# Intramuscular Ziprasidone Compared With Intramuscular Haloperidol in the Treatment of Acute Psychosis

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***Background:*** This 7-day, randomized, open-label, multicenter, international study compared the efficacy and tolerability of intramuscular (i.m.) ziprasidone with haloperidol i.m. and the transition from i.m. to oral treatment in hospitalized patients with acute psychotic agitation (related to DSM-III-R diagnoses).

***Method:*** Patients received up to 3 days of flexible-dose ziprasidone i.m. (N = 90) or haloperidol i.m. (N = 42) followed by oral treatment to day 7. After an initial ziprasidone i.m. dose of 10 mg, subsequent i.m. doses of 5 to 20 mg could be given every 4 to 6 hours (maximum daily dose = 80 mg) if needed, followed by oral ziprasidone, 80–200 mg/day. Haloperidol i.m. doses of 2.5 to 10 mg were given on entry, followed by 2.5 to 10 mg i.m. every 4 to 6 hours (maximum daily dose = 40 mg) if needed, then by oral haloperidol, 10–80 mg/day.

***Results:*** The mean reductions in Brief Psychiatric Rating Scale (BPRS) total, BPRS agitation items, and Clinical Global Impressions-Severity scale scores were statistically significantly greater ($p < .05$, $p < .01$, and $p < .01$, respectively) after ziprasidone i.m. treatment compared with haloperidol i.m. treatment. Further reductions in these scores also occurred in both groups following transition to oral treatment. Ziprasidone was associated with a lower incidence of movement disorders and a reduced requirement for anticholinergic medication during both i.m. and oral treatment compared with haloperidol. Movement disorder scale scores improved with ziprasidone i.m. and oral treatment, but deteriorated with haloperidol. Other adverse events were rare with both treatments.

***Conclusion:*** Ziprasidone i.m. was significantly more effective in reducing the symptoms of acute psychosis and was better tolerated than haloperidol i.m., particularly in movement disorders. The transition from ziprasidone i.m. to oral ziprasidone was effective and well tolerated.

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Over 20 years ago, it was noted that parenteral high-dose antipsychotics, including haloperidol, "have a marked propensity to cause extrapyramidal side effects, especially dystonic reactions. Acute dystonia may be experienced as a very traumatic event and can possibly induce resistance to the future establishment of drug therapy."[1(p599)] More recently, intramuscular (i.m.) administration of benzodiazepines, particularly lorazepam, has been studied as either an alternative or as an adjunct to high-potency i.m. antipsychotics in an attempt to avoid toxicity.[2–9] However, i.m. benzodiazepines are also associated with adverse effects that can lead to serious complications.[4,10,11] These include excessive sedation, confusion, disinhibition, ataxia, and respiratory depression, all of which are particularly undesirable in an emergency setting. Experience of these and other adverse treatment effects such as dysphoria, which can occur with parenteral antipsychotic treatment, often results in noncooperation by the patient at a very critical time and can impair compliance with subsequent maintenance antipsychotic therapy.[12,13] Such adverse reactions can also interfere with clinical assessment and make an accurate diagnosis difficult.

In an era when oral formulations of novel antipsychotics have revolutionized the treatment of psychotic disorders and raised expectations of what pharmacotherapy should achieve, overstretched emergency resources are still dependent on conventional i.m. treatment. Lack of superior alternatives means that these agents are still the standard treatments for acute agitation associated with psychosis in patients in whom parenteral administration is indicated.

A rapid-acting i.m. formulation of the novel antipsychotic ziprasidone has been developed and may offer advantages over conventional i.m. treatments in the treatment of acute psychotic agitation, particularly in tolerability. In addition to having a high serotonin-2A ($5\text{-}HT_{2A}$)/dopamine-2 ($D_2$) ratio, which in part accounts for the very low incidence of movement disorders observed in clinical trials,[14–16] ziprasidone has significant actions at other receptor sites, giving a pharmacologic profile that is distinct from all other antipsychotics. In vivo agonism of $5\text{-}HT_{1A}$ receptors in conjunction with very high affinities for $5\text{-}HT_{2C}$ and $5\text{-}HT_{1D}$ receptors and moderate inhibition of 5-HT and norepinephrine reuptake sites[16–18] comprise a unique collection of activities that may predict enhanced antipsychotic activity, efficacy in treating negative symptoms, and antidepressant and anxiolytic activity. These serotonergic and adrenergic activities may complement dopamine $D_2$ antagonism and in conjunction with modest $\alpha_1$, histamine $H_1$, and negligible muscarinic m1 affinities provide efficacy in the treatment of acute psychosis with a favorable tolerability profile.

On the basis of the pharmacologic activity of ziprasidone,[16–18] the established efficacy and favorable tolerability profile of oral ziprasidone in patients with acute and chronic schizophrenia,[14–16,19] and evidence of anxiolytic activity in the treatment of acute situational anxiety,[20] it was hypothesized that ziprasidone i.m. would be effective in ameliorating the symptoms of acute agitation associated with psychotic disorders and offer substantial tolerability advantages over conventional i.m. treatments. Results from a pilot study support this hypothesis.[21] Ziprasidone i.m. substantially reduced symptoms of agitation, but did not induce excessive sedation, acute dystonia, or parkinsonism in patients treated for 3 days for an acute episode of psychosis.[21] The present randomized, open-label, multicenter, international study compares ziprasidone i.m. with haloperidol i.m. in the treatment of hospitalized patients with acute agitation and psychosis for up to 3 days. The transition from i.m. to oral therapy with ziprasidone was also assessed up to 7 days after the start of i.m. therapy.

## METHOD

### Patients

Men or women recently hospitalized with acute psychosis related to schizophrenia, schizoaffective disorder, bipolar disorder, schizophreniform disorder, delusional disorder, brief psychotic disorder, or psychotic disorders not otherwise specified as defined by DSM-III-R[22] were allowed to enter. Patients were excluded if their acute psychosis was related to substance abuse (confirmed by screening urinalysis) or of organic origin. Patients were also excluded if they had any clinically relevant medical illness or an abnormal electrocardiogram (ECG), were at imminent risk of suicide or homicide, or had a history of substance abuse or dependence in the previous 2 months. Women were included only if they were unable to conceive and were not breastfeeding. After a complete description of the study and provision of an information sheet to the patients, written informed consent was obtained from the patient or authorized proxy, in accordance with local regulations and legislation. The study was conducted in accordance with the Helsinki declaration (1989 Hong Kong revision) and was approved by the local ethics review committees.

### Study Design

This 7-day, randomized, open-label, parallel-group study was conducted in 19 centers in 7 countries. Computerized randomization assigned patients to either ziprasidone or haloperidol in a 2:1 ratio. Antipsychotics being taken at baseline were discontinued, and the first i.m. dose was administered when clinically appropriate.

Intramuscular treatment was started 4 to 96 hours after screening and administered for up to 3 days, followed by twice-daily oral therapy until day 7 (endpoint). Ziprasidone i.m. was prepared by diluting lyophilized powder with sterile water to yield a ziprasidone mesylate solution of 20 mg/mL. An initial i.m. dose of 10 mg of ziprasidone was given, and, depending on clinical need, subsequent doses of 5 to 20 mg i.m. every 4 to 6 hours (maximum 4 injections and 80 mg in 24 hours) could be given until the end of day 3. After i.m. treatment, the initial total daily dose of oral ziprasidone was either twice the last daily i.m. dose or 80 mg, whichever was the highest. Patients then received oral ziprasidone, 80–200 mg/day, depending on clinical response, until day 7. Haloperidol i.m., 2.5–10 mg, was initially given, and subsequent doses were administered as needed every 4 to 6 hours (maximum 4 injections and 40 mg in 24 hours) for up to 3 days.The initial oral haloperidol daily dose was either equivalent to the total last daily i.m. dose or 10 mg/day, whichever was the highest. Thereafter, oral haloperidol, 10–80 mg/day, was administered until endpoint. Concomitant treatment with oral or i.m. lorazepam (up to 12 mg/day) for agitation, oral temazepam (up to 20 mg/day) for insomnia, oral anticholinergics for extrapyramidal side effects (EPS), and/or β-blockers for akathisia were allowed as required.

### Assessments

All assessments of efficacy and safety were made according to a predefined schedule. Efficacy assessments included the 18-item Brief Psychiatric Rating Scale (BPRS) anchored version,[23] rated 1 to 7, and the Clinical Global Impressions-Severity scale (CGI-S).[24] These instruments were rated at baseline, once every 24 hours while on i.m. treatment, and at endpoint. The CGI-Improvement scale (CGI-I)[24] was rated relative to baseline every 24 hours and at endpoint.

All treatment-emergent adverse events were classified using COSTART[25] along with the investigators' assessment of severity. At baseline, the end of i.m. treatment, and at endpoint (or on early discontinuation) the modified Simpson-Angus Scale,[26] with head dropping substituted for a head dropping/rotation item, and the Barnes Akathisia Scale[27] were administered. A 5-point, categorical sedation scale (1 = absent to 5 = sleep) was rated at baseline and within 6 hours of a dose of study medication on days 1 to 7 or on early termination. Systolic and diastolic blood pressures (after 5 minutes sitting and after 2 minutes standing) and pulse rates were measured at baseline, daily before the first i.m. dose, 30 minutes and 1 hour after each i.m. dose, and on each day of oral treatment. Twelve-lead ECGs and laboratory tests were conducted at baseline, after the last i.m. dose, and at endpoint. Urinalysis was also performed at baseline and at endpoint. All concomitant medication use was recorded. A comprehensive battery of standard laboratory tests was performed at screening, at the end of the i.m. treatment phase, and at the end of the study. Abnormal laboratory findings were predefined.

### Data Analysis

The BPRS agitation items score was derived from the BPRS and consisted of the sum of items 2 (anxiety), 6 (tension), 10 (hostility), and 17 (excitement). Mean changes from baseline in BPRS total, BPRS agitation items, and CGI-S scores after the last i.m. treatment and at the end of the oral treatment phase were compared between ziprasidone- and haloperidol-treatment groups. The scores at the last visit on i.m. treatment and on oral treatment were included in these analyses. An analysis of covariance (ANCOVA) was used to compare least squares mean changes from baseline between treatment groups. An ANCOVA compared mean CGI-I scores after the last i.m. treatment and at endpoint. All tests were 2-tailed. Mean changes from baseline in movement disorder rating scale scores were also calculated. Mean changes from baseline in sedation scores within 6 hours of the last i.m. injection and at the end of oral treatment were calculated. Only patients who had a baseline assessment and at least one assessment on i.m. treatment were included in the analysis of changes on i.m. treatment, and only patients who had at least one dose of oral therapy after i.m. treatment were included in the endpoint analysis.

## RESULTS

Of the 166 patients screened, 132 were randomly assigned to treatment with either ziprasidone i.m. (N = 90) or haloperidol i.m. (N = 42) at 19 centers. The 2 treatment groups had similar baseline patient characteristics and similar clinical characteristics (Table 1). Two thirds of patients were administered antipsychotics in the 48 hours before screening.

**Table 1. Baseline Patient Characteristics and Mean Psychopathology Scores[a]**

| Characteristics and Psychopathology Scores | Ziprasidone Group (N = 90) | Haloperidol Group (N = 42) |
|---|---|---|
| Schizophrenia,[b] N (%) | 67 (74.4) | 25 (59.5) |
| Men, N (%) | 83 (92.2) | 40 (95.2) |
| Race, N (%) | | |
| White | 55 (61.1) | 24 (57.1) |
| Black | 28 (31.1) | 12 (28.6) |
| Asian | 3 (3.3) | 3 (7.1) |
| Other | 4 (4.4) | 3 (7.1) |
| Age, y, mean (range) | 34.5 (20–66) | 32.8 (19–53) |
| Patients with CGI-S ≥ 5, N (%) | 63 (70.0) | 27 (64.3) |
| Psychopathology scores, mean (SD) | | |
| BPRS total | 45.9 (10.5) | 47.5 (9.3) |
| BPRS agitation items | 9.9 (3.3) | 10.5 (3.4) |
| CGI-S | 5.1 (0.8) | 4.9 (1.1) |
| Prestudy medication,[c] N (%) | | |
| Antipsychotics | 59 (65.6) | 28 (66.7) |
| Anxiolytics | 57 (63.3) | 30 (71.4) |

[a]Abbreviations: BPRS = Brief Psychiatric Rating Scale, CGI-S = Clinical Global Impressions-Severity scale.
[b]Other DSM-III-R-defined diagnoses for ziprasidone and haloperidol included schizophreniform disorders, 4 (4.4%) for ziprasidone and 4 (9.5%) for haloperidol; schizoaffective disorders, 3 (3.3%) for ziprasidone and 8 (19%) for haloperidol; delusional disorders, 3 (3.3%) for ziprasidone and 0 for haloperidol; bipolar disorders, 5 (5.6%) for ziprasidone and 1 (2.4%) for haloperidol; psychotic disorders, 1 (1.1%) for ziprasidone and 1 (2.4%) for haloperidol; and brief psychotic disorders, 7 (7.8%) for ziprasidone and 3 (7.1%) for haloperidol.
[c]Medication taken in the 48 hours before screening.

Overall, a lower percentage of patients discontinued from the ziprasidone group (8/90, 8.9%) than from the haloperidol group (8/42, 19%). Two patients treated with ziprasidone i.m. and 1 treated with haloperidol i.m. discontinued (for reasons unrelated to treatment). Six patients discontinued oral ziprasidone: 3 with treatment-related adverse events (details below), 1 because of lack of efficacy, and 2 for reasons not related to treatment. Seven patients discontinued oral haloperidol: 1 because of treatment-related adverse events (see below), 3 because of lack of efficacy, and 3 for reasons not related to treatment.

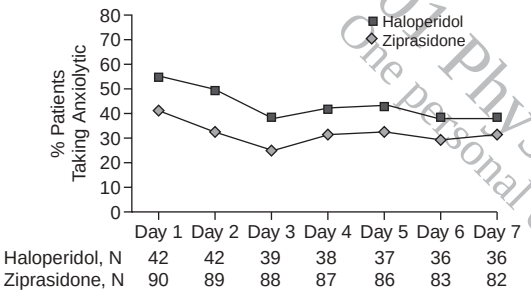
The mean daily doses and the percentage of patients treated according to the flexible dose and dosing regimen are summarized in Table 2. The percentage of patients requiring i.m. antipsychotic treatment decreased in both groups to a similar extent on days 2 and 3. Although treatment was required by fewer patients, the doses were higher on day 2 compared with day 1 with both ziprasidone and haloperidol i.m. The mean total daily i.m. doses required on days 2 and 3 were similar within each treatment group.

Anxiolytics were taken at some time during the study by 52/90 (57.7%) and 27/42 (64.3%) of the patients in the ziprasidone and haloperidol groups, respectively. Throughout the study, concomitant anxiolytic use was similar in each of the treatment groups (Figure 1). Hypnotics for nighttime sedation were taken at some time during the study by 9/90 (10%) and 3/42 (7.1%) of patients in the ziprasidone and haloperidol groups, respectively. Except for

**Table 2. Intramuscular and Oral Ziprasidone and Haloperidol Dosage Summary**

| | Dose | | | | Patients Treated | | | |
|---|---|---|---|---|---|---|---|---|
| | Ziprasidone (N = 90) | | Haloperidol (N = 42) | | Ziprasidone (N = 90) | | Haloperidol (N = 42) | |
| Treatment | Mean | SD | Mean | SD | N | % | N | % |
| Intramuscular treatment | | | | | | | | |
| Day 1 total, mg/d | 23.3 | 14.9 | 7.6 | 6.9 | 90 | 100 | 42 | 100 |
| Day 2 total, mg/d | 27.6 | 21.3 | 10.1 | 8.9 | 52 | 57.7 | 18 | 42.8 |
| Day 3 total, mg/d | 27.6 | 21.2 | 11.0 | 10.2 | 27 | 30 | 10 | 23.8 |
| Last single im dose, mg | 11.7 | 4.1 | 4.6 | 2.8 | 90 | 100 | 42 | 100 |
| Oral treatment | | | | | | | | |
| Last daily dose, mg/d | 90.5 | 44.9 | 14.0 | 10.1 | 88 | 97.8 | 41 | 97.6 |

**Figure 1. Anxiolytic Use Expressed as the Percentage of Patients Evaluated at Each Assessment**




2 patients treated with ziprasidone, the patients who took hypnotics also took anxiolytics during the day.

## Efficacy

Mean reductions from baseline in all 3 efficacy variables, BPRS total, BPRS agitation items, and CGI-S scores, were significantly greater with ziprasidone i.m. than with haloperidol i.m. (Table 3, Figure 2). The percentage improvement in efficacy variables with ziprasidone i.m. was at least double that observed with haloperidol i.m. (see Figure 2). Further reductions from baseline were observed after the transition from i.m. to oral treatment in both groups (see Table 3 and Figure 2). The mean reduction in the CGI-S score after the transition to oral ziprasidone was also statistically significantly greater compared with that after the transition to oral haloperidol, and the mean reductions in BPRS total and BPRS agitation items scores were numerically greater. The mean CGI-I scores during the i.m. treatment period were 3.38 with ziprasidone and 3.49 with haloperidol (p = .47). At endpoint, mean CGI-I scores were 3.07 with ziprasidone and 3.14 with haloperidol (p = .54).

**Table 3. Changes From Baseline in Psychopathology Assessment at the End of Intramuscular Treatment and at Endpoint (all subjects, observed cases)[a]**

| | Ziprasidone Group (N = 90) | | Haloperidol Group (N = 42) | | |
|---|---|---|---|---|---|
| Treatment Evaluation and Variable | Mean | SD | Mean | SD | p Value[b] |
| Intramuscular treatment[c] | | | | | |
| BPRS total | –6.24 | 8.30 | –3.18 | 6.55 | .02 |
| BPRS agitation items | –1.93 | 3.41 | –0.80 | 2.81 | .015 |
| CGI-S | –0.49 | 0.68 | –0.15 | 0.53 | .002 |
| Endpoint evaluation[d] | | | | | |
| BPRS total | –8.76 | 11.62 | –5.83 | 9.50 | .09 |
| BPRS agitation items | –2.09 | 4.41 | 1.59 | 3.61 | .19 |
| CGI-S | –0.89 | 1.23 | –0.38 | 1.17 | .025 |

[a]Abbreviations: BPRS = Brief Psychiatric Rating Scale, CGI-S = Clinical Global Impressions-Severity scale.
[b]p Value was determined by contrast within analysis of covariance using change from baseline as the dependent variable, center and treatment as fixed effects, and baseline score as a covariate.
[c]The value from the last assessment on i.m. treatment was included in the analysis for all patients who had a baseline assessment and at least one assessment on i.m. treatment.
[d]The value from the last assessment on oral treatment was included in the analysis for all patients who had a baseline assessment and at least one assessment on oral treatment. The number of patients evaluated at each assessment in each group is shown in Figure 2.

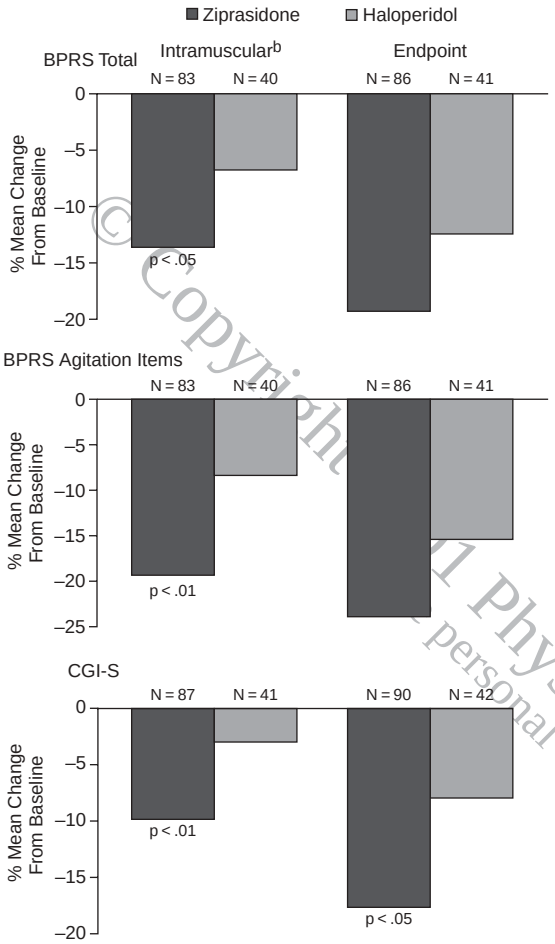
## Tolerability and Safety

The percentage of patients experiencing any adverse event was lower with ziprasidone i.m. compared with haloperidol i.m. (Table 4). This was also the case in the comparison of all adverse events reported during the entire study (i.m. and oral treatment combined) (see Table 4). The majority of adverse events were mild or moderate in severity. No patient discontinued i.m. treatment due to treatment-related adverse events. One patient (1.1%) discontinued oral ziprasidone owing to severe postural hypotension and 1 (1.1%) owing to akathisia. One patient (1.1%), a 41-year-old man with a history of dystonic reactions with neuroleptic treatment, also discontinued oral ziprasidone because of laryngospasm in association with acute dystonia. One patient (2.4%) discontinued oral haloperidol because of excessive sweating and dry mouth. No serious adverse events occurred during the study.

EPS were frequently associated with haloperidol i.m., but were not observed with ziprasidone i.m. treatment. Dystonia was also more frequent with haloperidol i.m. than with ziprasidone i.m.. After the transition to oral treatment, the incidence of movement disorders increased with haloperidol, and these were notably more frequent than reports with ziprasidone treatment (see Table 4).

Small decreases from baseline in mean Simpson-Angus Scale and Barnes Akathisia Scale scores were observed with ziprasidone both at the end of i.m. treatment and at endpoint (Table 5). By contrast, increases in mean Simpson-Angus Scale and Barnes Akathisia Scale scores were associated with haloperidol i.m., with further increases observed at endpoint. At the end of i.m. treatment

**Figure 2. Mean Percentage Change From Baseline in Efficacy Variables After Intramuscular Treatment and at Endpoint (all subjects, observed cases)[a]**




[a]Abbreviations: BPRS = Brief Psychiatric Rating Scale, CGI-S = Clinical Global Impressions-Severity scale.
[b]"Intramuscular" denotes last observations after i.m. injection and before oral administration. N is the number of patients included in the analysis: patients who were assessed at baseline and had at least 1 postbaseline assessment on i.m. treatment and at endpoint.

**Table 4. Treatment-Emergent Adverse Events Occurring in ≥ 10% of Patients in Either Group**

| | I.M. Treatment | | | | I.M. + Oral Treatment | | | |
|---|---|---|---|---|---|---|---|---|
| | Ziprasidone (N = 90) | | Haloperidol (N = 42) | | Ziprasidone (N = 90) | | Haloperidol (N = 42) | |
| Adverse Event | N | % | N | % | N | % | N | % |
| Total incidence of adverse events | 28 | 31.1 | 21 | 50.0 | 41 | 45.6 | 25 | 59.5 |
| Discontinuation due to adverse events | 1 | 1.1 | 0 | 0 | 4 | 4.4[a] | 1 | 2.4[b] |
| Incidence of individual adverse event | | | | | | | | |
| Tremor | 1 | 1.1 | 1 | 2.4 | 2 | 2.2 | 4 | 9.5 |
| Akathisia | 2 | 2.2 | 0 | 0 | 3 | 3.3 | 6 | 14.3 |
| Dystonia | 1 | 1.1 | 3 | 7.1 | 4 | 4.4 | 5 | 11.9 |
| EPS | 0 | 0 | 9 | 21.4 | 1 | 1.1 | 16 | 38.1 |
| Hypertonia | 0 | 0 | 3 | 7.1 | 3 | 3.3 | 5 | 11.9 |

[a]Adverse events were treatment related in 3 patients.
[b]Adverse event was treatment related.

**Table 5. Changes From Baseline on the Simpson-Angus Scale and Barnes Akathisia Scale**

| | Ziprasidone (N = 90)[a] | | Haloperidol (N = 41)[a] | |
|---|---|---|---|---|
| Scale | Mean | SD | Mean | SD |
| Simpson-Angus Scale | | | | |
| Baseline | 2.62 | 4.64 | 2.49 | 4.71 |
| Change at last im dose | –0.61 | 3.11 | 3.80 | 5.22 |
| Change at endpoint | –1.09 | 4.33 | 6.00 | 7.12 |
| Barnes Akathisia Scale | | | | |
| Baseline | 0.38 | 0.79 | 0.34 | 0.69 |
| Change at last im dose | –0.03 | 0.57 | 0.44 | 0.87 |
| Change at endpoint | –0.10 | 0.79 | 0.80 | 1.14 |

[a]Not all patients were available for all assessments.

and at endpoint, substantially higher percentages of patients treated with haloperidol had postbaseline increases in Simpson-Angus Scale and Barnes Akathisia Scale scores compared with ziprasidone (Figure 3).The percentage of patients who received anticholinergic medication at any time during the study was approximately 3-fold higher in haloperidol-treated patients (20/42, 47.6%) than in ziprasidone-treated patients (13/90, 14.4%). The percentage of patients treated with haloperidol who required benztropine increased substantially over the course of the 7-day study, but no apparent increase was found in the ziprasidone group (Figure 4).

Vomiting occurred with ziprasidone in 3 patients (3.3%) during the i.m. treatment period (2 mild, 1 moderate) and in 6 patients (6.7%) during the oral treatment period (all mild). None was reported in the haloperidol group. Somnolence was reported as an adverse event in 1 patient (1.1%) taking oral ziprasidone. No ataxia, akinesia, confusion, seizures, fainting, syncope, or respiratory depression was observed with ziprasidone or haloperidol.

Mean ± SD sedation scores were 1.37 ± 0.90 and 1.20 ± 0.51 in the ziprasidone and haloperidol groups respectively. At the end of the i.m. treatment period, the mean ± SD changes in sedation scores were 1.10 ± 1.56 and 0.46 ± 1.17 with ziprasidone i.m. and haloperidol i.m., respectively. The corresponding values at the end of the study were 0.02 ± 1.10 and 0 ± 0.71, respectively.

Tachycardia was reported as an adverse event in 2 patients (2.2%) treated with ziprasidone i.m. and in no patient in the haloperidol i.m. group. There were no notable changes in mean systolic or diastolic blood pressures during the 1 hour after i.m. injection with ziprasidone or with haloperidol. There were occasional reports of individual patients experiencing clinically relevant changes in blood pressures with both treatments. Median and mean changes from baseline in ECG variables were unremarkable in both the ziprasidone and haloperidol groups. No patient had an increase in QTc interval of ≥ 20% or had a QTc interval

Figure 3. Percentage of Patients Showing a Postbaseline Increase in Movement Disorder Rating Scale Scores

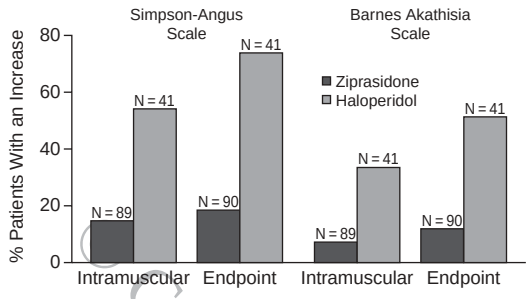
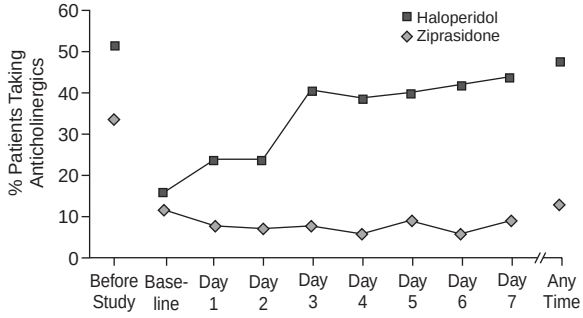



Figure 4. Anticholinergic Use by Day[a]




| | Before Study | Base-line | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | Any Time |
|---|---|---|---|---|---|---|---|---|---|---|
| Haloperidol, N | 42 | 42 | 42 | 42 | 39 | 38 | 37 | 36 | 36 | 42 |
| Ziprasidone, N | 90 | 90 | 90 | 89 | 88 | 87 | 86 | 83 | 82 | 90 |

[a]Expressed as the percentage of patients evaluated at each assessment and the cumulative percentage of patients who took anticholinergics at any time during treatment with ziprasidone or haloperidol.

> 500 ms during either i.m. or oral treatment with ziprasidone or haloperidol. The mean change in QTc interval from baseline to end of i.m. treatment was +2.14 ms with ziprasidone and +2.22 ms with haloperidol. Abnormal laboratory values were reported in 14% (10/74) of patients during ziprasidone i.m. treatment and 13% (4/30) during haloperidol i.m. treatment. During the entire study, abnormal laboratory values were reported in 19% (17/89) and 21% (8/39) of patients treated with ziprasidone and haloperidol, respectively. In both groups, elevated random glucose (> 1.2 × ULN) was the most frequently reported abnormality and occurred with similar frequency during ziprasidone and haloperidol i.m. treatment (both 10%) and during the entire study (12% [11/89] and 13% [5/39]). There was no evidence of hematologic or hepatic toxicity.

## DISCUSSION

The results from this randomized, open-label, parallel-group, multicenter study of 132 patients suggest that ziprasidone i.m. treatment is significantly more effective in reducing the symptoms of acute psychosis, including agitation, than haloperidol and has well-defined advantages in tolerability over haloperidol i.m. The results also demonstrate that patients can successfully make the transition from ziprasidone i.m. to oral ziprasidone with further reductions in symptoms and no increase in burden of adverse effects. In particular, ziprasidone i.m. appears to have a notably lower propensity for inducing movement disorders than does haloperidol i.m., an advantage that is maintained when patients are switched from up to 3 days of i.m. treatment to oral treatment.

Several considerations are relevant to the interpretation of findings of the present study, particularly since this was an open-label study. The need to obtain written informed consent, essential for this evaluation of an experimental treatment, excluded severely psychotic, very hostile, confused, and disorganized patients from entering the study. Some studies[2,4,8] of i.m. haloperidol and i.m. benzodiazepines have waived informed consent since both treatments are well established, and therefore those studies may have included more severely ill patients than the present study. However, the patients in the present study had sufficiently high levels of baseline psychopathology to enable demonstration of clinically meaningful treatment effects.

No patient discontinued the i.m. phase of the study because of insufficient therapeutic effect, and concomitant anxiolytic use was similar in both groups and lower over the course of the study than during the 48-hour period preceding randomization, suggesting that patients received effective doses of both agents. However, efficacy assessments indicated that ziprasidone i.m. was significantly more effective than haloperidol i.m. in reducing both illness severity and psychopathology, including symptoms of agitation. The robust improvement in the mean CGI-S, BPRS total, and BPRS agitation items scores observed with ziprasidone i.m., which were approximately double those observed with haloperidol i.m., is an expected finding in the light of evidence from other studies in which ziprasidone i.m., 10 and 20 mg, significantly and dose-dependently reduced behavioral activity in patients with psychosis and associated agitation.[28] In addition, patients treated with ziprasidone i.m. in the present study appeared calm, quiet, and apparently drowsy, but were still able to be roused (S.B., personal observation). Similar use of anxiolytics in both groups throughout the study meant any differences between agents in symptom reduction during i.m. treatment was not confounded by difference in anxiolytic use. The reduction in the mean BPRS total score in the haloperidol i.m. group in this open study is similar to the reduction observed after 3 days of double-blind treatment with i.m. haloperidol and i.m. remoxipride in a comparable study of acutely ill psychotic patients.[29]

The further reduction in symptoms at the end of oral treatment indicates that patients can be easily switched to oral ziprasidone or haloperidol treatment without an exac-

erbation of symptoms, an essential requirement for any single agent to have utility as both a parenteral and an oral treatment for acute psychosis. The additional reduction in symptoms after just days of oral treatment also concurs with the results from a trial of oral ziprasidone, 80 and 160 mg/day, in more than 300 patients with an acute exacerbation of schizophrenia or schizoaffective disorder, in which significant suppression of symptoms, including both positive and negative symptoms, was observed by the first week of treatment.[14]

In this study, the difference in the occurrence and severity of movement disorders between ziprasidone and haloperidol treatment was apparent. With both i.m. and oral ziprasidone treatment, movement disorders, including akathisia, dystonia, EPS, and hypertonia, either were not reported or were uncommon (≤ 4%), unlike with haloperidol treatment, for which they were reported in 12% to 38% of patients. The percentage of haloperidol-treated patients taking anticholinergics in this study, which increased from 16% at baseline to over 40% by day 7, was in marked contrast to the ziprasidone group, in which fewer than 10% of patients were administered anticholinergics during either the i.m. or oral treatment phases.

To ensure that the substantially greater frequency of patients who experienced an increase in the Barnes Akathisia Scale score in the haloperidol i.m. group (34.1% vs. 6.7% in the ziprasidone i.m. group) did not confound efficacy assessments, a comparison of baseline means and mean changes from baseline in BPRS total and BPRS agitation items scores between the all-patient group and the subset who did not have an increase in Barnes Akathisia Scale scores was conducted within each treatment group. Baseline scores and mean changes from baseline at the i.m. and endpoint assessments in the all-patient group and the subset were almost identical within each treatment group, indicating that differing levels of akathisia did not confound efficacy ratings.

The propensity for haloperidol to induce movement disorders in the present study, particularly EPS and dystonia, is reflected in the reports of adverse events and the marked worsening in movement disorder rating scale scores and is consistent with reports from double-blind studies of conventional i.m. neuroleptics.[2,30] The anticholinergic requirement in the haloperidol group in this study is also similar to the requirement in large, double-blind studies of comparable duration in acutely psychotic patients, in which concomitant anticholinergics were taken by over 50% of patients on i.m. treatment with conventional neuroleptics, including haloperidol.[29,30] The very low liability of i.m. and oral ziprasidone treatment for inducing movement disorders observed in the present study is consistent with reports from extensive clinical trials of both the i.m. and oral formulations[14,28,31] and with its pharmacologic profile, in particular its substantially higher occupancy of 5-$HT_2$ receptors compared with $D_2$ receptors.[32]

Postural hypotension, caused by $\alpha_1$-adrenergic receptor antagonism, is a potentially dangerous side effect in the emergency setting that limits the use of low-potency i.m. antipsychotics such as chlorpromazine in favor of higher-potency agents such as haloperidol.[33–35] Although 1 patient discontinued oral ziprasidone treatment on day 4 because of postural hypotension, thorough and precise investigation of the effects of treatment on cardiovascular function in this study revealed no definite trends for either formulation of ziprasidone to induce clinically relevant postural hypotension or any notable differences between ziprasidone and haloperidol. This reflects the relatively modest $\alpha_1$-adrenergic receptor antagonism, compared with $D_2$ antagonism, by ziprasidone,[17] which enables oral treatment to be initiated at an effective dose without titration,[14] a feature that contrasts with other novel agents such as risperidone, clozapine, and quetiapine.[16,36] Similar, small changes in QTc interval were observed in both groups.

Sedation rating scores remained low throughout the study in both groups. Neither excessive sedation nor other complications sometimes associated with i.m. benzodiazepines, such as confusion, respiratory depression, ataxia, or disinhibition, were associated with ziprasidone or haloperidol i.m. Somnolence was not reported as an adverse event in either treatment group. In double-blind studies, somnolence has been reported in approximately 10% of patients treated with ziprasidone i.m.,[28] and in short-term trials of the oral formulation, somnolence attenuates with time.[17] The fact that somnolence was not reported as an adverse event with either treatment during i.m. administration may be because somnolence was not perceived by the investigators as an adverse event, but rather as a desirable therapeutic effect.

The flexibility in dosage and in the frequency and duration of administration of i.m. treatment in this study mimicked real-life clinical practice, with some patients making the transition to oral treatment within a day of being calmed with i.m. treatment. The percentage of patients who required i.m. treatment decreased over the 3 days to a similar extent in both groups. The requirement for higher mean doses on days 2 and 3 compared with day 1 is most likely due to the lower need for i.m. treatment in patients with less severe symptoms before being transferred to oral treatment, thus leaving those with higher levels of symptoms who require higher doses of i.m. treatment for longer. The mean daily doses of ziprasidone i.m. given on days 2 and 3, both 27.6 mg, are consistent with expectations based on responses in another study of i.m. ziprasidone[28] in which a 20-mg dose of ziprasidone i.m. rapidly (by 15 min) and significantly (by 30 min) reduced the symptoms of acute agitation in psychotic patients for at least 4 hours. The daily doses of haloperidol i.m. for days 2 and 3 (10.1 and 11.0 mg) also accord with dosing levels

in acutely psychotic patients with similar levels of symptoms encountered in clinical practice.

Both the last single dose of ziprasidone i.m. (11.7 mg) and haloperidol i.m. (4.6 mg) are at the lower end of the effective dose range in acutely agitated patients, an expected finding given that patients were sufficiently calmed to be transferred to oral treatment. The mean oral daily doses on the last day of treatment for both ziprasidone (90.5 mg/day) and haloperidol (14.0 mg/day) are in the therapeutic dose range for these agents as used in patients with an acute exacerbation of schizophrenia.[14,16,19] By fixing the initial ziprasidone i.m. dose at 10 mg, an effective dose in acutely agitated psychotic patients,[28] investigators were able to gauge the clinical effect and make subsequent adjustments based on each patient's response to the first dose. Therefore, it is unlikely that ziprasidone i.m. doses were either inflated or diminished because investigators either were too conservative or overcompensated because of the possibility of lack of clinical effect.

Randomization ensured that there was no bias in treatment selection, although there may have been bias in evaluations of both efficacy and safety that could have favored either treatment. However, both the efficacy and tolerability of haloperidol i.m. in this study were in strong agreement with several double-blind, randomized studies in acutely ill patients.[2,29,30,37] On the basis of the doses given in the present study and the extent of agreement between the activities of both formulations of both agents with the literature, we believe the findings of the present study are generalizable to a large group of patients encountered in the broader population who require parenteral treatment for acute psychosis.

The availability of a novel antipsychotic as an i.m. formulation that is predictably and reliably effective and offers advantages in tolerability over conventional parenteral treatments is an important advance in the acute control and short-term management of the agitated psychotic patient. The value of such a formulation extends beyond the acute situation. Patients may make the transition to oral ziprasidone quickly and smoothly, once acute symptoms are controlled, which will rapidly resolve the underlying psychosis in the short term. With long-term treatment, oral ziprasidone significantly reduces core negative symptoms, improves global function, and offers significant protection against psychotic relapse while maintaining a very low liability for movement disorders and weight gain.[38] In conclusion, the rapid-acting ziprasidone i.m. formulation complements the oral formulation, extending the usefulness of ziprasidone to cover all phases in the cycle of psychotic illness.

*Drug names:* benztropine (Cogentin and others), chlorpromazine (Thorazine and others), clozapine (Clozaril and others), haloperidol (Haldol and others), lorazepam (Ativan and others), quetiapine (Seroquel), risperidone (Risperdal), temazepam (Restoril and others).



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