Differential Response to Treatment Across Countries in a Randomized Clinical Trial of Ziprasidone and Haloperidol in Patients With Bipolar Mania

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ABSTRACT

Introduction: International trials are designed to reduce inter-country differences in operation, but regional prescribing practices and cultural differences may affect outcomes. Results from a study on the treatment of acute mania in the United States (US), Russia, and India revealed country variations in outcomes and adverse events. The placebo response was highest in the US and post hoc analyses examined demographic disparities, and differences in outcome and discontinuations in patients treated with ziprasidone or haloperidol.

Methods: Data from a 12-week, double-blind, 2-part study in 438 adults with acute bipolar mania were analyzed. Patients received flexibly dosed ziprasidone (80–160 mg/d), haloperidol (8–30 mg/d), or placebo for the first 3 weeks, followed by maintenance treatment with ziprasidone (40–160 mg/d) or haloperidol (8–30 mg/d) for 9 weeks. Baseline values, discontinuations, adverse events, and Mania Rating Scale (MRS) scores were assessed by country.

Results: Mean weight at baseline was significantly higher in the US (82.4 kg) and Russia (73.9 kg) than in India (57.1 kg). The mean dose of ziprasidone at week 3 was 128.4 mg in India, 121.8 mg in Russia, and 126.5 mg in the US and the mean dose of haloperidol was 20.7 mg/d in India, 15.2 mg/d in Russia and 15.3 mg/d in the US. Baseline MRS scores were higher in India (34.4) than in Russia (28.0) or the US (23.8). MRS change at week 3 was higher in India (ziprasidone –11.8; haloperidol –19.1) than in the US (ziprasidone –11.7; haloperidol –13.2) and Russia (ziprasidone –8.1; haloperidol –13.6). Fewer patients discontinued in Russia (ziprasidone 44.6%; haloperidol 21.8%) than in India (ziprasidone 67.8%; haloperidol 52.2%) or the US (ziprasidone 62.5%; haloperidol 85.1%). Mean time to discontinuation with ziprasidone was 63.8 ± 4.0 (Russia), 43.8 ± 3.5 (India), and 46.2 ± 4.6 days (US) and with haloperidol was 74.9 ± 4.0 (Russia), 60.5 ± 4.1 (India), and 32.9 ± 5.1 (US).

Conclusions: Differences among these countries in discontinuations, time to discontinuation, and drug treatments highlights the need for research into the cultural differences and health care systems available in these countries and their impact on clinical trials results.

BACKGROUND

- International trials are designed to be conducted in the same manner across all countries; however, prescribing practices and cultural differences may affect enrollment and outcomes
- This may have implications for design of international clinical trials and also for drug development
- Following an exploratory analysis of the results of a recent controlled study on the treatment of acute mania in India, Russia, and the United States that revealed some variation in outcomes and adverse events results between countries, we conducted further post hoc analyses of the data
- We were particularly interested in the higher placebo response observed in the United States, which initially appeared to correlate with the findings of Sysko and Walsh[1,2]

OBJECTIVE

- Our post hoc analyses of the data from a controlled study on the treatment of acute mania were designed to examine demographic disparities and further probe differences in outcome and discontinuations in patients treated with placebo, ziprasidone, or haloperidol in India, Russia, and the United States
- Assess whether these differential responses are likely to impact the methodology and results of clinical trials

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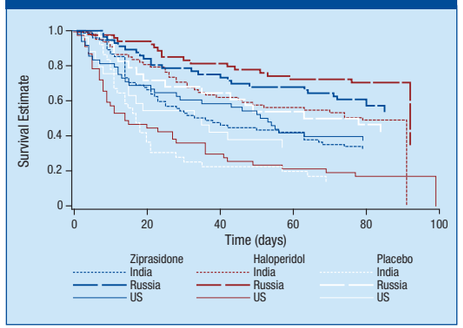
METHODS

- Data from a 12-week, double-blind, 2-part study in 438 adults with acute bipolar mania were analyzed
- During the first 3 weeks patients received flexibly dosed ziprasidone (80–160 mg/d), haloperidol (8–30 mg/d), or placebo
- During the subsequent 9-week maintenance phase patients either continued with ziprasidone (40–160 mg/d) or continued with haloperidol (8–30 mg/d)
- Baseline values, response measured by Mania Rating Scale (MRS) scores, and discontinuations were assessed on a country-wide basis
- For inclusion in this trial patients were required to have an MRS score > 14 at screening with scores of ≥ 2 on at least 4 items

Statistical Analyses

- Kaplan-Meier analyses were conducted on time to discontinuation for each treatment group (Figure 1); country and quartile estimates as well as mean and standard error of the mean (SEM) values were determined for each country
- *P* values from placebo responder rates were determined using a Fisher exact test

Figure 1. Kaplan-Meier Curves for Discontinuations Over Time by Country and Treatment

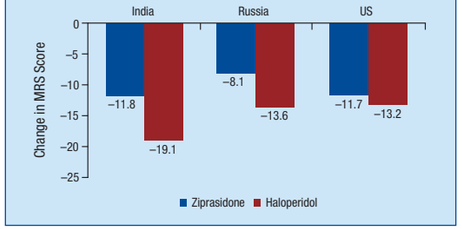


RESULTS

Efficacy

- Baseline MRS scores were higher in India (34.4) than in Russia (28.0) or the United States (23.8)
- Within-group MRS change at week 3 was higher in India (ziprasidone –11.8; haloperidol –19.1) than in the United States (ziprasidone –11.7; haloperidol –13.2) and Russia (ziprasidone –8.1; haloperidol –13.6) (Figure 2)

Figure 2. Change in MRS Score at Week 3 Following Treatment With Ziprasidone or Haloperidol by Country



Placebo Response

- Response was classified as a change in MRS score from baseline to visit of ≥ 50%
- The United States consistently had the highest placebo response with the exception of week 1 day 7 (Table 1)
- For weeks 2 and 3 placebo response was comparable between India and Russia (Table 1)

Table 1. Placebo Responders by Country

Visit	India n (%)	Russia n (%)	US n (%)	*p* Value
Day 2	0	0	1 (4.2)	0.27
Day 4	3 (8.3)	0	3 (12.5)	0.17
Day 7	5 (13.9)	0	3 (8.8)	0.11
Week 2	5 (13.9)	3 (10.7)	7 (29.2)	0.23
Week 3	7 (19.4)	4 (14.2)	7 (29.2)	0.42

Dosage

- Mean dose of ziprasidone at week 3 was 128.4 mg in India, 121.8 mg in Russia, and 126.5 mg in the United States (Table 2)
- Mean dose of haloperidol at week 3 was 20.7 mg/d in India, 15.2 mg/d in Russia, and 15.3 mg/d in the United States (Table 2)

Demographics

- A total of 437 patients were included in the post hoc analysis (Table 2)
- Mean weight at baseline was considerably higher for patients from the United States (82.4 kg) and Russia (73.9 kg) than for patients from India (57.1 kg) (Table 2)

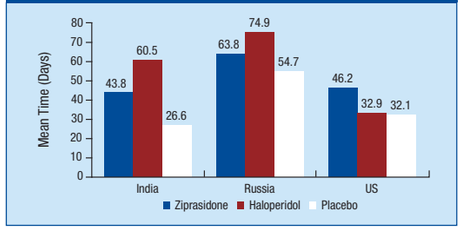
Table 2. Patient Demographics and Drug Dosage

	India	Russia	US
Number of patients, n	179	139	119
Ziprasidone	74	56	48
Haloperidol	69	55	47
Placebo	36	28	24
Mean baseline weight, kg	57.1	73.9	82.4
Mean dosage (week 3), mg/d			
Ziprasidone	128.4	121.8	126.5
Haloperidol	20.7	15.2	15.3

Discontinuation

- Fewer patients discontinued in Russia (ziprasidone 44.6%; haloperidol 21.8%) than in India (ziprasidone 67.8%; haloperidol 52.2%) or the United States (ziprasidone 62.5%; haloperidol 85.1%)
- Mean time to discontinuation (± SEM) with ziprasidone was 43.8 ± 3.5 (India), 63.8 ± 4.0 (Russia), and 46.2 ± 4.6 days (United States) and with haloperidol was 60.5 ± 4.1 (India), 74.9 ± 4.0 (Russia), and 32.9 ± 5.1 (United States) (Figure 3)

Figure 3. Mean Time to Discontinuation by Country



- For ziprasidone-treated patients, the median time until discontinuation in the United States was 52 days, whereas for India it was 34.5 days and less than 50% of the patients in Russia discontinued (no median is estimable) (Table 3)
- For haloperidol patients, the median time until discontinuation in the United States was 14 days, whereas, for India it was 79 days and for Russia it was 92 days (Table 3)
- For placebo patients, the median time until discontinuation in the United States was 34 days, for India it was 17 days, and for Russia it was 70.5 days (Table 3)
- Total discontinuations and discontinuations due to AEs are shown in Table 4

Table 3. Median Time to Discontinuation by Country and Treatment

	Treatment		
	Ziprasidone	Haloperidol	Placebo
India			
Median time to discontinuation, days	34.5	79	17
95% CI median	23–63	45–91	12–21
% discontinuation	67.57	52.17	86.11
Russia			
Median time to discontinuation, days	n/e	92	70.5
95% CI median	71–n/e	92–n/e	35–n/e
% discontinuation	44.64	21.81	57.14
US			
Median time to discontinuation, days	52	14	34
95% CI median	28–n/e	9–28	15–n/e
% discontinuation	62.50	85.11	66.67
p value	0.0117	< 0.0001	0.0092

CI, confidence interval; n/e, not estimable (eg, not enough patients discontinued to estimate the parameter of interest, median or upper limit of the median).

Table 4. Total Discontinuations and Discontinuations Due to AEs by Country and Treatment

	Ziprasidone n (%)	Haloperidol n (%)	Placebo n (%)
Discontinuations due to AEs related to study drug			
India	7 (3.9)	13 (7.6)	1 (1.1)
Russia	4 (2.2)	4 (2.3)	1 (1.1)
US	3 (1.7)	12 (7.0)	0
Discontinuations due to AEs not related to study drug			
India	2 (1.1)	3 (1.8)	1 (1.1)
Russia	0	3 (1.8)	1 (1.1)
US	1 (0.6)	1 (0.6)	0
Total discontinuations			
India	50 (28.1)	36 (21.1)	31 (35.2)
Russia	25 (14.0)	17 (9.9)[a]	16 (18.2)
US	30 (16.9)	40 (23.4)	16 (18.2)

[a]1 patient in this treatment group died.

DISCUSSION

- Our investigation has highlighted some variations in both baseline patient demographics and treatment response to ziprasidone, haloperidol, and placebo between countries
- While the inclusion criteria required MRS scores of > 14, the baseline MRS scores were considerably higher in India (34.4) than in Russia (28.0) or the United States (23.8); whether this is the result of prioritization of patients with more severe disease in India, or due to other influences, warrants further investigation
- There are large differences in weight of patients among countries, particularly between India and Russia. Although the doses do not appear to have been corrected for weight, the use of higher doses in India in particular may also be the result of differences in culture and psychiatry methodology
- Although there are numerically large differences in placebo response across countries, the power was insufficient to demonstrate signficance
- The lack of consistency in dosage between countries appears to be driving a difference in outcomes; however, the differential response may also be attributed to the severity of mania at baseline, where a greater response is observed with increasing baseline severity of mania
- Discontinuations differ by country in both number and time to discontinuation, which could indicate a cultural difference in tolerance of side effects, since the Indian population appears to tolerate side effects far better than patients from Russia and the United States
- Different cultures may also respond differently to being in a clinical trial, as evidenced by the disproportionately high placebo response observed in the United States. It would be interesting to examine the placebo response between countries further, to clarify whether this is indeed a cultural issue or a methodologic issue bound up in the inherent design of the trial[2,3]
- While psychiatry is well established in Western countries, it is still an evolving specialism in India, where the number of psychiatry training institutions is quite low
- This, in combination with the lack of a coherent approach to psychiatry in India, may have a bearing on the higher baseline MRS severity and the higher dosages prescribed throughout the trial as well as the apparent higher tolerance of unpleasant AEs[4]
- Since there is a move toward globalization of clinical trials, these differences may have considerable implications for clinical study design

CONCLUSIONS

- Within each treatment group there is a significant difference in the distribution of time until discontinuation by country, which indicates a need for further research to determine whether this is the result of cultural differences, baseline MRS severity differences, or differing health care practices among these countries
- Differential country responses, particularly in placebo response, discontinuation rates, and persistence with treatment, need to be fully explained so that international and intercontinental clinical trials may be designed to ensure globally useful results
- Further analyses into dose:weight ratios may be valuable in determining whether the higher efficacy observed in India is a result of the higher dose per kilogram, is related to the MRS severity at baseline, or is due to cultural differences among countries

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