Efficacy of Ziprasidone Against Hostility in Schizophrenia: Post Hoc Analysis of Randomized, Open-Label Study Data

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Objective: The objective was to determine the effects of sequential intramuscular/oral ziprasidone on hostility.

Method: A total of 572 inpatients diagnosed with DSM-IV schizophrenia or schizoaffective disorder were the subjects in a randomized, rater-blinded, 6-week, open-label study comparing sequential intramuscular and oral ziprasidone with haloperidol. The Brief Psychiatric Rating Scale (BPRS) was the principal outcome measure. To determine the effect of ziprasidone on hostility, post hoc analyses of scores on the hostility item from the BPRS were conducted. Introducing positive symptoms and akathisia as covariates tested specific antihostility effect. The study was conducted from October 23, 1998, to August 15, 2000.

Results: Ziprasidone demonstrated specific antihostility effects over time throughout the 42-day study period and statistically significant superiority to haloperidol on this measure in the first week of treatment ($p = .0149$ at first evaluation [day 1, 2, or 3]; $p = .0358$ at day 7).

Conclusion: Ziprasidone is an effective treatment for hostility in patients with schizophrenia or schizoaffective disorder.

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Ziprasidone is a second-generation antipsychotic with a metabolic side effect profile that is more benign than those of other medications in its class.[1] Its antipsychotic and antimanic properties have been demonstrated in a number of double-blind randomized clinical trials.[2–5] Assessing the antiaggressive effects of antipsychotics is important for their clinical use.[6] Agitated or hostile behavior is a frequent reason for admission to a psychiatric inpatient facility. Moreover, if such behaviors continue after admission, they can prolong hospitalization and interfere with discharge. Violence by psychiatric patients in the hospital and the community is increasingly seen as a major burden for caregivers.[7]

The standard of care for agitated behavior in patients with psychotic disorders has been the short-term use of intramuscular haloperidol (at times combined with lorazepam), followed by oral antipsychotics.[8] A disadvantage in using haloperidol is its propensity to cause extrapyramidal side effects,[9] including akathisia, which in itself has been associated with aggressive behavior.[10,11] Choice of acute agent has expanded recently to include rapid-acting intramuscular formulations of second-generation antipsychotics,[12,13] and the reduction of aggressive behavior over time has been an area of study for several of the second-generation antipsychotics.[6,14,15] Clozapine has robust antiaggressive effects as demonstrated in randomized clinical trials.[15,16] Risperidone was superior to haloperidol in reducing hostility in a post hoc analysis of a registration trial[17]; however, this was not replicated in another study using a more chronically ill patient population.[15] Aripiprazole was superior to placebo but not significantly different from haloperidol in reducing hostility in a post hoc analysis of 5 short-term double-blind studies.[18] Olanzapine was superior to haloperidol (but inferior to clozapine) in reducing aggressive behavior in a randomized clinical trial that enrolled only aggressive patients.[16]

We describe a post hoc analysis of the data of a randomized open-label study that compared the efficacy of sequential intramuscular/oral administration of ziprasidone with that of haloperidol in patients with schizophrenia or schizoaffective disorder. The goal was to explore

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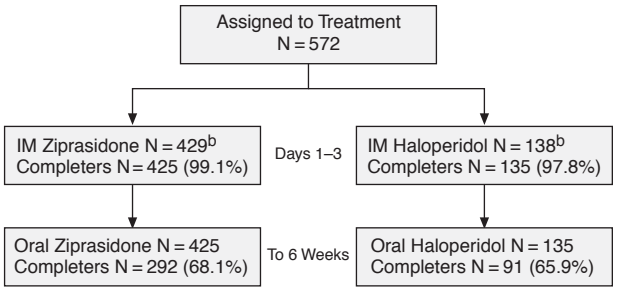
Figure 1. Disposition of Patients[a]



[a]Detailed flowchart available in Brook et al.[20]
[b]Received 1 or more doses.
Abbreviation: IM = intramuscular.

Table 1. Baseline Demographic, Clinical, and Treatment Characteristics

Characteristic	Ziprasidone (N = 429)	Haloperidol (N = 138)
Men, N (%)	286 (66.7)	91 (65.9)
Race, N (%)		
White	338 (78.8)	110 (79.7)
Black	64 (14.9)	19 (13.8)
Asian	8 (1.9)	3 (2.2)
Other	19 (4.4)	6 (4.3)
Age, mean (SD)/range, y	34.0 (10.5)/18–67	34.6 (10.5)/17–65
Schizophrenia, N (%)	384 (89.5)	121 (87.7)
BPRS total, mean (SD)	57 (10.5)	57 (9.6)
BPRS positive symptoms, mean (SD)[a]	19.44 (4.85)	19.24 (4.46)
BPRS hostility item, mean (SD)	2.82 (1.45)	2.44 (1.45)
BAS global score, mean (SD)	0.35 (0.72)	0.51 (0.86)
IM medication on day 2, N (%)	280 (65)	86 (62)
IM medication on day 3, N (%)	166 (39)	48 (35)

[a]Sum of the BPRS items of suspiciousness, grandiosity, unusual thought content, conceptual disorganization, and hallucinatory behavior.
Abbreviations: BAS = Barnes Akathisia Scale, BPRS = Brief Psychiatric Rating Scale, IM = intramuscular.

the effect of ziprasidone on hostility, using the hostility item from the Brief Psychiatric Rating Scale (BPRS).[19]

METHOD

This 42-day, international (20 countries), multicenter (76 sites) study used a randomized, parallel-group, open-label, flexible-dose design.[20] All assessments were conducted by evaluators blinded to drug allocation. The study was carried out in accordance with the Declaration of Helsinki of 1996 and with local laws and regulations. Protocols were approved by the institutional ethics committees and internal review boards. All patients provided informed written consent and agreed to at least 2 IM injections. The study was conducted from October 23, 1998, to August 15, 2000.

Hospitalized men and women aged 18 to 70 years with a diagnosis of acute exacerbation of schizophrenia or schizoaffective disorder according to DSM-IV criteria and a BPRS total score of 40 or more were eligible to participate. Patients were excluded from the study if they had been treated with an investigational agent within the past 6 months, clozapine within the past 3 months, an antipsychotic within the past 12 hours, a depot injection of an antipsychotic within the past 2 weeks (or 1 cycle), or antidepressants or mood stabilizers within the past 7 days (monoamine oxidase inhibitors and moclobemide within the past 2 weeks or fluoxetine within the past 5 weeks). Patients were also excluded from randomization if they had a history of resistance to conventional drugs on at least 2 occasions within the past 2 years, previous substance abuse within the past 3 months (or a positive urine screen for amphetamines, cocaine, or opioids), previous diagnosis of organic mental disease including mental retardation, or history of psychosurgery or presented with an immediate risk of harm to themselves or others.

Subjects were randomly assigned in a 3:1 ratio to receive either ziprasidone or haloperidol. Of the 572 randomized patients, 567 patients received 1 or more doses of medication; 429 patients received intramuscular ziprasidone for up to 3 days (initial dose of 10 or 20 mg, maximum 40 mg/day; means on days 1–3 ranged from 20.1 to 21.3 mg/day) and then oral ziprasidone (80–160 mg/day, mean [SD] 116 [30.4] mg/day), and 138 patients received intramuscular haloperidol for up to 3 days (initial dose of 2.5 or 5 mg/day, maximum 10 mg/day; means on days 1–3 ranged from 6.8 to 7.1 mg/day) and then oral haloperidol (5–20 mg/day, mean [SD] = 11.5 [3.6] mg/day). Transition from intramuscular to oral administration was done when clinically appropriate. Oral ziprasidone was started at 80 mg/day, and oral haloperidol at 10 mg/day. Permitted concurrent medications included anticholinergic medications p.r.n. (as needed) for extrapyramidal symptoms, propranolol p.r.n. for akathisia, benzodiazepines for additional sedation, and temazepam (up to 20 mg p.r.n. per night) for insomnia.

The BPRS was used at baseline; day 1, 2, or 3 (1 rating when transition to oral medication began); day 5; week 1; week 2; week 4; and week 6 or at early termination. The Barnes Akathisia Scale (BAS)[21] was used at baseline; day 1, 2, or 3 (1 rating when transition to oral medication began); week 1; week 4; and week 6 or at early termination. The study flow is summarized in Figure 1. Demographic and clinical characteristics of the patients are summarized in Table 1.

Statistical Analysis

The primary outcome measure for this post hoc analysis was the BPRS hostility item. This item is defined as

Table 2. Decreases in Hostility With Ziprasidone and Haloperidol

Day	Odds Ratio (95% CI)			p Value (ziprasidone vs haloperidol)
	Ziprasidone Improvement Over Baseline[a]	Haloperidol Improvement Over Baseline[a]	Ziprasidone vs Haloperidol[b]	
1–3 (IM period)	2.89 (2.48 to 3.38)	1.85 (1.43 to 2.39)	1.56 (1.16 to 2.11)	.0032
7	3.84 (3.12 to 4.72)	2.43 (1.73 to 3.41)	1.58 (1.06 to 2.35)	.0232
14	5.64 (4.38 to 7.27)	3.15 (2.09 to 4.75)	1.79 (1.11 to 2.90)	.0177
28	9.97 (7.12 to 13.98)	4.38 (2.53 to 7.60)	2.27 (1.20 to 4.32)	.0119
42	20.27 (13.44 to 30.59)	9.37 (4.73 to 18.57)	2.16 (0.98 to 4.77)	.0557

[a]Time effect.
[b]Treatment and time interaction effect.
Abbreviation: IM = intramuscular.

Table 3. Decreases in Hostility With Ziprasidone and Haloperidol, After Adjustment for Covariates (specific antihostility effect)

Day	Odds Ratio (95% CI)			p Value (ziprasidone vs haloperidol)
	Ziprasidone Improvement Over Baseline[a]	Haloperidol Improvement Over Baseline[a]	Ziprasidone vs Haloperidol[b]	
1–3 (IM period)	1.64 (1.38 to 1.96)	1.09 (0.81 to 1.47)	1.50 (1.08 to 2.09)	.0149
7	1.56 (1.22 to 1.99)	0.98 (0.66 to 1.46)	1.59 (1.03 to 2.47)	.0358
14	1.64 (1.21 to 2.21)	1.01 (0.62 to 1.65)	1.62 (0.95 to 2.76)	.0765
28	1.57 (1.04 to 2.36)	0.82 (0.43 to 1.56)	1.91 (0.95 to 3.83)	.0683
42	1.93 (1.16 to 3.19)	1.06 (0.49 to 2.26)	1.83 (0.80 to 4.14)	.1496

[a]Time effect.
[b]Treatment and time interaction effect.
Abbreviation: IM = intramuscular.

"animosity, contempt, belligerence, and disdain for other people outside the interview situation" and is scored on a scale ranging from 1 (indicating not present) to 7 (very severe). Safety measures included the BAS global score. The p = .05 level (2-sided) was adopted for all analyses for statistical significance.

The technique of generalized estimating equations (GEE) was adopted as the principal statistical approach for this analysis. GEE is a method of analyzing categorical data (binary or polychotomous). This method is an extension of traditional linear repeated-measures models to handle nonnormally distributed categorical data. Since the hostility item is essentially a polychotomous categorical variable, GEE permitted appropriate analysis of change in the presence of a very skewed distribution of the hostility variable. Treatment group was used as the between-subject variable. Time served as the within-subject (repeated-measures) factor. The time (overall change over time) and the interaction effect between group and time (group difference in change over time) constituted the main effects of interest in the analysis.

The effect size for change in hostility status over time was estimated using the odds ratios (ORs) computed from the GEE. The analysis comparing ziprasidone with haloperidol was set up so that the OR indicates the likelihood (odds) of shifting 1 point down on the hostility item in the ziprasidone group compared to the haloperidol group (thus an OR > 1 would indicate superiority for ziprasidone).

Controlling for general antipsychotic effect, as well as akathisia, permitted the testing for specific antihostility effect. Controlling general antipsychotic effect was done by introducing into the model the change in the sum of the BPRS items of suspiciousness, grandiosity, unusual thought content, conceptual disorganization, and hallucinatory behavior as a single covariate. For akathisia, this was accomplished by introducing the BAS global score as a covariate.

RESULTS

Efficacy

Without accounting for any covariates, both the ziprasidone group and the haloperidol group improved with respect to hostility over time. However, ziprasidone was superior to haloperidol in the likelihood of reduction of hostility, as noted by OR > 1 for the effect of treatment and time (Table 2). Statistically significant differences are maintained until day 42, at which point the differences reached trend levels (p = .0557).

When BPRS positive symptoms (suspiciousness, grandiosity, unusual thought content, conceptual disorganization, and hallucinatory behavior) and akathisia were added as covariates, only the ziprasidone group demonstrated a statistically significant improvement over time. The OR favoring ziprasidone over haloperidol (effect of treatment and time) remained > 1 and remained statistically significant until day 14 (Table 3).

Safety

Mean (SD) baseline BAS global scores were 0.51 (0.86) for haloperidol and 0.35 (0.72) for ziprasidone.

Mean endpoint change for haloperidol was 0.41 (1.09), indicating worsening of akathisia (paired t test, $t = 4.32$, $p < .0001$). Mean endpoint change for ziprasidone was –0.03 (0.82), indicating non–statistically significant improvement ($t = 0.72$, $p = .4739$). The worsening of akathisia with haloperidol compared to ziprasidone's neutral effect was statistically significant as early as on transition from intramuscular to oral treatment during days 1 through 3 (mean [SD] change at days 1–3 was 0.30 [0.81] for haloperidol, indicating worsening [paired t test, $t = 4.24$, $p < .0001$]); mean change for ziprasidone was –0.02 (0.55), indicating non–statistically significant improvement ($t = 0.63$, $p = .5319$). Incidence of new cases for treatment-emergent akathisia was 32.6% and 13.2% in the haloperidol and ziprasidone groups, respectively. The corresponding proportions of patients who experienced resolution of akathisia were 17.5% and 46.8%.

Because of the baseline differences in the BAS global scores between the ziprasidone and haloperidol groups, we conducted additional tests. Analysis of covariance using the baseline BAS score in order to adjust for the baseline difference did not substantially impact the results we have reported. In another test, we stratified the sample based on baseline presence or absence of akathisia. A 2-way analysis of variance confirmed that ziprasidone was associated with less akathisia overall and that ziprasidone's superiority to haloperidol for akathisia was heightened in the group with baseline akathisia. In addition, haloperidol appears to cause deterioriation in akathisia more or less uniformly across baseline severities, whereas ziprasidone produces improvement in those who initially had akathisia and leads to no (or very little) deterioration in those who initially had no akathisia (incidence of new cases is low).

DISCUSSION

We have demonstrated that ziprasidone's specific effect on hostility is superior to that for haloperidol, even after correcting for the akathisia observed in the latter group. These results also demonstrate that sequential intramuscular to oral treatment using ziprasidone is associated with continued improvement of hostility. Transition to oral ziprasidone was initiated at a dose of 40 mg b.i.d. Unanswered is whether starting oral ziprasidone at a dose higher than 40 mg b.i.d. would have resulted in enhanced efficacy in this population (and/or a higher rate of adverse effects).

Although we did not directly measure overt acts of aggression, the hostility item of the BPRS (or of the Positive and Negative Syndrome Scale [PANSS][22]) has been extensively used as a proxy measure to estimate potential antiaggressive effects of antipsychotics.[15,17,23] Clinical experience as well as empirical evidence[24] indicates that increased hostility may precede overt aggression.

Our report is consistent with the idea that, in general, second-generation antipsychotics are superior to haloperidol in specific antihostility effect.[15–17] Our report is also consistent with a double-blind randomized clinical trial of sequential intramuscular/oral olanzapine compared with haloperidol in which patients received injections in the first 24 hours and oral treatment for the following 4 days.[25] Both groups experienced an alleviation of agitation as measured by the excited component of the PANSS, but olanzapine had a more favorable extrapyramidal symptom safety profile than haloperidol.

Limitations of our study include the lack of a double-blind design. In addition, the patients in our study were not specifically selected for a history of hostile and aggressive behavior, and their baseline levels of hostility were accordingly not high. Therefore, the results may not be generalizable to seriously aggressive patients. Furthermore, the results may not generalize to treatment-resistant patients. However, a recent naturalistic observational study supports the effectiveness of intramuscular ziprasidone (20 mg) in the real-world emergency department setting.[26] A possible limitation of our study is the initial dose of haloperidol (2.5 mg or 5 mg IM, and a daily maximum of 10 mg IM). This dose range may appear low, but is in line with contemporary international usage patterns,[27,28] and the 2.5-mg dose is appropriate when treating older patients (the study permitted patients up to the age of 70 years).

CONCLUSION

Ziprasidone is an effective treatment of hostility in patients with schizophrenia or schizoaffective disorder. Sequential intramuscular/oral ziprasidone was superior to haloperidol in reducing hostility, with a specific antihostility effect evident in the first week of treatment. Ziprasidone was also superior to haloperidol in terms of tolerability. Appropriately powered head-to-head double-blind randomized clinical trials comparing sequential intramuscular/oral use of the new second-generation antipsychotics, with haloperidol as an active control, would be desirable.

Drug names: aripiprazole (Abilify), clozapine (Clozaril, FazaClo, and others), fluoxetine (Prozac and others), haloperidol (Haldol and others), lorazepam (Ativan and others), olanzapine (Zyprexa), propranolol (Inderal, Innopran, and others), risperidone (Risperdal), temazepam (Restoril and others), ziprasidone (Geodon).

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