A 12-Week, Randomized, Double-Blind, Placebo-Controlled, Sequential Parallel Comparison Trial of Ziprasidone as Monotherapy for Major Depressive Disorder

George I. Papakostas, MD; Ottavio V. Vitolo, MD; Waguih W. IsHak, MD; Mark H. Rapaport, MD; John M. Zajecka, MD; Gustavo Kinrys, MD; David Mischoulon, MD; Samuel H. Lipkin, BA; Katherine A. Hails, BA; Jonah Abrams, BA; Sean G. Ward, MBA; Allison Meisner, MA; David A. Schoenfeld, PhD; Richard C. Shelton, MD; Andrew Winokur, MD; Mahmoud S. Okasha, MD; Mohammed A. Bari, MD; and Maurizio Fava, MD

ABSTRACT

Objective: To study ziprasidone monotherapy for major depressive disorder, defined according to the *DSM-IV*.

Method: One hundred twenty outpatients were enrolled between June 2008 and September 2010 in a 12-week study that was divided into two 6-week periods according to the sequential parallel comparison design. Patients were randomized in a 2:3:3 fashion to receive ziprasidone for 12 weeks, placebo for 6 weeks followed by ziprasidone for 6 weeks, or placebo for 12 weeks. The main outcome measure was the 17-item Hamilton Depression Rating Scale (HDRS-17), with the Quick Inventory of Depressive Symptomatology, Self-Rated (QIDS-SR), and Clinical Global Impressions-Severity of Illness scale (CGI-S) serving as the study secondary measures.

Results: One hundred twenty patients (53 women [44.1%]) were randomized to treatment. The mean (SD) age of these patients was 43.7 (11.0) years. Mean (SD) baseline HDRS-17, CGI-S, and QIDS-SR scores were 19.9 (5.0), 4.3 (0.6), and 15.6 (3.0), respectively. There was no statistically significant difference in reduction of depressive symptoms, response rates, or remission rates between ziprasidone- or placebo-treated patients. This was true for both the study primary as well as secondary outcome scales.

Conclusions: In conclusion, treatment with ziprasidone monotherapy was not associated with any statistically significant advantage in efficacy over placebo. Although studies involving larger sample size would be required to have adequate statistical power to detect treatment differences smaller than 2.5 points on the HDRS-17, such differences would be of questionable clinical relevance.

Trial Registration: ClinicalTrials.gov identifier: NCT00555997

J Clin Psychiatry 2012;73(12):1541–1547

Submitted: *January 24, 2012; accepted August 15, 2012 (doi:10.4088/JCP.12m07670).*
Corresponding author: *George I. Papakostas, MD, Center for Treatment-Resistant Depression, Depression Clinical and Research Program, Massachusetts General Hospital, Harvard Medical School, One Bowdoin Sq, 6th Floor, Boston, MA 02114 (gpapakostas@partners.org).*

Despite the progressive increase in the number of pharmacologic agents with antidepressant activity,[1] converging evidence suggests that a substantial proportion of patients suffering from MDD remains symptomatic despite treatment. For example, in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial, Trivedi et al[2] studied 2,876 outpatients with major depressive disorder (MDD) who received open-label treatment with citalopram and reported remission rates of 28%–33%. Similarly, Petersen et al[3] report a 20.5%–30.7% remission rate among outpatients with MDD enrolled in 1 of 2 hospital-based, academically affiliated depression specialty clinics following a single treatment. Clearly, in light of the treatment challenge that MDD poses to clinicians and patients alike, novel treatment strategies for MDD are needed to enhance the care of patients with depression.

A review of the pharmacodynamic properties of atypical antipsychotic agents suggests that some of them possess a spectrum of activity consistent with that observed with antidepressant medications.[4] As a result, the atypical antipsychotics have emerged as a popular *adjunctive therapy* for nonpsychotic MDD.[5] Although the majority of trials involving the use of the atypicals in MDD have focused on their use as adjunctive therapy, it is quite possible that some of the atypical antipsychotic medications might represent effective monotherapy options for MDD.

Atypical antipsychotic medications are a heterogeneous group of agents with complex pharmacokinetic and pharmacodynamic profiles that modulate a wide array of neurotransmitter networks in the brain, including dopamine, serotonin, norepinephrine, histamine, acetylcholine, and glutamate. More specifically, all atypicals, to different degrees, act as serotonin-2 (5-HT_2) receptor antagonists.[6,7] Ziprasidone possesses the highest $5\text{-HT}_{2A}/D_2$ affinity ratio of all US Food and Drug Administration (FDA)–approved antipsychotic medications.[6,8] This is of potential relevance to the treatment of MDD, since 5-HT_{2A} receptor antagonists, such as trazodone[9] and nefazodone,[10] have demonstrated antidepressant efficacy. In addition, ziprasidone, like risperidone, acts as a 5-HT_{1D} antagonist while, similar to aripiprazole, ziprasidone also acts as a 5-HT_{1A}-receptor partial agonist.[6] Serotonin-1D is a presynaptic autoreceptor that inhibits serotonin release. Blockade at this site enhances serotonin transmission, which may confer antidepressant efficacy.[11] Serotonin-1A receptor partial agonists, such as gepirone,[10] buspirone,[12] ipsapirone,[13] and zalospirone[14] have demonstrated antianxiety and antidepressant properties. Animal studies provide evidence directly implicating the role of 5-HT_{1A}[15–20] receptors in atypical antipsychotic–induced central nervous system monoamine release. Ziprasidone increases dopamine, norepinephrine, and serotonin

concentrations in several brain areas involved in the regulation of mood, including the prefrontal cortex, nucleus accumbens, hippocampus, and striatum.[15,19–21] Most importantly, with respect to antidepressant efficacy, ziprasidone has been shown (in vitro) to inhibit the neuronal uptake of serotonin and norepinephrine, with potency comparable to that of the antidepressants imipramine and desipramine,[22] as well as to inhibit the neuronal uptake of dopamine properties, which also set it apart from the other atypical agents.[8] Taken together, the unique properties of ziprasidone on monoaminergic receptors and transporters suggest that it may be an efficacious monotherapy for patients with MDD.

In summary, in light of the challenge MDD poses to clinicians and patients alike, identifying novel treatments is urgently needed to help further refine the standard of care. Judging by their rich receptor-binding profile as well as their effects on brain neurotransmitter concentrations, the atypical antipsychotic agents offer a spectrum of activities prognostic of antidepressant efficacy. Because of its unique affinity for several monoaminergic receptors and transporters, the atypical antipsychotic agent ziprasidone appears to be particularly suited for study as monotherapy in MDD. In this report, we describe results from a 12-week, multisite, randomized, double-blind, placebo-controlled trial of oral ziprasidone as monotherapy for the treatment of MDD. In order to enhance the statistical power of our study to detect a difference in antidepressant effect between drug and placebo, the sequential parallel comparison design (SPCD)[23] was selected as the preferred study design.

METHOD

This study was a multicenter, 12-week, randomized, double-blind, SPCD trial of ziprasidone monotherapy for MDD (ClinicalTrials.gov identifier: NCT00555997). The study was conducted at the following sites: Massachusetts General Hospital (principal investigator: G.I.P.), Cedars-Sinai Medical Center (principal investigator: W.W.I.), Cambridge Health Alliance (principal investigator: G.K.), Vanderbilt University (principal investigator: R.C.S.), Synergy Research Center (principal investigator: M.A.B.), Comprehensive Psychiatric Care (principal investigator: M.S.O.), Rush University (principal investigator: J.M.Z.), and the University of Connecticut (principal investigator: A.W.).

Institutional review board–approved written informed consent was obtained from all study patients before any study procedures were conducted. Eligibility was assessed by trained psychiatrists, primarily, during the screening visit, and, secondarily, during the baseline visit, which occurred 14 days after the screening visit.

Inclusion Criteria

Patients were eligible for study participation if they were between the ages of 18–65 years; met criteria during the screening and baseline visits for MDD, current according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*), as diagnosed by the Mini-International Neuropsychiatric Interview[24]; and scored at least 10 at both screening and baseline visits on the Quick Inventory of Depressive Symptomatology, Self-Rated (QIDS-SR).[25]

Exclusion Criteria

Patients were excluded from the study if they were taking antidepressant, antipsychotic, or anticonvulsant agents up to 2 weeks prior to the screening visit and if they had been taking lithium up to 2 weeks prior to the screening visit. Patients receiving psychotherapy were also excluded. Breastfeeding women, pregnant women, and women of childbearing potential who were not using a medically accepted means of contraception were excluded, as well as patients who demonstrated a greater than 25% decrease in depressive symptoms as reflected by the QIDS-SR total score between the screening and baseline visits. Patients who were at serious risk for suicide or homicide, had unstable medical illness as assessed by an evaluating clinician, or had active alcohol or drug use disorders within the month prior to screening were excluded. Patients were also excluded if they had a history of mania, hypomania (including antidepressant-induced), psychotic symptoms, or seizure disorder, as well as patients with significant cardiac conduction problems on screening electrocardiogram, such as atrial fibrillation, atrial flutter, atrioventricular block, prolonged or abnormal QTc interval (ie, QTc >450 milliseconds), or prolonged QRS interval. In addition, patients who had suffered a myocardial infarction within the past 12 months, with uncompensated heart failure, or a history of QTc prolongation were excluded. Patients were also excluded if they were found to have abnormal serum potassium or magnesium levels upon screening. Patients who were currently taking other drugs that prolong the QTc, including dofetilide, sotalol, quinidine, class IA antiarrhythmics, class III antiarrhythmics, mesoridazine, thioridazine, chlorpromazine, droperidol, pimozide, sparfloxacin, gatifloxacin, moxifloxacin, halofantrine, mefloquine, pentamidine, arsenic trioxide, levomethadyl acetate, dolasetron mesylate, probucol, or tacrolimus were excluded, as were patients who demonstrated clinical evidence of untreated hypothyroidism. Also excluded were patients who had failed to experience sufficient symptom improvement following more than 2 antidepressant trials during the current major depressive episode, who had had a course of ziprasidone or intolerance to ziprasidone at any dose, or who had used any investigational psychotropic drug within the last 3 months.

Study Procedures

Patients found eligible during the baseline visit were enrolled and randomized according to the SPCD model in a 2:3:3 fashion. The study was divided into two 6-week phases. One group (randomization probability 3:8) received oral placebo during phases I and II (placebo-placebo group). The second group (randomization probability 3:8) received placebo during phase I and ziprasidone during phase II (placebo-drug group). The third group (randomization probability 2:8) received ziprasidone during phases I and II. Postbaseline study visits occurred every 7 days, with a study

visit window of ± 3 days. Ziprasidone was initiated at 20 mg by mouth twice a day and increased, at the treating psychiatrist's clinical discretion, by weekly increments of 20 mg by mouth twice a day to a maximum of 80 mg by mouth twice a day. Decreases in ziprasidone dose were allowed for reasons of intolerance. However, subjects unable to tolerate at least 20 mg by mouth twice a day of ziprasidone were withdrawn from the study. Placebo-treated subjects followed a similar titration schedule.

Trained psychiatrists (MD degree) administered the 17-item Hamilton Depression Rating Scale (HDRS-17)[26] QIDS-SR, and Clinical Global Impressions-Severity of Illness and -Improvement scales (CGI-S and CGI-I)[27] during all postscreening visits.

General Statistical Considerations

The primary outcome measure for this study was the difference in the degree of change in HDRS-17 scores during treatment between the 2 treatment groups. The sample size of the study was selected based on power calculations with specific assumptions about response rates in the 2 phases, according to the SPCD analytic method described in Fava et al.[23] Secondary outcome measures included continuous change in QIDS-SR and CGI-S scores during treatment. Additional secondary outcome measures also included the proportion of patients meeting response criteria according to the HDRS-17 or QIDS-SR (50% or greater reduction in scores during treatment regardless of whether remission status has been achieved), remission status according to the QIDS-SR (final score of 5 or less), and remission status according to the HDRS-17 (final score of 7 or less). Definitions of response and remission were not mutually exclusive.

SPCD Analysis Model

A standard, intent-to-treat (ITT)/last-observation-carried-forward (LOCF) analysis approach was employed for phase I. According to the SPCD model, the phase II dataset of interest was limited to patients treated with placebo during phase I who completed phase I and did not experience a clinical response (response defined as a reduction ≥ 50% from baseline) according to the HDRS-17 during phase I. Drug was compared to placebo in phase II for this patient subset alone. The ITT/LOCF approach was then applied to the analysis of the phase II dataset, as defined by the SPCD, with the final visit of phase I/first visit of phase II serving as the baseline visit for phase II. Finally, data comparing drug and placebo during phase I were combined with data comparing drug and placebo according to the SPCD model for phase II and analyzed according to the statistical model described by Fava et al[23] by using a weight, "w," and a randomization fraction, "a," chosen to maximize the power of the test. When calculating the pooled treatment effect from treatment effects obtained in phases I and II, equal weights were given for each phase.

Dichotomous measures were analyzed as described in Fava et al.[23] A seemingly unrelated regression, controlling for baseline scores, was employed for the comparison of continuous outcomes according to the method of Tamura and Huang.[28] All tests were conducted as 2-tailed, with α set at .05. Safety and tolerability analyses were conducted based on all data available (all patients randomized, all study visits).

Table 1. Discontinuation Rates

Reason for Discontinuation	n
Total discontinued	
Any	37
Ziprasidone phase I	
Any	12
Lack of efficacy	2
Adverse events (insomnia and sedation)	2
Other (withdrawal of consent for unknown reasons)	1
Lost to follow-up	7
Placebo phase I	
Any	15
Lack of efficacy/worsening symptoms	2
Adverse events (tooth pain, upper respiratory infection, headache, insomnia)	4
Other (withdrawal of consent, schedule conflict)	3
Lost to follow-up	6
Ziprasidone phase II	
Any	7
Lack of efficacy	1
Adverse events (orthostatic hypotension)	1
Noncompliance	1
Lost to follow-up	4
Placebo phase II	
Any	3
Lack of efficacy	1
Other (moved out of state)	1
Lost to follow-up	1

Power Calculation

Given a total sample size of 120 and utilizing the present allocation scheme to 1 of 3 treatment groups, setting α at .05 for a 2-tailed test, and assuming a 15% attrition rate at the end of phase I, the power of the present trial to detect a 2.5 unit difference in HDRS-17 scores between ziprasidone monotherapy and placebo would be more than 80% (assuming a marginal standard deviation in the placebo group of 6.5, a conditional standard deviation in the placebo group in phase II of 5.5, a marginal standard deviation for the ziprasidone group of 6.5, and a proportion of placebo nonresponders in phase I of 65%).

RESULTS

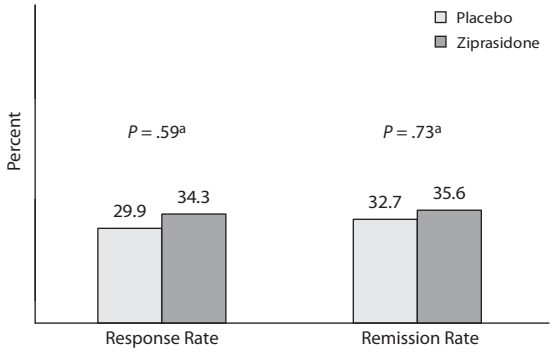
One hundred twenty patients (53 women [44.1%]) were randomized to treatment between June 2008 and September 2010. The mean (SD) age of these patients was 43.7 (11.0) years. Mean (SD) baseline HDRS-17, CGI-S, and QIDS-SR scores were 19.9 (5.0), 4.3 (0.6), and 15.6 (3.0), respectively. Twenty-nine patients were randomized to the drug-drug sequence (ziprasidone 20–80 mg by mouth twice a day in phases I and II), 48 to the placebo-drug sequence (placebo in phase I and ziprasidone 20–80 mg by mouth twice a day in phase II), and 43 to the placebo-placebo sequence (placebo in both phase I and phase II). There was no difference in mean baseline HDRS-17, QIDS-SR, or CGI-S scores between ziprasidone- and placebo-treated patients

Table 2. Efficacy Results

Outcome	Phase I Ziprasidone (n = 29)	Phase I Placebo (n = 91)	Phase II Ziprasidone (n = 21)[a]	Phase II Placebo (n = 25)[a]	Pooled Ziprasidone[b]	Pooled Placebo[b]	*P* Value[c]
Completers, n (%)	17 (58.6)	76 (83.5)	19 (90.4)	24 (96.0)			
HDRS-17							
Baseline score, mean (SD)	20.1 (5.5)	19.9 (4.8)	14.7 (3.9)	15.6 (5.9)	17.4[d]	17.7[d]	
Response, % (n)	44.8 (13)	31.8 (29)	23.8 (5)	28.0 (7)	34.3[e]	29.9[e]	.59
Remission, % (n)	37.9 (11)	25.2 (23)	33.3 (7)	40.0 (10)	35.6[e]	32.7[e]	.73
Score reduction, mean (SD)	−8.8 (7.3)	−7.1 (7.0)	−2.1 (5.2)	−4.3 (6.0)	−5.4[d]	−5.7[d]	.96
QIDS-SR							
Baseline score, mean (SD)	15.9 (2.8)	15.4 (3.1)	11.3 (3.6)	12.1 (4.7)	13.6[d]	13.7[d]	
Response, % (n)	48.2 (14)	35.1 (32)	19.0 (4)	20.0 (5)	33.6[e]	27.5[e]	.44
Remission, % (n)	31.0 (9)	23.0 (21)	38.0 (8)	28.0 (7)	34.5[e]	25.5[e]	.22
Score reduction, mean (SD)	−5.7 (5.7)	−5.2 (4.7)	−2.1 (3.9)	−2.3 (4.9)	−3.9[d]	−3.7[d]	.80
CGI-S							
Baseline score, mean (SD)	4.3 (0.7)	4.3 (0.6)	3.6 (0.8)	3.6 (0.7)	3.9[d]	3.9[d]	
Score reduction, mean (SD)	−1.2 (1.3)	−1.6 (1.3)	−0.9 (1.1)	−0.8 (1.2)	−1.0[d]	−1.2[d]	.19

[a]According to the sequential parallel comparison design model, only phase I completers/nonresponders (according to the HDRS-17) are analyzed in phase II.
[b]Pooled results from phases I and II.
[c]Sequential parallel comparison design analyses using Fava et al[23] method for dichotomous measures and Tamura and Huang[28] method for continuous measures.
[d]Value represents mean.
[e]Value represents percentage.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale; HDRS-17 = 17-item Hamilton Depression Rating Scale; QIDS-SR = Quick Inventory of Depressive Symptomatology Scale, Self-Rated.

Figure 1. HDRS-17 Response and Remission (pooled phases)



[a]Sequential parallel comparison design analysis according to Fava et al.[23]
Abbreviation: HDRS-17 = 17-item Hamilton Depression Rating Scale.

in phases I (*P* = .84, .46, and .97, respectively) or II (SPCD approach: *P* = .54, .53, and .77, respectively). Mean (SD) daily ziprasidone doses during phases I and II were 81.4 (48.3) mg and 113.8 (48.9) mg, respectively. Maximum daily doses for patients who received ziprasidone during phase I were as follows: 15 patients received 40 mg daily of ziprasidone, 3 received 80 mg daily, 6 received 120 mg daily, and 5 received 160 mg daily. Maximum daily doses for all patients who received ziprasidone during phase II were as follows: 6 patients received 40 mg daily of ziprasidone, 3 received 80 mg daily, 6 received 120 mg daily, and 11 received 160 mg daily. Discontinuation rates are reported in Table 1.

Efficacy analyses of phases I and II are reported in Table 2 and Figure 1. In summary, ziprasidone therapy did not result in superior efficacy than placebo overall or in either phase of the study with respect to primary or secondary outcome measures. *P* values for the pooled (across phases I and II) difference (ziprasidone versus placebo) in reduction in HDRS-17 scores, response rates, and remission rates were .96, .59, and .73, respectively. *P* values for the pooled (across phases I and II) difference (ziprasidone versus placebo) in reduction in QIDS-SR scores, response rates, and remission rates were .80, .44, and .22, respectively. Finally, the *P* value for the pooled (across phases I and II) difference (ziprasidone versus placebo) in reduction in CGI-S scores was .19.

Table 3. Adverse Events Reported

Adverse Event, n (%)	Placebo (n = 125)[a]	Ziprasidone (n = 80)[a]
Central nervous system		
Sedation/fatigue	3 (2.4)	13 (16.2)[b]
Headache	2 (1.6)	3 (3.7)
Insomnia	3 (2.4)	2 (2.5)
Dizziness	2 (1.6)	2 (2.5)
Blurry/double vision	2 (1.6)	2 (2.5)
Akathisia/agitation	1 (1.0)	1 (1.2)
Gastrointestinal		
Dry mouth	6 (4.8)	6 (7.5)
Constipation	3 (2.4)	3 (3.7)
Increased appetite	0 (0.0)	3 (3.7)
Nausea	2 (1.6)	1 (1.2)
Weight gain	1 (1.0)	0 (0.0)
Other		
Sexual dysfunction	2 (1.6)	1 (1.2)

[a]Because of the presence of a placebo-drug crossover group, frequency is determined by dividing the number of patients exposed to an intervention (drug versus placebo) who developed an adverse event while on that intervention divided by the total number of patients exposed to that intervention who had at least 1 postbaseline visit allowing for the assessment of adverse events. Patients who received placebo during phase I and ziprasidone during phase II who had at least 1 postbaseline assessment in phase II are counted toward placebo as well as ziprasidone. For these patients, the emergence of an adverse event is attributed to ziprasidone versus placebo depending on which period(s) it was reported. Adverse events thought by investigators to be possibly, probably, or definitely related to ziprasidone or placebo use are listed.
[b]*P* = .0007 (Fisher exact test, 2-sided). All other adverse events *P* > .05.

Study adverse events are presented in Table 3, and changes in key laboratory parameters are listed in Table 4.

Table 4. Laboratory Values at Baseline and Week 12

	Placebo[b]		Ziprasidone[b]		*P*
Variable[a]	Mean	SD	Mean	SD	Value[c]
Prolactin at baseline, ng/mL	7	3.75	8.66	7.75	.137
Prolactin at week 12, ng/mL	0.19	3.11	2.63	6.06	.019
HbA_{1c} at baseline, %	5.61	0.38	5.58	0.42	.787
HbA_{1c} at week 12, %	−0.03	0.25	0.007	0.25	.949
Glucose at baseline, mg/dL	87.14	14.07	91.53	15.43	.118
Glucose at week 12, mg/dL	−0.21	12.58	−0.6	23.37	.128
Triglycerides at baseline, mg/dL	143.19	103.54	137.16	87.43	.750
Triglycerides at week 12, mg/dL	3.83	58.36	14.64	82.4	.832
HDL cholesterol at baseline, mg/dL	47.88	14.54	49.06	15.91	.690
HDL cholesterol at week 12, mg/dL	−0.68	7.46	−0.25	8.37	.387
LDL cholesterol at baseline, mg/dL	109.15	24.95	115.06	30.55	.279
LDL cholesterol at week 12, mg/dL	1.85	16.48	−7.82	26.42	.812
Weight at baseline, lb	185.7	43.92	192.64	53.5	.460
Weight at week 12, lb	23.56	16.17	−4.82	17.82	.705
QTc at baseline, ms	412.35	18.76	411.55	18.02	.820
QTc at week 12, ms	3.15	15.85	1.98	13.9	.732
QTc endpoint > 450 ms, n	1		0		.999
QTc at week 12 > 75 ms, n	0		0		.999

[a]Change reflects difference in value for each variable from baseline to week 12.
[b]Patients received placebo for 12 weeks or ziprasidone at some point during the trial.
[c]*P* value for change baseline to week 12 is generated controlling for baseline values.
Abbreviations: HbA_{1c} = glycosylated hemoglobin, HDL = high-density lipoprotein, LDL = low-density lipoprotein.

Statistically significant differences in the probability of developing an adverse event on ziprasidone versus placebo were found only for sedation/fatigue. No statistically significant baseline differences in key laboratory values were observed between patients who received placebo throughout the trial or ziprasidone at some point during the trial. Similarly, statistically significant differences in changes in laboratory variable scores between these 2 groups were noted only for prolactin (mean increase of 2.63 ng/mL for ziprasidone versus 0.19 ng/mL for placebo, $P = .019$). A QTc greater than 450 milliseconds at endpoint (week 12) was noted only in the case of a single placebo-treated patient.

DISCUSSION

In this article, we report the results of the first placebo-controlled study ever conducted focusing on the use of ziprasidone as monotherapy in nonpsychotic MDD. The present study is also the first-ever monotherapy trial conducted employing the SPCD study design in patients with MDD. The results of the present trial do not support the efficacy of ziprasidone as monotherapy for patients with MDD. Specifically, there was no statistically significant difference in the reduction of depressive symptoms, response or remission rates between ziprasidone- or placebo-treated patients throughout the trial. This was true for both the study primary (HDRS-17) as well as the secondary outcome scales (QIDS-SR, CGI).

Ziprasidone monotherapy appeared to be relatively well tolerated, with only 3 patients discontinuing ziprasidone treatment due to adverse events. In addition, the prevalence of side effects reported by patients was relatively low, with sedation/fatigue being the only adverse event being statistically more frequent among ziprasidone- than placebo-treated patients. Finally, aside from a greater increase in serum prolactin levels among ziprasidone-treated than placebo-treated patients (approximately 2.5 ng/mL, of doubtful clinical relevance), ziprasidone-treated therapy was not more likely to result in perturbations in metabolic or cardiac conduction parameters than placebo.

Several possibilities may explain why ziprasidone was not found to be superior to placebo in MDD, despite affinity for several molecular targets known to be associated with antidepressant activity. One possibility is that the in vivo affinity of ziprasidone for the serotonin and norepinephrine transporter is not sufficient in order to bring about consistent antidepressant effects in humans. For example, the selective serotonin reuptake inhibitors have been proven to be efficacious at doses at which a minimum of 80%–85% serotonin transporter occupancy is observed in vivo.[29] Unfortunately, positron-emission tomography studies examining the degree of serotonin transporter occupancy achieved with various doses of ziprasidone have not been conducted. However, it should be pointed out that several antidepressants have been approved for MDD by the FDA that, like ziprasidone, possess affinity for the $5\text{-}HT_2$ receptor but, unlike ziprasidone, not the serotonin transporter (mirtazapine, nefazodone, trazodone), suggesting that monoamine transporter occupancy is not a requirement for antidepressant activity as monotherapy.

A second possibility is that doses at which ziprasidone was prescribed in the present study may have been insufficient to consistently produce an antidepressant response. This is consistent with the generally low incidence of reported adverse events during this study (with only 3 patients discontinuing ziprasidone due to adverse events) and with mean daily doses of ziprasidone being less than 120 mg (study maximum daily dose allowed was 160 mg). In order to optimize tolerability, we chose a flexible dosing schedule for the present study, and perhaps future studies should employ a more assertive dosing schedule (eg, studies that did demonstrate superiority for quetiapine versus placebo were designed to achieve target doses of 150 mg or 300 mg daily within days[30]).

A third possibility is that relatively high pooled placebo response and remission rates in phase II (29.9% and 32.7%) prevented us from detecting a statistically significant efficacy advantage of ziprasidone versus placebo in this study. Contrary to all recent SPCD trials (which include in phase II as nonresponders only those subjects with certain minimal depression severity, such as a HDRS-17 score ≥ 16), this SPCD trial involved the use of a severity threshold for inclusion in the study but not for the selective analysis of phase II data. Since the mean HDRS-17 score at baseline was 19.9 and the inclusion of patients in phase II required nonresponse to placebo in phase I (less than 50% improvement in depressive symptoms), it is quite possible that many patients with very low severity were included in the phase II analysis (patients who inherently have high placebo response and remission rates).

In fact, the severity of patients entering phase II who were analyzed according to the SPCD was only 15.1 points on the HDRS-17. This is particularly important since, according to the SPCD, phase II data hold particular statistical weight in deriving the overall study effect size (equal weight as phase I despite fewer patients).[23] As shown in Table 2, the mean reduction in HDRS-17, QIDS-SR, and CGI-S scores observed in phase II were approximately 60.6%, 44.2%, and 50.0%, respectively, of the mean reduction in these scores observed in phase I. This suggests a significant drop in the degree of improvement with placebo in phase II compared to phase I. However, given the fact that a significant proportion of patients presented very mild severity at the baseline visit of phase II, even a relatively small reduction in scores could have led to response or remission. Future SPCD studies should clearly employ a severity threshold criterion for the inclusion of phase II data in the analysis.

Finally, it should also be pointed out that the protocol instructed for ziprasidone dose increases at 20 mg twice a day in per-week increments, with 20 mg twice a day as the starting dose. Sequential parallel comparison design phases of 6 weeks each may have been insufficient to evaluate efficacy for the subgroup of patients who required 4 dose increases (80-mg twice-a-day dose), since the titration alone would require 3 weeks, leaving only 3 weeks, at best, for evaluation of efficacy. This is particularly important since a recent meta-analysis by Tedeschini et al[31] demonstrated that the minimum adequate duration of a trial in order to reliably detect drug versus placebo differences is 4 weeks and that shortening trials to less than 4 weeks in duration would primarily increase the risk of erroneously concluding that an effective treatment is ineffective.

CONCLUSION

In conclusion, the present study found that treatment with ziprasidone monotherapy did not demonstrate any statistically significant advantage in efficacy over placebo. Possible reasons may include inadequate dosing, inadequate study duration, as well as a sizeable pooled placebo response and remission rates. Although studies involving larger sample size would be required to have adequate power to detect treatment differences smaller than 2.5 points on the HDRS-17 scores, such differences would be of questionable clinical relevance.

Drug names: aripiprazole (Abilify), arsenic trioxide (Trisenox), citalopram (Celexa and others), desipramine (Norpramin and others), dofetilide (Tikosyn), dolasetron (Anzemet), droperidol (Inapsine and others), gatifloxacin (Zymar, Zymaxid, and others), imipramine (Tofranil and others), lithium (Lithobid and others), mirtazapine (Remeron and others), moxifloxacin (Moxeza, Vigamox, and others), pentamidine (Nebupent, Pentam, and others), pimozide (Orap), quetiapine (Seroquel and others), risperidone (Risperdal and others), sotalol (Betapace, Sorine, and others), tacrolimus (Prograf, Protopic, and others), trazodone (Oleptro and others), ziprasidone (Geodon and others).

Author affiliations: Center for Treatment-Resistant Depression, Depression Clinical and Research Program (Drs Papakostas, Vitolo, Mischoulon, and Fava and Mr Lipkin and Ms Hails), Department of Psychiatry (Dr Kinrys), and Biostatistics Center (Dr Schoenfeld), Massachusetts General Hospital, Harvard Medical School; Clinical Trials Network and Institute (CTNI), Massachusetts General Hospital, (Drs Kinrys, Mischoulon, and Fava and Messrs Abrams and Ward); Department of Epidemiology, Harvard School of Public Health (Ms Meisner), Boston, Massachusetts; Department of Psychiatry and Behavioral Neurosciences, Cedars-Sinai Medical Center, and the David Geffen School of Medicine at UCLA, Los Angeles (Dr IsHak); Synergy Research Center, San Diego (Dr Bari), California; Department of Psychiatry and Behavioral Sciences, Emory School of Medicine, Atlanta, Georgia (Dr Rapaport); Department of Psychiatry, Rush University Medical Center, Chicago, Illinois (Dr Zajecka); Department of Psychiatry, Vanderbilt University School of Medicine, Nashville, Tennessee (Dr Shelton); Department of Psychiatry, University of Connecticut Health Center, Farmington (Dr Winokur); and Comprehensive Psychiatric Care, Norwich (Dr Okasha), Connecticut.

Potential conflicts of interest: Over the past 12 months, **Dr Papakostas** has served as an advisor/consultant for Brainsway Ltd, Eli Lilly, Pamlab, Takeda, Theracos, and Ridge Diagnostics; has received honoraria from AstraZeneca PLC, Hoffman-LaRoche AG, Lundbeck A/S, Otsuka, and Pfizer; and has received research support from Forest, National Institute of Mental Health (NIMH), Pamlab, Pfizer, Ridge Diagnostics, and Sunovion. Over the past 12 months, **Dr IsHak** has received research support from Pfizer. Over the past 12 months, **Dr Rapaport** has served as an advisor/consultant to the NIMH, the National Institute on Drug Abuse (NIDA), the National Center for Complimentary and Alternative Medicine, and PAX (unpaid). Over the past 12 months, **Dr Zajecka** has served as a consultant/advisor for Abbott, Pamlab, Shire, and Takeda and has received research support from AstraZeneca, Cyberonics, Hoffman-LaRoche, NIMH, Novartis, Otsuka, Pfizer, Shire, and Takeda. Although Dr Zajecka has served on the speaker's bureau for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Otsuka, and Pamlab during the past 12 months, he has divested himself of these relationships effective September 1, 2011. Over the past 12 months, **Dr Kinrys** has received research support from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Forest, and Pfizer and has also served as an advisor/consultant for AstraZeneca, Forest, and Pfizer. Over the past 12 months, **Dr Mischoulon** has received research support from the Bowman Family Foundation, Bristol-Myers Squibb, Cederroth, FisherWallace, Ganeden, Lichtwer Pharma, and Nordic Naturals; has received honoraria for consulting, speaking, and writing from Pamlab, Bristol-Myers Squibb, and Nordic Naturals; and has received royalties from Back Bay Scientific for PMS Escape, and from Lippincott Williams & Wilkins for his book, entitled *Natural Medications for Psychiatric Disorders: Considering the Alternatives*. Over the past 12 months, **Dr Schoenfeld** has served as a consultant/advisor for Averion, Gerson Lehrman Group, Guidepoint Global, Neuronova, Cytokinetics, GlaxoSmithKline, Merck, Aggennix, Pfizer, and Baker Botts and has received research support from AstraZeneca, Roche, CytRx, and ISIS. Over the past 12 months, **Dr Shelton** has served as a consultant for Eli Lilly, Cyberonics, Janssen, Medtronic, Pamlab, Pfizer, Ridge Diagnostics, and Takeda Pharmaceuticals and has received grant/research support from Bristol-Myers Squibb, Eli Lilly, Elan, Euthymics Bioscience, Forest, Janssen, Novartis, Otsuka, Pamlab, Pfizer, Repligen, Ridge Diagnostics, St. Jude Medical, and Takeda. Over the past 12 months, **Dr Okasha** has received research support from Bristol-Myers Squibb, Euthymics Bioscience, Forest Research Institute, Pfizer, and Takeda Global Research and has served as a guest speaker for Forest. In his lifetime, **Dr Fava** has received research support from Abbot Laboratories, Alkermes, Aspect Medical Systems, AstraZeneca, BioResearch, BrainCells, Bristol-Myers Squibb, CeNeRx BioPharma, Cephalon, Clinical Trials Solutions, Clintara, Covance, Covidien, Eli Lilly, ElMindA, EnVivo Pharmaceuticals, Euthymics Bioscience, Forest Pharmaceuticals, Ganeden Biotech, GlaxoSmithKline, Icon Clinical Research, i3 Innovus/Ingenix, Johnson & Johnson Pharmaceutical Research & Development, Lichtwer Pharma GmbH, Lorex Pharmaceuticals, National Alliance for Research on Schizophrenia & Depression, National Center for Complementary and Alternative Medicine, NIDA, NIMH, Novartis AG, Organon, Pamlab, Pfizer, Pharmavite, Photothera, Roche, RCT Logic, Sanofi-Aventis, Shire, Solvay, Synthelabo, and Wyeth-Ayerst; has been a consultant or advisor to Abbott, Affectis AG, Alkermes, Amarin Pharma, Aspect Medical Systems, AstraZeneca, Auspex, Bayer AG, Best Practice Project Management, BioMarin Pharmaceuticals, Biovail, BrainCells, Bristol-Myers Squibb, CeNeRx BioPharma, Cephalon, Clinical Trials Solutions, CNS Response, Compellis, Cypress, DiagnoSearch Life Sciences (P), Dainippon Sumitomo Pharma, Dov, Edgemont, Eisai, Eli Lilly, EnVivo, ePharmaSolutions, EPIX, Euthymics Bioscience, Fabre-Kramer, Forest, GenOmind, GlaxoSmithKline, Grunenthal GmbH,

i3 Innovus/Ingenis, Janssen, Jazz, Johnson & Johnson Pharmaceutical Research & Development, Knoll, Labopharm, Lorex, Lundbeck, MedAvante, Merck, MSI Methylation Sciences, Naurex, Neuronetics, NextWave Pharmaceuticals, Novartis AG, Nutrition 21, Orexigen Therapeutics, Organon, Otsuka, Pamlab, Pfizer, PharmaStar, Pharmavite, PharmoRx Therapeutics, Precision Human Biolaboratory, Prexa Pharmaceuticals, Puretech Ventures, PsychoGenics, Psylin Neurosciences, Rexahn, Ridge Diagnostics, Roche, RCT Logic, Sanofi-Aventis, Sepracor, Servier, Schering-Plough, Solvay, Somaxon, Somerset, Sunovion, Supernus, Synthelabo, Takeda, Tal Medical, Tetragenex, TransForm, Transcept, and Vanda; has received speaking/publishing fees from Adamed, Advanced Meeting Partners, American Psychiatric Association, American Society of Clinical Psychopharmacology, AstraZeneca, Belvoir Media Group, Boehringer Ingelheim GmbH, Bristol-Myers Squibb, Cephalon, CME Institute/Physicians Postgraduate Press, Eli Lilly and Company, Forest Pharmaceuticals, GlaxoSmithKline, Imedex, Massachusetts General Hospital (MGH) Psychiatry Academy/Primedia, MGH Psychiatry Academy/Reed Elsevier, Novartis AG, Organon, Pfizer, PharmaStar, United BioSource, and Wyeth-Ayerst; has equity holdings in Compellis; receives copyright royalties for the MGH Cognitive & Physical Functioning Questionnaire, Sexual Functioning Inventory, Antidepressant Treatment Response Questionnaire, Discontinuation-Emergent Signs & Symptoms, and SAFER; and has a patent application for a combination of azapirones and bupropion in major depressive disorder. Dr Fava also has a patent for Sequential Parallel Comparison Design (SPCD) and a patent for research and licensing of SPCD with RCT Logic; Lippincott, Williams & Wilkins; Wolkers Kluwer; and World Scientific Publishing. **Drs Vitolo**, **Winokur**, and **Bari**; **Mss Hails** and **Meisner**; and **Messrs Lipkin**, **Abrams**, and **Ward** report no potential or other conflicts of interest.
Funding/support: This trial was funded by Pfizer, Inc. Massachusetts General Hospital assisted with the coordination of this study.

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