] but, unlike the original version and similar to the French version, distinguishes 2 main factors, the overall subjective attitude toward taking the medication (Factor I) and the specific attitude (especially toward side effects) and decision to take the medication (Factor II). The SUMD (abbreviated version) is a 9-item scale that assesses awareness of illness among psychiatric patients, particularly those who have psychosis.[38] The SUMD has 2 main components: awareness of illness and attribution of current illness. The DAI-30 and the SUMD were administered at baseline, at week 2, and at discharge. No training session on the scales used in this study was run prior to initiating the study.

Adverse events were evaluated through an open-ended question and recorded on all follow-up visits, regardless of whether they were considered to be related to the medication.

Statistical Analysis

Demographic and baseline clinical characteristics were described using the mean and standard deviation for continuous measures (e.g., age, BPRS score) and the frequency and percentage for categorical variables (e.g., sex, concomitant medications).

The primary effectiveness variable was the response rate, defined as a 30% reduction in the BPRS total score, which is the usual way to define clinical responsiveness or improvement in clinical trials in schizophrenia.[39] Other effectiveness variables were the BPRS factor scores, the CGI-S total score, and the CGI-I response rate, defined as the percentage of patients who had a score of 1 or 2 on the CGI-I. In addition, changes in the BPRS and CGI scores were analyzed. The significance of changes versus baseline in scores on the different scales and subscales at the different study times was calculated using Student t test. In order to also assess the clinical significance of the changes in the different measures, the effect size was obtained by calculating the difference between the mean values of a specific measure before and after treatment, and then dividing that difference by the standard deviation of that measure before treatment.[40] The effect size was interpreted according to the criterion established by Cohen, which considered an effect size of 0.20 as small, 0.50 as moderate, and 0.80 as large.[40]

All of these efficacy analyses were carried out in the intent-to-treat population, defined as all patients included who received at least 1 dose of ziprasidone and had at least 1 postbaseline assessment for any of the efficacy variables. In these effectiveness analyses, missing data were imputed using the last observation carried forward. Analyses of the DAI-30 score and its 2 factors, as well as the SUMD scores, were done in the same way as described for the effectiveness scales. All patients included in the study were also included in the analyses of tolerability. A stepwise logistic regression analysis was performed to explore the potential relationship between some patients' characteristics and confounders, and the primary outcome (i.e., the BPRS response rate). The following independent variables were included: age, sex, illness duration, BPRS total score at baseline, presence of comorbid substance use disorder, cotreatment with other antipsychotics, length of stay, and mean final dose of ziprasidone

All statistical analyses were performed using SAS, version 8.2 (SAS Institute, Inc., Cary, N.C.). All analyses were 2-tailed and considered significant if $p < .05$.

RESULTS

Study Participants

A total of 196 patients were included, of whom 180 patients (92%) completed the follow-up. These 196 patients constituted the intent-to-treat and safety population. Nine patients (5%) discontinued treatment with ziprasidone: 5 due to lack of efficacy, 3 because of side effects, and 1 due to other reasons.

Baseline patient and illness characteristics are presented in Table 1. The mean patient age was 38 years, with men comprising 60% of the population and with a majority of patients diagnosed with schizophrenia of the paranoid subtype (54%) or schizoaffective disorder (26%). The mean baseline BPRS total score and CGI-S score indicate that patients had moderate to severe symptomatology. Patients showed a negative subjective response to medication and had poor insight, as measured with the DAI-30 and SUMD, respectively. The most frequent causes for admission were relapse following noncompliance with medication (n = 90, 46%) and breakthrough of symptoms because of poor response to their antipsychotic treatment (n = 84, 43%).

Ziprasidone Treatment, Concomitant Medications, and Length of Stay

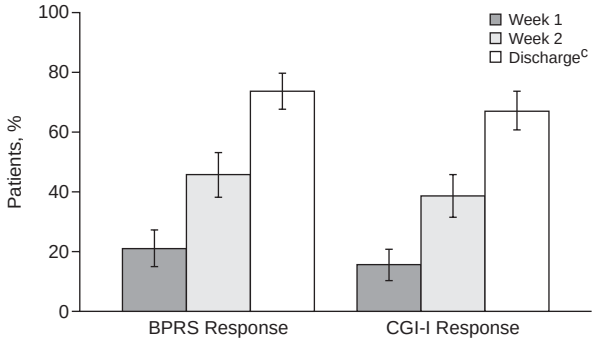
The mean (SD) initial dose of ziprasidone was 136.9 (54.7) mg/day. The initial doses of ziprasidone most frequently prescribed were 160 mg/day (34%) and 120 mg/day (25%). Overall, 72% of patients were prescribed an initial dose equal to or greater than 120 mg/day. The mean (SD) doses at week 1 and 2 were 166.0 (54.0) mg/day and 184.5 (58.2), respectively. The mean (SD) dose at discharge was 186.3 (67.6) mg/day, and the median dose was 160 mg/day (interquartile range, 120–240 mg/day). At discharge, three quarters of the patients were receiving a dose of at least 160 mg/day (45% of the patients were receiving a dose above 160 mg/day). The mean (SD) length of stay was 23.4 (34.2) days.

Table 1. Baseline Demographic and Clinical Characteristics of Inpatients With an Acute Exacerbation of Schizophrenia or Schizoaffective Disorder (N = 196)

Characteristic/Variable	N[a]	Value
Age, mean (SD), y	195	38.4 (12.2)
Sex, n (%)	193	
Men		116 (60.1)
Women		77 (39.9)
Diagnosis, n (%)	195	
Schizophrenia		130 (66.7)
Paranoid		105 (53.8)
Disorganized		4 (2.1)
Undifferentiated		7 (3.6)
Residual		14 (7.2)
Schizophreniform disorder		14 (7.2)
Schizoaffective disorder		51 (26.2)
Age at onset of first psychotic episode, mean (SD), y	151	25.0 (8.9)
Previous antipsychotic treatment, n (%)	196	
Total		105 (53.6)
Risperidone		32 (16.3)
Olanzapine		24 (12.2)
Other[b]		49 (25.0)
Psychopathology scale scores, mean (SD)		
BPRS total	191	58.3 (12.6)
BPRS-positive	184	16.9 (4.0)
BPRS-negative	185	11.8 (4.4)
CGI-S	192	5.3 (0.8)
DAI-30	107	–1.5 (14.1)
SUMD-awareness of illness	183	10.8 (3.6)
SUMD-attribution of current illness	183	3.8 (1.2)

[a]Number of patients that could be evaluated.
[b]None of the antipsychotics included in this category reached a frequency of 10% of the patients.
Abbreviations: BPRS = Brief Psychiatric Rating Scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, DAI-30 = 30-item Drug Attitude Inventory, SUMD = Scale to Assess Unawareness of Mental Disorder.

Figure 1. Percentage of Responders According to the BPRS and CGI-I[a,b]



[a]BPRS response defined as those patients with a reduction in total BPRS score equal to or greater than 30%; CGI-I response defined as those patients having a score of 1 (very much improved) or 2 (much improved) on the CGI-I.
[b]The vertical bars represent the 95% confidence interval.
[c]The mean (SD) time to discharge was 23.4 (34.2) days, with a median of 20 (IQR, 14 to 23) days.
Abbreviations: BPRS = Brief Psychiatric Rating Scale, CGI-I = Clinical Global Impressions-Improvement scale, IQR = interquartile range.

Fifty-four patients (28%) received concomitantly another antipsychotic, the most commonly coprescribed antipsychotics being risperidone (n = 22, 11%), haloperidol (n = 11, 6%), and quetiapine (n = 9, 5%). Other psychotropics concomitantly prescribed with ziprasidone were clonazepam (n = 75, 38%), lorazepam (n = 32, 16%), lormetazepam (n = 19, 10%), venlafaxine (n = 15, 8%), and biperiden (n = 10, 5%).

Effectiveness Outcomes

Overall, 74% (95% CI = 68% to 80%) of patients according to the BPRS response criterion, and 67% (95% CI = 61% to 74%) according to the CGI-I criterion, were responders (Figure 1). In the stepwise logistic regression analysis, the only factors that influenced treatment response were the ziprasidone dose and cotreatment with another antipsychotic. Doses of ziprasidone greater than 120 mg/day but below 240 mg/day were associated with a greater likelihood of response compared with doses up to 120 mg/day (odds ratio [OR] = 3.7, 95% CI = 1.5 to 8.8), and doses of 240 mg/day or above were also associated, although less strongly, with greater likelihood of response (OR = 2.8, 95% CI = 1.2 to 6.2). In contrast, cotreatment with other antipsychotics was associated with a lower likelihood of response compared with ziprasidone monotherapy (OR = 0.4, 95% CI = 0.2 to 0.8). Progressive and statistically significant improvements in the BPRS total score, BPRS positive and negative symptoms cluster scores, and BPRS factor scores were observed from the first week through discharge (Table 2, Figure 2). All of these changes in the BPRS measures at discharge were clinically significant, as demonstrated by the large effect sizes (Figure 3). However, by week 1, moderate effect sizes, also indicating a clinically relevant improvement, were only observed in the BPRS total, BPRS positive symptoms cluster score, and the scores of Factors III–V (Figure 3). Changes observed in the negative symptoms, anxiety/depression (Factor I), and anergia (Factor II) at week 1 were small (Figure 3). By the time of discharge, the mean CGI-S score had been reduced 1.7 points from baseline ($p < .0001$, effect size: 1.87).

Patients showed a significant and, except for Factor II, clinically relevant improvement in attitude toward medication over the course of the study, as shown by the significant increase in the DAI-30 total score and its 2 factors (Table 2), with an effect size at discharge for these scores of 0.79, 0.72, and 0.57, respectively. The insight into illness also improved significantly, both at week 2 and at discharge (Table 2). The effect sizes at discharge were 0.74 and 0.99 for the global awareness of illness and current attribution of symptoms, respectively.

Adverse Events

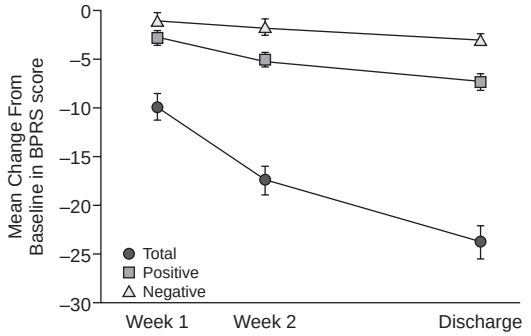
Treatment-emergent adverse events were experienced by 86 patients (44%). Reported adverse events were

Table 2. Secondary Efficacy Assessments (mean ± SD)

Assessment	Baseline	Week 1	Week 2	Discharge
BPRS[a]				
Total	58.3 ± 12.6	48.6 ± 14.8*	41.1 ± 13.0*	34.4 ± 11.7*
Positive	16.9 ± 4.0	14.1 ± 4.5*	11.6 ± 4.0*	9.5 ± 3.7*
Negative	9.8 ± 4.0	8.6 ± 3.6*	7.7 ± 3.5*	6.8 ± 3.1*
Factor I (anxiety/depression)	12.9 ± 4.5	11.1 ± 4.0*	9.5 ± 3.5*	8.1 ± 3.0*
Factor II (anergia)	11.8 ± 4.4	10.3 ± 4.0*	9.2 ± 3.9*	8.1 ± 3.4*
Factor III (thought disturbance)	15.2 ± 4.0	13.0 ± 4.3*	10.8 ± 3.8*	8.8 ± 3.4*
Factor IV (activation)	8.6 ± 2.9	6.9 ± 2.9*	5.8 ± 2.3*	4.8 ± 1.7*
Factor V (hostile/suspiciousness)	10.8 ± 3.8	8.7 ± 3.7*	7.1 ± 2.9*	5.8 ± 2.8*
CGI-S	5.3 ± 0.78	4.7 ± 1.0*	4.2 ± 1.0*	3.6 ± 1.0*
DAI-30				
Total score	–1.5 ± 14.4	NA	4.9 ± 14.2*	9.1 ± 12.6*
Factor I	1.3 ± 9.1	NA	5.3 ± 8.7*	7.3 ± 7.4*
Factor II	–1.3 ± 3.5	NA	–0.3 ± 3.7**	0.7 ± 3.5*
SUMD				
Awareness of illness	10.8 ± 3.6	NA	9.3 ± 3.2*	8.5 ± 2.5*
Attribution of current illness	3.8 ± 1.2	NA	3.0 ± 1.3*	2.6 ± 1.2*

[a]The item composition of the BPRS clusters and factors is as follows. Positive cluster: conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content; Negative cluster: emotional withdrawal, motor retardation, and blunted affect; Factor I (anxiety/depression): somatic concern, anxiety, guilt feelings, and depressive mood; Factor II (anergia): emotional withdrawal, motor retardation, blunted affect, and disorientation; Factor III (thought disturbance): conceptual disorganization, grandiosity, hallucinatory behavior, and unusual thought content; Factor IV (activation): tension, mannerism, and excitement; and Factor V (hostile/suspiciousness): hostility, suspiciousness, and uncooperativeness.
*p < .0001 vs. baseline, Student t test.
**p < .001 vs. baseline, Student t test.
Abbreviations: BPRS = Brief Psychiatric Rating Scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, DAI-30 = 30-item Drug Attitude Inventory, NA = not applicable, SUMD = Scale to Assess Unawareness of Mental Disorder.

Figure 2. Mean Changes in the Brief Psychiatric Rating Scale (BPRS) Total Score and Positive and Negative Symptom Cluster Scores[a]



[a]The vertical bars represent the 95% confidence interval.

sedation (n = 32, 16.3%), somnolence (n = 14, 7.1%), restlessness (n = 12, 6.1%), akathisia (n = 8, 4.1%), insomnia (n = 6, 3.1%), anxiety (n = 5, 2.6%), tremor (n = 5, 2.6%), increased salivation (n = 5, 2.6%), parkinsonism (n = 2, 1.0%), psychomotor retardation (n = 2, 1.0%), constipation (n = 1, 0.5%), and dry mouth (n = 1, 0.5%). None of these events were considered serious by the investigators.

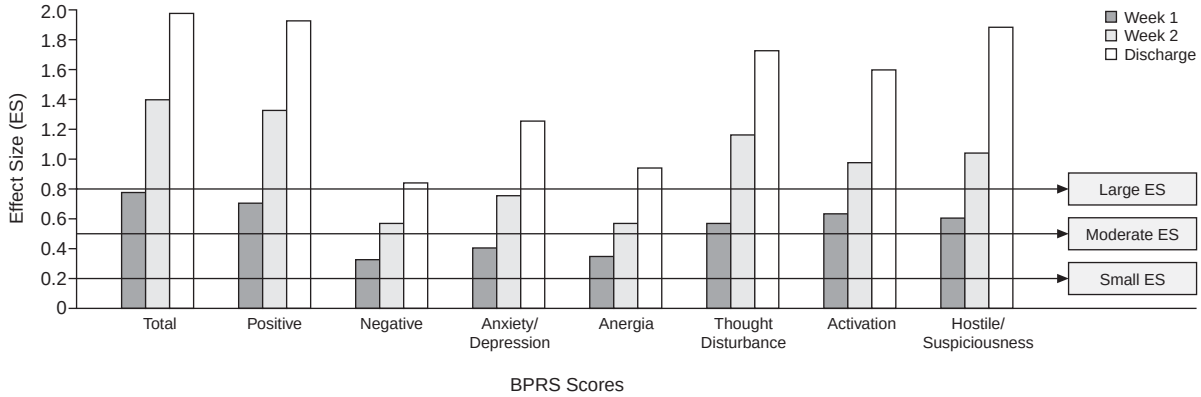
In 19 of 28 patients (68%) who reported sedation at week 1 or 2 of the study, the adverse event disappeared at discharge. In 9 of 13 (69%) reporting somnolence, the adverse event disappeared, and in 2 (15%), there was a reduction in the severity of the adverse event at discharge. Finally, in 16 of 17 patients (94%) reporting restlessness/akathisia, the adverse event disappeared, and in 1 (6%) there was a reduction in the severity at discharge.

DISCUSSION

To our knowledge, this is the first observational prospective study that assesses, in the clinical practice setting, the effectiveness and tolerability of ziprasidone in the treatment of psychiatric inpatients with acute exacerbation of schizophrenia or schizoaffective disorder. Overall, our study suggests that ziprasidone is effective and well tolerated for the treatment of this population, improving a wide range of psychopathologic symptoms, as well as the attitude toward the medication and the insight into the illness.

Although our results should be interpreted with caution, it is noteworthy that our efficacy results with ziprasidone appear to be better than those previously reported in clinical trials with this drug in hospitalized patients.[7,11,12] In a 6-week, double-blind comparison with olanzapine, ziprasidone (mean daily dose: 130 mg) produced an 11-point reduction in the BPRS total score at week 4,[11] while the BPRS total score reduction observed in our study at discharge (approximately 23 days after admission) was over 23 points. Similarly, BPRS total score reduction (derived score from the Positive and Negative Syndrome Scale [PANSS]) in 2 double-blind studies at

Figure 3. Magnitude of Treatment Effect on Psychopathology Symptoms as Measured With the Brief Psychiatric Rating Scale (BPRS)[a]



[a]The item composition of the BPRS clusters and factors is as follows. Positive cluster: conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content; Negative cluster: emotional withdrawal, motor retardation, and blunted affect; Factor I (anxiety/depression): somatic concern, anxiety, guilt feelings and depressive mood; Factor II (anergia): emotional withdrawal, motor retardation, blunted affect and disorientation; Factor III (thought disturbance): conceptual disorganization, grandiosity, hallucinatory behavior, and unusual thought content; Factor IV (activation): tension, mannerism, and excitement; and Factor V (hostile/suspiciousness): hostility, suspiciousness, and uncooperativeness.

week 2 (i.e., the last week of mandatory hospitalization in these 2 studies) was 8 points with the higher dose of ziprasidone (160 mg/day) in a placebo-controlled study[7] and 10 points in a 4-week comparison of ziprasidone (mean modal dose: 149 mg/day) with aripiprazole.[12] In our study, the mean reduction from baseline in the BPRS total score at week 2 was 17 points. The proportion of CGI responders at the endpoint with ziprasidone was 49% in the 6-week comparison with olanzapine[11] and 42.7% with the higher dose in the 6-week placebo-controlled study[7]; in this latter study, patients could be discharged after week 2. Similar results are observed in the CGI-S, with reductions at the endpoint of approximately 1.2 points in the olanzapine comparison, in which study patients were required to be hospitalized for the whole study duration,[11] and 0.8 and 1.1 in the 6-week placebo-controlled[7] and 4-week aripiprazole comparison,[12] respectively. In our study, the reduction in the CGI-S score at discharge was 1.7 points, with an effect size for this change (1.87) that almost doubles that of ziprasidone at the endpoint (1.0) in the 4-week comparison with aripiprazole.[12]

Certainly, an uncontrolled and unmasked design, such as that of our study, overestimates treatment effects. In addition, since our study is much closer to actual clinical practice than randomized clinical trials, it is also more likely that confounding factors (including unknown factors) have affected our results.[32] However, we think that these limitations do not entirely explain the large and consistent differences between our results and those coming from randomized clinical trials with ziprasidone. Our patients had more severe illness than patients included in randomized clinical trials of ziprasidone in hospitalized patients, with a CGI-S score of 5.3 in our study compared to 4.8–4.9 in the ziprasidone trials.[7,11,12]

In addition, due to the selection criteria, it is also unlikely that our sample was less treatment refractory than that included in the ziprasidone trials. Although few observational and prospective studies evaluate the effectiveness of antipsychotics in inpatients with schizophrenia,[41–43] interestingly, all of them show results similar to ours. In 36 patients newly admitted to a state hospital in the United States with a diagnosis of schizophrenia or schizoaffective disorder and treated with atypical antipsychotics (56%), conventional antipsychotics (31%), or both (13%), Sajatovic et al.[41] observed that the BPRS total score dropped from 45.8 to 31.1 points (32% reduction) at discharge (mean length of stay: 12.7 days), which is equivalent to the drop observed in our study at a similar time point, that is, from 58.3 at admission to 41.1 at week 2 (29% reduction). In a prospective, nonrandomized, naturalistic comparison of olanzapine with conventional antipsychotics run in Spain in 904 inpatients with schizophrenia,[42] mean reductions in the BPRS total score and CGI-S score in both treatment groups (approximately 26 and 1.7 points, respectively) almost overlap those of our study; the length of stay in the former study was 22 days as compared to 23 days in our study. In another prospective, nonrandomized, naturalistic study, also run in Spain, which compared quetiapine (n = 323) with risperidone (n = 112) in inpatients with schizophrenia,[43] the mean reductions in the BPRS total scores were also 25 and 24 points, respectively.

With the exception of the study reported by Sajatovic et al.,[41] which does not provide the dose of the antipsychotics, the other 3 naturalistic studies report doses of antipsychotics that are above those reported in clinical trials. In the mentioned naturalistic studies, the mean final doses for olanzapine and haloperidol were 18 and

15 mg/day, respectively[42]; the mean final doses for quetiapine and risperidone were 710 and 8 mg/day, respectively[43]; and the mean final dose for ziprasidone in our study was 186 mg/day. Overall, we think that our results, indicating that high doses of ziprasidone are used in clinical practice and are possibly associated with better treatment outcome, are consistent with previous experience with ziprasidone and other atypical antipsychotics. Thus, in outpatients with schizophrenia treated in the clinical practice setting, lower doses of ziprasidone[21,44–46] or quetiapine[47] were associated with a higher risk of treatment discontinuation. These differences between dosage recommendations derived from clinical trials and those used in clinical practice have been noted by other authors.[48,49] In fact, with the exception of risperidone, experts' recommendations regarding the adequate dose of antipsychotics for the acute treatment of psychotic disorders[50] are closer to those reported in observational studies, such as those discussed above, than to those used in clinical trials. The results of our exploratory regression analysis support that ziprasidone dose was a key factor in our results. Although it is only speculative, the association between coadministration of other antipsychotics with ziprasidone and a lower likelihood of response might be due to the prescription of these combinations to treatment-resistant patients.

An important issue when selecting an antipsychotic for the treatment of acutely ill inpatients with schizophrenia is the speed of response.[2] In a randomized clinical trial of 269 acutely ill inpatients with schizophrenia, ziprasidone (mean dose: 130 mg/day) at week 1 demonstrated a significantly greater improvement than olanzapine in the reduction of the BPRS total score; however, it should be noted that the mean final dose of olanzapine in this trial (11 mg/day) was quite low.[11] Ziprasidone (modal dose: 149 mg/day) was also faster than aripiprazole (modal dose: 21 mg/day) in a randomized clinical trial involving 256 inpatients with schizophrenia.[12] In this study, after 4 days of treatment, PANSS total scores were reduced by 11.5 points with ziprasidone and by 9.6 points with aripiprazole ($p < .05$).[12] Our results seem to confirm ziprasidone's rapid onset of action. A clinically relevant improvement was observed at week 1 in the overall symptomatology (i.e., BPRS total score), as well as specific domains such as the positive symptoms cluster and the thought disturbance, activation, and hostility factors of the BPRS. The slower and, overall, lesser response of the negative symptoms to ziprasidone observed in our study is explained by the fact that negative symptoms are considered more persistent and associated with a poorer treatment outcome.[51] However, according to a recently reported double-blind and randomized clinical trial, long-term treatment with ziprasidone seems to be associated with greater improvement than haloperidol in negative symptoms.[52]

Insight into illness is another important issue in the management of these patients. Lack of insight is associated with poorer attitude toward medication[53] and lower treatment adherence.[54] Although a causal relationship with treatment adherence has not been clearly established, insight also seems to correlate with better long-term functioning.[54] Our results also show that ziprasidone improves insight into illness to a clinically relevant extent. Other authors have reported similar improvements in insight in other naturalistic studies in an inpatient setting.[41]

Despite the high doses used in our study, ziprasidone was well tolerated, with a tolerability profile differing neither from that previously reported in a clinical practice setting in outpatients[21] nor from that reported in clinical trials.[17] Only 9 patients (5%) discontinued ziprasidone, 3 (1.5%) of them because of side effects. These results contrast with the much higher discontinuation rate (32.5% overall and 8.6% due to side effects) reported in a retrospective study of 151 hospitalized patients with several psychiatric diagnoses who were treated with relatively low doses of ziprasidone (mean ± SD = 83 ± 46 mg/day at discharge).[55] As we have mentioned before, low doses of ziprasidone seem to be associated with higher discontinuation rates in the clinical practice setting [21,44–46] and might explain these differences between this retrospective study and ours. This good tolerability profile of ziprasidone is reinforced by the significant and clinically relevant improvement in the overall attitude toward the medication we observed during our study.

Finally, it is important to mention that the administration of ziprasidone with food is considered crucial to ensure optimal dose-dependent bioavailability and thus a better symptom control and tolerability.[56] Since, except when otherwise indicated, in the hospital setting medications are administered with food, it is possible that in our study we reached that optimal condition for a majority of patients, contributing to the favorable results seen with ziprasidone.

Overall, although our results should be interpreted with caution because of the uncontrolled design of our study, they suggest that, in acutely ill inpatients with schizophrenia or schizoaffective disorder, the use of ziprasidone under routine clinical conditions is associated with a rapid and progressive improvement in psychopathologic symptoms and a clinically relevant improvement in the insight into their illness. Ziprasidone seems to be also well tolerated. Whether high doses of ziprasidone, such as those used in our study, are truly more effective than standard doses (i.e., those derived from clinical trials and recommended in the package insert) should be further evaluated in randomized clinical trials.

Drug names: biperiden (Akineton), clonazepam (Klonopin and others), haloperidol (Haldol and others), lorazepam (Ativan and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal and others), venlafaxine (Effexor and others), ziprasidone (Geodon).

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REFERENCES

1. Chiles JA, Miller AL, Crismon ML, et al. The Texas Medication Algorithm Project: development and implementation of the schizophrenia algorithm. Psychiatr Serv 1999;50:69–74
2. Osser DN, Sigadel R. Short-term inpatient pharmacotherapy of schizophrenia. Harv Rev Psychiatry 2001;9:89–104
3. Allen MA, Currier GW, Carpenter D, et al. The Expert Consensus Guidelines: Treatment of Behavioral Emergencies 2005. J Psychiatr Pract 2005;11(suppl 1):1–108
4. Greenberg WM, Citrome L. Ziprasidone for schizophrenia and bipolar disorder: a review of the clinical trials. CNS Drug Rev 2007;13:137–177
5. Daniel DG, Potkin SG, Reeves KR, et al. Intramuscular (IM) ziprasidone 20 mg is effective in reducing acute agitation associated with psychosis: a double-blind, randomized trial. Psychopharmacology (Berl) 2001;155: 128–134
6. 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
7. Daniel DG, Zimbroff DL, Potkin SG, et al., and the Ziprasidone Study Group. Ziprasidone 80 mg/day and 160 mg/day in the acute exacerbation of schizophrenia and schizoaffective disorder: a 6-week placebo-controlled trial. Neuropsychopharmacology 1999;20:491–505
8. 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
9. Davis JM, Chen N, Glick ID. A meta-analysis of the efficacy of second-generation antipsychotics. Arch Gen Psychiatry 2003;60:553–564
10. Addington DEN, Pantelis C, Dineen M, et al. Efficacy and tolerability of ziprasidone versus risperidone in patients with acute exacerbation of schizophrenia or schizoaffective disorder: an 8-week, double-blind, multicenter trial. J Clin Psychiatry 2004;65:1624–1633
11. Simpson GM, Glick ID, Weiden PJ, et al. Randomized, controlled, double-blind multicenter comparison of the efficacy and tolerability of ziprasidone and olanzapine in acutely ill inpatients with schizophrenia or schizoaffective disorder. Am J Psychiatry 2004;161:1837–1847
12. Zimbroff D, Warrington L, Loebel A, et al. Comparison of ziprasidone and aripiprazole in acutely ill patients with schizophrenia or schizoaffective disorder: a randomized, double-blind, 4-week study. Int Clin Psychopharmacol 2007;22:363–370
13. Breier A, Berg PH, Thakore JH, et al. Olanzapine versus ziprasidone: results of a 28-week double-blind study in patients with schizophrenia. Am J Psychiatry 2005;162:1879–1887
14. Kinon BJ, Lipkovich I, Edwards SB, et al. A 24-week randomized study of olanzapine versus ziprasidone in the treatment of schizophrenia or schizoaffective disorder in patients with prominent depressive symptoms. J Clin Psychopharmacol 2006;26:157–162
15. Lieberman JA, Stroup TS, McEvoy JP, et al., for the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. N Engl J Med 2005;353:1209–1223
16. Stroup TS, Lieberman JA, McEvoy JP, et al, for the CATIE Investigators. Effectiveness of olanzapine, quetiapine, risperidone, and ziprasidone in patients with chronic schizophrenia following discontinuation of a previous atypical antipsychotic. Am J Psychiatry 2006;163:611–622
17. Daniel DG. Tolerability of ziprasidone: an expanding perspective. J Clin Psychiatry 2003;64(suppl 19):40–49
18. Bagnall A, Lewis RA, Leitner ML. Ziprasidone for schizophrenia and severe mental illness (Cochrane Review). Cochrane Database Syst Rev 2000;(4):CD001945
19. Allison DB, Mentore JL, Heo M, et al. Antipsychotic-induced weight gain: a comprehensive research synthesis. Am J Psychiatry 1999;156: 1686–1696
20. Weiden PJ, Newcomer JW, Loebel AD, et al. Long-term changes in weight and plasma lipids during maintenance treatment with ziprasidone. Neuropsychopharmacology 2008;33:985–994
21. Arango C, Gomez-Beneyto M, Brenlla J, et al, on behalf of the ZIS Study Group. A 6-month prospective, observational, naturalistic, uncontrolled study to evaluate the effectiveness and tolerability of oral ziprasidone in patients with schizophrenia. Eur Neuropsychopharmacol 2007;17:456–463
22. Ratner Y, Gibel A, Yorkov V, et al. Effectiveness, safety, and tolerability of ziprasidone for treating schizophrenia patients undergoing usual care: a 12-month, open-label, flexible-dose, naturalistic observational trial. Prog Neuropsychopharmacol Biol Psychiatry 2007;31:1401–1409
23. Norquist G, Lebowitz B, Hyman S. Expanding the frontier of treatment research [published online Mar 21, 1999]. Prev Treatment 1999;2(1):ArtID1a. doi: 10.1037/1522-3736.2.1.21a
24. Expert Consensus Guideline Series: Treatment of Schizophrenia 1999. J Clin Psychiatry 1999;60(suppl 11):1–80
25. Wells KB. Treatment research at the crossroads: the scientific interface of clinical trials and effectiveness research. Am J Psychiatry 1999;156:5–10
26. Woods SW, Ziedonis DM, Sernyak MJ, et al. Characteristics of participants and nonparticipants in medication trials for treatment of schizophrenia. Psychiatr Serv 2000;51:79–84
27. Peralta V, Cuesta MJ, Caro F, et al. Neuroleptic dose and schizophrenic symptoms: a survey of prescribing practices. Acta Psychiatr Scand 1994; 90:354–357
28. De Heert M, Wampers M, Peuskens J. Pharmacological treatment of hospitalized schizophrenic patients in Belgium. Int J Psychiatry Clin Pract 2006;10:285–290
29. Barbui C, Nose M, Mazzi MA, et al. Persistence with polypharmacy and excessive dosing in patients with schizophrenia treated in four European countries. Int Clin Psychopharmacol 2006;21:355–362
30. Barbui C, Biancosino B, Esposito E, et al. Factors associated with antipsychotic dosing in psychiatric inpatients: a prospective study. Int Clin Psychopharmacol 2007;22:221–225
31. Dickey B. Outcome measurement from research to clinical practice. In: IsHak WW, Burt T, Sederer LI, eds. Outcome Measurement in Psychiatry: A Critical Review. Washington, DC: American Psychiatric Publishing Inc; 2002:15–22
32. Streiner DL. The 2 "Es" of research: efficacy and effectiveness trials. Can J Psychiatry 2002;47:552–556
33. Overall JE, Gorham DR. The Brief Psychiatric Rating Scale. Psychol Rep 1962;10:799–812
34. Guy W. ECDEU Assessment Manual for Psychopharmacology-Revised. US Dept Health, Education, and Welfare publication (ADM) No 76-338. Rockville, Md: National Institute of Mental Health; 1976:157–165
35. Guy W. ECDEU Assessment Manual for Psychopharmacology-Revised. US Dept Health, Education, and Welfare publication (ADM) No 76-338. Rockville, Md: National Institute of Mental Health; 1976:218–222
36. Hogan TP, Awad AG, Eastwood R. A self-report scale predictive of drug compliance in schizophrenics: reliability and discriminative validity. Psychol Med 1983;13:177–183
37. Garcia I, Hormaechea JA, Arango C, et al. El Cuestionario de Actitud hacia la Medicación (Drug Attitude Inventory: DAI-30) en población española. Arch Psiquiatr 2001;64;261–272

38. Amador XF, Flaum M, Andreason NC, et al. Awareness of illness in schizophrenia and schizoaffective and mood disorders. Arch Gen Psychiatry 1994;51:826–836
39. Stroup TS, Alves WM, Hamer RM, et al. Clinical trials for antipsychotic drugs: design conventions, dilemmas, and innovations. Nat Rev Drug Discov 2006;5:133–146
40. Kazis LE, Anderson JJ, Meenan RF. Effect sizes for interpreting changes in health status. Med Care 1989;27:S178–S189
41. Sajatovic M, Rosch DS, Sivec HJ, et al. Insight into illness and attitudes toward medications among inpatients with schizophrenia. Psychiatr Serv 2002;53:1319–1321
42. Alvarez E, Bobes J, Gomez JC, et al, for the EUROPA Study Group. Safety of olanzapine versus conventional antipsychotics in the treatment of patients with acute schizophrenia: a naturalistic study. Eur Neuropsychopharmacol 2003;13:39–48
43. Perez V, Cañas F, Tafalla M, et al. Tolerability and effectiveness of quetiapine in inpatients with schizophrenia: results from the acute phase of the TESIS study [Abstract]. Eur Neuropsychopharmacol 2005; 15(suppl 3):S493
44. Mullins CD, Shaya FT, Zito JM, et al. Effect of initial ziprasidone dose on treatment persistence in schizophrenia. Schizophr Res 2006;83:277–284
45. Kudla D, Lambert M, Domin S, et al. Effectiveness, tolerability, and safety of ziprasidone in patients with schizophrenia or schizoaffective disorder: results of a multi-centre observational trial. Eur Psychiatry 2007;22:195–202
46. Citrome L, Reist C, Palmer L, et al. Impact of real-world ziprasidone dosing on treatment discontinuation rates in subjects with schizophrenia or bipolar disorder. In: New Research Program and Abstracts of the 161st annual meeting of the American Psychiatric Association; May 3–8, 2008; Washington, DC. Abstract NR6-105:323
47. Gibert J, Giner J, Bobes J, et al, for the SOS GROUP. The "Seroquel" Outcomes Study (SOS): efficacy and tolerability of quetiapine in a long-term, naturalistic study of patients with schizophrenia. Int J Psychiatry Clin Pract 2007;11:222–232
48. Citrome L, Volavka J. Optimal dosing of atypical antipsychotics in adults: a review of the current evidence. Harv Rev Psychiatry 2002; 10:280–291
49. Kane JM. Dose selection and comparator drugs in schizophrenia research. J Clin Psychiatry 2001;62(suppl 9):29–32
50. Kane JM, Leucht S, Carpenter D, et al. The Expert Consensus Guideline Series: Optimizing Pharmacologic Treatment of Psychotic Disorders: Introduction: methods, commentary, and summary. J Clin Psychiatry 2003;64(suppl 12):5–19
51. Tamminga CA, Buchanan RW, Gold JM. The role of negative symptoms and cognitive dysfunction in schizophrenia outcome. Int Clin Psychopharmacol 1998;13(suppl 3):S21–S26
52. Stahl SM, Malla AK, Newcomer JW, et al. The relationship between clinical efficacy and quality of life: a randomized, 40-week, double-blind study of ziprasidone versus haloperidol followed by a 3-year, double-blind extension phase. In: New Research Program and Abstracts of the 160th annual meeting of the American Psychiatric Association; May 19–24, 2007; San Diego, Calif. Abstract NR 515:221
53. Rocca P, Crivelli B, Marino F, et al. Correlations of attitudes toward antipsychotic drugs with insight and objective psychopathology in schizophrenia. Compr Psychiatry 2008;49:170–176
54. Lincoln TM, Lullmann E, Rief W. Correlates and long-term consequences of poor insight in patients with schizophrenia: a systematic review. Schizophr Bull 2007;33:1324–1342
55. Centorrino F, MacLean E, Salvatore P, et al. Ziprasidone: first year experience in a hospital setting. J Psychiatr Pract 2004;10:361–367
56. Miceli JJ, Glue P, Alderman J, et al. The effect of food on the absorption of oral ziprasidone. Psychopharmacol Bull 2007;40:58–68