Ziprasidone Augmentation of Escitalopram for Major Depressive Disorder:

Cardiac, Endocrine, Metabolic, and Motoric Effects in a Randomized, Double-Blind, Placebo-Controlled Study

David Mischoulon, MD, PhD[a,*]; Richard C. Shelton, MD[b]; Lee Baer, PhD[a]; William V. Bobo, MD, MPH[c]; Laura Curren, MA[a]; Maurizio Fava, MD[a]; and George I. Papakostas, MD[a]

ABSTRACT

Objective: To examine motoric, cardiovascular, endocrine, and metabolic effects of adjunctive ziprasidone in adults with major depressive disorder (MDD) and prior nonresponse to 8 weeks of open-label escitalopram.

Methods: A multicenter, parallel, randomized, double-blind, placebo-controlled trial was conducted at 3 US academic medical centers from July 2008 to October 2013. Recruited were 139 outpatients with persistent *DSM-IV* MDD following an 8-week open-label trial of escitalopram. Subjects were then randomized to adjunctive ziprasidone (escitalopram + ziprasidone, n = 71) or placebo (escitalopram + placebo, n = 68) for 8 additional weeks. Cardiac and metabolic measures were obtained at each treatment visit. Barnes Akathisia Scale and Abnormal Involuntary Movement Scale (AIMS) scores were also obtained. Changes in outcome measures for each treatment group were compared by independent-samples *t* test.

Results: A trend toward significance ($P = .06$) in corrected QT interval (QTc) increase was observed for ziprasidone (mean [SD] = 8.8 [20.2] milliseconds) versus placebo (–0.02 [25.5] milliseconds). Ziprasidone-treated patients had a significantly greater increase in global akathisia scores ($P = .01$) and significant weight increase (mean [SD] = 3.5 [11.8] kg, or 7.7 [26.1] lb) compared to placebo (1.0 [6.4] kg, or 2.2 [14.1] lb) ($P = .03$). No significant changes in AIMS scores were observed for either treatment group.

Conclusions: Adjunctive ziprasidone, added to escitalopram, led to a greater weight gain and greater but modest akathisia compared to placebo. The effect of ziprasidone on QTc showed a trend toward significance, and therefore caution should be used in the administration of ziprasidone. While ziprasidone augmentation in patients with MDD appears safe, precautions should be taken in practice, specifically regular monitoring of electrocardiogram, weight, extrapyramidal symptoms, and involuntary movements.

Trial Registration: ClinicalTrials.gov identifier: NCT00633399

J Clin Psychiatry 2017;78(4):449–455
dx.doi.org/10.4088/JCP.15m10426

[a]Depression Clinical and Research Program, Massachusetts General Hospital, Boston
[b]Department of Psychiatry, University of Alabama, Birmingham
[c]Department of Psychiatry & Psychology, Mayo Clinic, Rochester, Minnesota
**Corresponding author:* David Mischoulon, MD, PhD, Massachusetts General Hospital, One Bowdoin Sq, 6th Floor, Boston MA 02114 (dmischoulon@partners.org).

Despite the many antidepressant medications approved as monotherapy for major depressive disorder (MDD),[1] many depressed patients remain symptomatic after treatment,[2] and adjunctive treatments are often needed to achieve remission.[3] Atypical antipsychotics as adjunctive therapy for treatment-resistant MDD have been growing in popularity in recent years.[4–6] Several randomized, double-blind, placebo-controlled trials have been published with adjunctive aripiprazole, olanzapine, quetiapine, or risperidone in samples with MDD,[7,8] and aripiprazole, olanzapine (in combination with fluoxetine), and quetiapine are currently approved in the United States for this indication.

The antipsychotic agent ziprasidone has also shown promise as an adjunctive therapy for MDD, most likely due to its various mechanisms of action. It has the highest serotonin-2A ($5HT_{2A}$)/dopamine-2 (D_2) receptor binding affinity ratio of all US Food and Drug Administration (FDA)–approved antipsychotic medications.[9,10] $5HT_{2A}$ blockade is a property shared by certain antidepressants such as trazodone,[11] mirtazapine,[3] nefazodone,[11] and mianserin[3] as well as other antipsychotics such as aripiprazole, quetiapine, olanzapine, and risperidone.[3] Ziprasidone is also an antagonist for serotonin-1D ($5HT_{1D}$) receptors,[9] which enhance serotonin neurotransmission.[12] Ziprasidone also acts as a partial agonist of serotonin-1A ($5HT_{1A}$) receptors,[9] similar to buspirone[13] and aripiprazole,[14] which have anxiolytic and antidepressant properties.[15–17] Additionally, ziprasidone also inhibits neuronal uptake of serotonin and norepinephrine via their relevant transporters in vitro,[10] similar to imipramine and desipramine,[18] and also inhibits neuronal dopamine uptake.[10]

Other compelling features of ziprasidone are its lower likelihood than olanzapine to cause weight gain, dyslipidemias, or elevated glycosylated hemoglobin levels[19–23] and its lower likelihood than risperidone to cause elevations in prolactin levels.[22,24] Ziprasidone is associated with less weight gain than nearly all other antipsychotics, as shown in a meta-regression analysis[25] of body weight changes associated with 10 different typical and atypical antipsychotics. Ziprasidone was associated with the second-lowest degree of weight gain (after molindone), with a mean weight increase of 0.04 kg (0.09 lb). These clinical properties would suggest an advantage in efficacy and tolerability for adjunctive ziprasidone versus other atypical antipsychotic drugs in MDD.

Our group[26] has recently reported a significant antidepressant and anxiolytic advantage for ziprasidone compared to placebo in an 8-week, randomized, double-blind, controlled trial of

Clinical Points

- Ziprasidone augmentation was recently shown to be effective in depressed individuals who did not respond adequately to escitalopram. However, the safety of this intervention requires further characterization.
- We found modest increases in the corrected QT interval, akathisia, and weight in the study subjects who received ziprasidone augmentation versus placebo. There was no evidence of increased involuntary movements with ziprasidone augmentation.
- Ziprasidone augmentation may be safely and effectively used for depressed patients, but regular precautions should be taken, including regular monitoring of electrocardiograms, weight, extrapyramidal symptoms, and involuntary movements.

ziprasidone augmentation of the selective serotonin reuptake inhibitor (SSRI) escitalopram for patients with persistent MDD symptoms after an 8-week open-label trial of flexible-dose lead-in treatment with escitalopram. Here, we report on the motoric, endocrine, cardiac, and metabolic profiles for ziprasidone in our study sample.

METHODS

Detailed methods have been described by Papakostas et al.[26] In brief, this was an 8-week, randomized, double-blind, parallel-group, placebo controlled trial of ziprasidone augmentation of escitalopram for subjects with MDD and persistent depressive symptoms following an 8-week, prospective, open-label, flexible-dose trial of escitalopram (ClinicalTrials.gov identifier NCT00633399). The study was conducted at 3 US academic medical centers (Massachusetts General Hospital, Boston; University of Alabama, Birmingham; and Vanderbilt University, Nashville, Tennessee) from July 2008 to October 2013. Local institutional review boards approved the study, and written informed consent was obtained from all study subjects before any study procedures were carried out.

Subjects were men or women 18–65 years of age with a primary diagnosis of MDD according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*) criteria, confirmed by the Structured Clinical Interview for *DSM-IV* (SCID-I/P),[27] and a 16-item Quick Inventory of Depressive Symptomatology-Self Rated scale (QIDS-SR)[28] total score ≥ 10 at screening.

Exclusion criteria are fully detailed by Papakostas et al.[26] Among these criteria, we excluded patients who had received an adequate trial of escitalopram during the current major depressive episode (prior to study entry) or any lifetime trial of ziprasidone, had failed more than 3 antidepressant trials of adequate dose and duration during the current major depressive episode, or were currently taking an antidepressant or antipsychotic medication.

Eligible subjects began an 8-week, flexible-dose, open-label trial of escitalopram 10–30 mg/d. During the first 4 weeks, escitalopram doses were increased by 10-mg increments each week as deemed clinically necessary by the treating clinician and with subjects' consent. All subjects remained on a stable escitalopram dose after week 4 and during the subsequent double-blind trial, unless reductions in escitalopram dose were deemed clinically necessary. Patients were allowed benzodiazepine or benzodiazepine-like agents, anticonvulsants, lithium, and buspirone, provided that daily doses remained stable throughout the study and had been stable for at least 2 weeks prior to screening.

At the end of the open-label trial, subjects who continued to meet *DSM-IV* criteria for MDD, had a QIDS-SR score ≥ 10, and did not have serum potassium or magnesium levels outside of reference limits, evidence of untreated hypothyroidism, a positive urine drug screen, or significant cardiac conduction problems such as atrial fibrillation, atrial flutter, atrioventricular block, or disqualifying electrocardiogram (ECG) changes (prolonged corrected QT interval [QTc] or QRS interval) were enrolled in the double-blind phase of the study for 8 weeks.

Patients were randomized in a 1:1 fashion to receive adjunctive ziprasidone or placebo. Following the first double-blind visit and throughout the 8 subsequent weekly visits, study clinicians could increase the dose of the study drug in 1-capsule, twice-per-day, weekly increments, yielding a possible ziprasidone dosage range of 20–80 mg twice daily. Study clinicians could also, when deemed appropriate, lower the dose to address uncomfortable or intolerable side effects. Patients unable to tolerate a minimum dosage of 10 mg of escitalopram and 20 mg of study drug (ziprasidone or placebo) were withdrawn from the study.

Adverse effects were recorded at each visit. The Barnes Akathisia Scale (BAS)[29] was used to assess akathisia at each visit. The Abnormal Involuntary Movement Scale (AIMS)[30] was used to assess for extrapyramidal symptoms and other abnormal movements.

Body mass index (BMI), body weight, fasting lipids (total cholesterol, high-density lipoprotein [HDL] cholesterol, low-density lipoprotein [LDL] cholesterol, triglycerides), fasting glucose, glycosylated hemoglobin (HbA_{1c}), thyroid-stimulating hormone (TSH), and prolactin levels were assessed at the beginning (baseline) and end of the double-blind phase. Blood samples were obtained after a 12- to 14-hour fast. Clinically significant weight gain was defined as an increase in body weight of 7% or greater at the end of the double-blind phase as compared with baseline body weight. Patients were weighed in the morning in the fasting state while wearing light clothing. Standard 12-lead ECGs were also obtained at the beginning, at week 2, and at the end of the study.

The intent-to-treat dataset including all randomized patients was analyzed by treatment group. Categorical baseline characteristics were compared between treatment groups with χ^2 tests. Continuous baseline data were analyzed and compared via *t* tests. Change in continuous outcome measures were compared between groups using analysis of covariance, adjusting for baseline values. All tests were conducted with a significance level of .05 (2-sided), with no

Table 1. Comparison of Cardiac Effects Between Ziprasidone and Placebo Augmentation of Escitalopram[a]

QTc Variable[a]	Ziprasidone + Escitalopram (n = 71), Mean (SD)	Placebo + Escitalopram (n = 68), Mean (SD)	*P* Value
Baseline	417.3 (19.8)	419.2 (17.8)	.56
Change at week 2	5.2 (16.45)	1.8 (20.7)	.31
Change at week 8	8.8 (20.2)	−0.02 (25.5)	.06
	n (%)	n (%)	
Change > 75 at week 2	0 (0)	0 (0)	.99
Change > 75 at week 8	0 (0)	0 (0)	.99
Baseline			
> 450	1 (1)	1 (1)	.97
> 480	0 (0)	0 (0)	.99
> 500	0 (0)	0 (0)	.99
Week 2 (new)			
> 450	5 (7)	4 (6)	.77
> 480	1 (1)	0 (0)	.96
> 500	1 (1)	0 (0)	.96
Week 8 (new)			
> 450	7 (10)	6 (9)	.83
> 480	1 (1)	1 (1)	.97
> 500	1 (1)	0 (0)	.96

[a]QTc values shown in ms. The designation of "new" refers to patients whose QTc values were within the specified range for the first time at that time point.
Abbreviation: QTc = corrected QT interval.

Table 2. Comparison of Metabolic Effects Between Ziprasidone and Placebo Augmentation of Escitalopram

Variable[a]	Ziprasidone + Escitalopram (n = 71)[b]	Placebo + Escitalopram (n = 68)[b]	*P* Value[c]
Glucose, mg/dL			
Baseline	92.7 (18.6)	96.3 (31.7)	.41
Change at week 8	0.6 (14.5)	1.5 (17.0)	.09
HbA_{1c}, % of total hemoglobin			
Baseline	5.7 (1.2)	5.7 (1.2)	.82
Change at week 8	0.1 (0.3)	0.1 (1.1)	.33
> 7% at baseline, n (%)	3 (4)	3 (4)	.87
> 7% at week 8 (new), n (%)	1 (1)	1 (1)	.78
Total cholesterol, mg/dL			
Baseline	198.8 (35.1)	191.3 (42.6)	.26
Change at week 8	−3.3 (23.1)	1.7 (28.9)	.62
HDL cholesterol, mg/dL			
Baseline	53.7 (17.2)	52.4 (26.6)	.72
Change at week 8	0.7 (12.1)	1.9 (11.4)	.66
LDL cholesterol, mg/dL			
Baseline	111.5 (30.3)	110.1 (34.4)	.80
Change at week 8	−1.1 (24.9)	−1.2 (24.8)	.89
Triglycerides, mg/dL			
Baseline	163.2 (120.9)	186.9 (138.5)	.28
Change at week 8	−14.8 (103.7)	−20.3 (110.2)	.31
Baseline height, m	1.68 (0.9)	1.68 (1.1)	.97
Baseline weight			
kg	81.7 (25.1)	87.9 (27.2)	.17
lb	180.1 (55.3)	193.8 (60.0)	…
BMI, kg/m^2, mean	28.9	31.1	.11
Change in weight at week 8			
kg	3.5 (11.8)	1.0 (6.4)	**.03**
lb	7.7 (26.0)	2.2 (14.1)	…
Prolactin, ng/mL			
Baseline	8.0 (3.6)	9.0 (6.2)	.22
Change at week 8	4.0 (10.4)	6.2 (26.2)	.55
TSH, mIU/L			
Baseline	1.5 (0.7)	1.5 (0.8)	.96
Change at week 8	0.1 (0.7)	0.1 (0.6)	.49

[a]Measurements of glucose, cholesterol, triglycerides, prolactin, and TSH are shown as serum levels. The designation of "new" refers to patients whose QTc values were within the specified range for the first time at that time point.
[b]Values shown as mean (SD) unless otherwise noted.
[c]Boldface indicates statistical significance.
Abbreviations: BMI = body mass index, HDL = high-density lipopoprotein, HbA_{1c} = hemoglobin A_{1c}, LDL = low-density lipoprotein, TSH = thyroid-stimulating hormone.
Symbol: … = not applicable.

adjustments for multiplicity, using STATA SE Version 12 statistical software (StataCorp LP).

RESULTS

A total of 531 outpatients were screened, and 458 (86.2%) were eligible to enroll. Of these patients, 311 (67.9%) completed the open phase, and 139 were then randomly assigned to double-blind treatment with adjunctive ziprasidone (20-80 mg twice daily) or placebo.

Baseline demographic and clinical data for these patients were reported by Papakostas et al.[26] The mean (SD) attained dose of adjunctive ziprasidone was 98 (40) mg/d. Mean (SD) doses of escitalopram were 21.0 (5.8) mg/d in the ziprasidone group and 19.2 (3.1) mg/d in the placebo group.[26] Seven patients randomized to ziprasidone (9.8%) received escitalopram at a dose of 30 mg/d, and 3 patients randomized to placebo (4.4%) received escitalopram doses of 30 mg/d. All other subjects received 20 mg/d or less of escitalopram.

Rates of somnolence/fatigue were 33.8% for the combination therapy and 11.7% for placebo ($P = .002$).[26] Baseline QTc measures were not significantly different between treatment arms. QTc increased by a mean of 8.8 milliseconds by week 8 in the ziprasidone group, which trended toward statistical significance ($P = .06$) against placebo (Table 1). We found no significant association between ziprasidone dose and QTc prolongation ($P = .96$).

Baseline serum fasting glucose, HbA_{1c}, body weight, BMI, prolactin, and TSH levels were comparable at baseline between both treatment arms ($P > .05$). By week 8, no significant difference in changes in any of these measures between ziprasidone and placebo were observed, except for weight, with ziprasidone resulting in a significantly greater weight increase than placebo ($P = .03$) (Table 2).

Akathisia scores (including restlessness) are summarized in Table 3. Among the 4 BAS items—1 (objective), 2 (subjective awareness of restlessness), 3 (distress related to restlessness), and 4 (global clinical assessment of akathisia)—item 1 was significantly higher at baseline in the ziprasidone group compared to the placebo group ($P = .02$), but the other 3 items did not differ significantly between the 2 groups. With regard to change in BAS scores over 8 weeks of treatment, item 4 scores increased for ziprasidone and decreased for placebo, and the difference between treatment groups reached statistical significance ($P = .01$). All other comparisons were nonsignificant (Table 3).

There was no statistically significant difference between the 2 groups in the proportion of patients who developed clinically significant findings on the AIMS scale during treatment (Table 4).

Table 3. Comparison of Barnes Akathesia Scale (BAS) Scores Between Ziprasidone and Placebo Augmentation of Escitalopram

BAS Score	Ziprasidone + Escitalopram (n = 71)[a]	Placebo + Escitalopram (n = 68)[a]	*P* Value[b]
Item 1: Objective			
Baseline	0.23 (0.59)	0.04 (0.21)	**.02**
Change at week 8	−0.15 (0.63)	0 (0.29)	.8
Item 2: Subjective awareness of restlessness			
Baseline	0.41 (0.71)	0.26 (0.51)	.18
Change at week 8	−0.2 (0.76)	−0.2 (0.54)	.23
Item 3: Distress related to restlessness			
Baseline	0.10 (0.34)	0.12 (0.42)	.68
Change at week 8	0.07 (0.48)	0.02 (0.39)	.52
Item 4: Global clinical assessment of akathisia			
Baseline	0.31 (0.69)	0.23 (0.52)	.41
Change at week 8	0.07 (0.94)	−0.15 (0.36)	**.01**
Total			
Baseline	1.0 (1.9)	0.6 (1.3)	.2
Change at week 8	−0.49 (2.3)	−0.61 (1.0)	.12

[a]Values shown as mean (SD) unless otherwise noted.
[b]Boldface indicates statistical significance.

Table 4. Comparison of Abnormal Involuntary Movements Scale (AIMS) Scores Between Ziprasidone and Placebo Augmentation of Escitalopram

Time Point	Ziprasidone + Escitalopram (n = 71), n (%)[a]	Placebo + Escitalopram (n = 68), n (%)[a]	*P* Value
Baseline	3 (4)	0 (0)	.81
Week 4	0 (0)	0 (0)	.99
Week 8	0 (0)	0 (0)	.99

[a]Subjects with an AIMS score of 3 in one body area or score of 2 in two or more body areas.

DISCUSSION

In this first randomized, double-blind, placebo-controlled trial comparing the efficacy of adjunctive ziprasidone, an atypical antipsychotic agent, with adjunctive placebo in outpatients with MDD, we examined whether ziprasidone might have any significant adverse cardiovascular, endocrine, motoric, and metabolic effects. Patients in our study received ziprasidone at doses between 40 and 160 mg/d with a mean (SD) dose of 98 (40) mg/d.[26] Our results showed a trend toward significantly greater QTc increase (8.8 milliseconds) in the ziprasidone group compared to placebo. This finding is generally in line with the known risks of ziprasidone on the QTc.[31] On the other hand, we found no significant association between ziprasidone dose and QTc changes ($P = .96$), whereas the literature generally suggests that QTc changes with ziprasidone are dose-related.[31] Furthermore, no participant in either treatment arm experienced an increase of > 75 milliseconds after 8 weeks of treatment. By week 8, 7 subjects on ziprasidone treatment and 6 on placebo had a QTc > 450 milliseconds, and only 1 subject in the ziprasidone group had a QTc > 500 milliseconds. The FDA has recommended that prescribers weigh the comparative benefits and risks between ziprasidone and other antipsychotic drugs in part by considering ziprasidone's greater capacity to prolong the QT/QTc interval.[31] Our findings, in the context of the risk of QTc prolongation with ziprasidone as well as with SSRIs,[32] suggest that the combination of ziprasidone and SSRIs is very likely safe but should be undertaken with caution, and clinicians who administer such combinations should monitor ECGs regularly.

The design of the study allowed high doses and flexible dosing. Doses of escitalopram ranged between 10 and 30 mg/d, with a mean (SD) of 21.0 (5.8) mg/d in the ziprasidone group and 19.2 (3.1) mg/d in the placebo group.[26] A total of 9.8% of subjects randomized to adjunctive ziprasidone and 4.4% of subjects randomized to adjunctive placebo received an escitalopram dose of 30 mg/d, which is above the maximum licensed dose of 20 mg/d. At the time of study design, the current guidelines on the QTc effects of escitalopram, which was reported safe only up to 20 mg/d by the FDA and up to the lower dose of 10 mg in Europe, had not yet emerged. We designed the study to maximize possibility of response to treatment. In our field, higher-than-recommended doses of SSRIs are frequently used, and this applies to escitalopram and citalopram, which remain in use at high doses in some exceptional cases, with appropriate ECG monitoring. In this study, the mean dose of escitalopram attained in both treatment arms was at around 20 mg/d, which is considered safe, and too few patients were on escitalopram doses greater than 20 mg/d to draw any firm conclusions about the safety of higher doses in this setting. Nonetheless, clinicians who are interested in prescribing escitalopram, alone or in combination with ziprasidone, should be watchful for potential cumulative QTc effects of the combination and attempt to keep the doses within the current guidelines, and preferably at the minimum effective dose, to maximize patient safety.

Patients on ziprasidone treatment had a significant increase in weight compared to placebo, with a net difference in weight-gain of 2.5 kg (5.5 lb) (3.5 kg [7.7 lb] vs 1.0 kg [2.2 lb]). This finding was surprising given the previous reports of ziprasidone as being weight neutral,[25] as well as reports of other atypical antipsychotics such as aripiprazole, which produced minimal weight gain in schizophrenia[33,34] but a significant weight gain in resistant depression.[35] These findings collectively suggest that depressed patients, especially those with treatment-resistant depression, may be at greater risk of weight gain than previously reported, for example as a result of poorer eating habits. Likewise, the combination of an antipsychotic plus an antidepressant may have also contributed to the observed weight gain. Although modest, a net weight gain of 2.5 kg (5.5 lb) could be distressing to some patients in clinical practice, and for this reason clinicians should inform patients about the risk of weight gain and monitor weight closely. Ziprasidone did not appear to have a significant effect on plasma glucose, triglycerides, HbA_{1c}, total cholesterol, LDL cholesterol, prolactin, and TSH. Thus, as a basis for treatment selection, metabolic parameters during treatment of MDD with adjunctive ziprasidone appear to be more similar to those reported with aripiprazole[36] and quetiapine[37] in this patient

population and substantially lower than with adjunctive olanzapine therapy.[38]

Finally, ziprasidone-treated patients demonstrated a statistically significant worsening in akathisia scores in only 1 of 4 BAS score measures (global akathisia), a net increase that was generally mild in magnitude (Cohen *d* effect size of 0.1) and principally due to a decrease in scores in the placebo group. In fact, the incidence of akathisia with adjunctive ziprasidone therapy was reported as 15.4% (vs 7.3% for placebo),[26] lower than that reported for aripiprazole (25%).[35] In the aripiprazole trials,[35,36] akathisia and restlessness were rated separately, whereas in our study we collapsed restlessness into the akathisia measurements, which suggests better tolerability for ziprasidone. It should be noted, however, that much of the literature's data on akathisia for aripiprazole and other atypical antipsychotics were based on spontaneous reports, and therefore comparisons between our targeted findings and those in the literature need to be made with caution. Thus, in this respect, adjunctive ziprasidone appears to be associated with a risk of akathisia somewhere between that of aripiprazole (higher) and that of more sedating atypical antipsychotics such as olanzapine and quetiapine.[39] Finally, the rate of emergence of clinically significant abnormal involuntary movements did not differ significantly between the 2 treatment groups; however, the sample size is small for estimation of rarely occurring events. Long-term monitoring for the emergence of such adverse events is, therefore, clinically prudent.

About one-third of patients on the combination therapy experienced sedation, a significant difference from those taking placebo.[26] As it stands, the 3 adverse effects of greatest concern that differentiate olanzapine, quetiapine, and aripiprazole are weight gain, akathisia, and sedation. While ziprasidone appears advantageous with regard to akathisia and weight gain, the rate of sedation was notable, and therefore clinicians should make sure to inform patients about this.

Several limitations should be considered. The study was designed to focus on the efficacy, safety, and tolerability of adjunctive ziprasidone when combined with the SSRI escitalopram. Whether results would have been similar or different had we also augmented other antidepressants with ziprasidone remains unclear. Second, the present trial involved a number of inclusion and exclusion criteria. Whether adjunctive ziprasidone is more likely to have cardiovascular or metabolic effects among patients who would not meet our inclusion criteria (eg, those with unstable medical illness, the elderly) is unknown.

In conclusion, in the present study, adjunctive ziprasidone when combined with the SSRI escitalopram in MDD patients versus placebo demonstrated a mild increase in QTc that is deemed unlikely to be of broad clinical relevance, greater weight gain, and a mild tendency to akathisia compared to adjunctive placebo. The positive efficacy findings for this combination supported its use as an effective augmentation of an SSRI,[26] and our current results also support relative safety of the combination therapy. However, in view of the developing concerns and warnings about SSRIs and QTc prolongation, clinicians should carefully weigh the pros and cons of this combination and consider the patient's medical history and past response or nonresponse to other agents and combinations used for treatment resistant depression, and, if they choose to prescribe and SSRI-ziprasidone combination, they should regularly monitor the patient's ECG. Likewise, our results also support regular monitoring of weight, extrapyramidal symptoms, and involuntary movements.

Submitted: September 30, 2015; accepted December 17, 2015.

Online first: November 8, 2016.

Drug names: aripiprazole (Abilify), citalopram (Celexa and others), desipramine (Norpramin and others), escitalopram (Lexapro and others), fluoxetine (Prozac and others), imipramine (Tofranil and others), mirtazapine (Remeron and others), olanzapine (Zyprexa and others), quetiapine (Seroquel and others), risperidone (Risperdal and others), ziprasidone (Geodon and others).

Potential conflicts of interest: **Dr Mischoulon** has received research support from the Bowman Family Foundation, FisherWallace, Nordic Naturals, Methylation Sciences, Inc (MSI), and PharmoRx Therapeutics; has received honoraria for consulting, speaking, and writing from Pamlab and the Massachusetts General Hospital Psychiatry Academy; and has received royalties from Lippincott Williams & Wilkins for published book *Natural Medications for Psychiatric Disorders: Considering the Alternatives*. **Dr Shelton** has been a consultant for Bristol-Myers Squibb Company, Cerecor, Inc, Clintara, LLC, Cyberonics, Inc, Forest Pharmaceuticals, Janssen Pharmaceutica, Medtronic, Inc, MSI Methylation Sciences, Inc, Naurex, Inc, Pamlab, Inc, Pfizer, Inc, Ridge Diagnostics, Shire Pic, and Takeda Pharmaceuticals and has received grant/research support from Alkermes, Inc, Assurex Health, Avanir Pharmaceuticals, Inc, Bristol-Myers Squibb, Elan, Corp, Forest Pharmaceuticals, Janssen Pharmaceutica, Naurex, Inc, Novartis Pharmaceuticals, Otsuka Pharmaceuticals, Pamlab, Inc, and Takeda Pharmaceuticals. **Dr Bobo** has received grant funding from National Institute of Mental Health, Mayo Foundation, Cephalon, and National Alliance for Research on Schizophrenia & Depression (NARSAD) and has served on speaker bureaus for Janssen and Pfizer (previous). **Dr Fava** has served as a consultant for Abbott Laboratories, Affectis Pharmaceuticals AG, Alkermes, Inc, Amarin Pharma Inc, Aspect Medical Systems, AstraZeneca, Auspex Pharmaceuticals, Bayer AG, Best Practice Project Management, Inc, BioMarin Pharmaceuticals, Inc, Biovail Corporation, BrainCells Inc, Bristol-Myers Squibb, CeNeRx BioPharma, Cephalon, Inc, Cerecor, CNS Response, Inc, Compellis Pharmaceuticals, Cypress Pharmaceutical, Inc, DiagnoSearch Life Sciences (P) Ltd, Dinippon Sumitomo Pharma Co, Inc, DOV Pharmaceuticals, Inc, Edgemont Pharmaceuticals, Inc, Eisai Inc, Eli Lilly and Company, EnVivo Pharmaceuticals, Inc, ePharmaSolutions, EPIX Pharmaceuticals, Inc, Euthymics Bioscience, Inc, Fabre-Kramer Pharmaceuticals, Inc, Forest Pharmaceuticals, Inc, GenOmind, LLC, GlaxoSmithKline, Grunenthal GmbH, i3 Innovus/Ingenis, Janssen Pharmaceutica, Jazz Pharmaceuticals, Inc, Johnson & Johnson Pharmaceutical Research & Development, LLC, Knoll Pharmaceuticals Corp, Labopharm Inc, Lorex Pharmaceuticals, Lundbeck Inc, MedAvante, Inc, Merck & Co, Inc, MSI Methylation Sciences, Inc, Naurex, Inc, Neuralstem, Inc, Neuronetics, Inc, NextWave Pharmaceuticals, Novartis AG, Nutrition 21, Orexigen Therapeutics, Inc, Organon Pharmaceuticals, Otsuka Pharmaceuticals, Pamlab, LLC, Pfizer Inc, PharmaStar, Pharmavite LLC, PharmoRx Therapeutics, Precision Human Biolaboratory, Prexa Pharmaceuticals, Inc, Puretech Ventures, PsychoGenics, Psylin Neurosciences, Inc,RCT Logic, LLC (formerly Clinical Trials Solutions, LLC), Rexahn Pharmaceuticals, Inc, Ridge Diagnostics, Inc, Roche; Sanofi-Aventis US LLC, Sepracor Inc, Servier Laboratories, Schering-Plough Corporation, Solvay Pharmaceuticals, Inc, Somaxon Pharmaceuticals, Inc, Somerset Pharmaceuticals, Inc, Sunovion Pharmaceuticals, Supernus Pharmaceuticals, Inc, Synthelabo, Takeda Pharmaceutical Company Limited, Tal Medical, Inc, Tetragenex Pharmaceuticals, Inc, TransForm Pharmaceuticals, Inc, Transcept Pharmaceuticals, Inc, and Vanda Pharmaceuticals, Inc; has received grant/research support from Abbot Laboratories, Alkermes, Inc, American Cyanamid, Aspect Medical Systems, AstraZeneca, Avanir Pharmaceuticals, BioResearch, BrainCells Inc, Bristol-Myers Squibb, CeNeRx BioPharma, Cephalon, Clintara, LLC, Covance, Covidien, Eli Lilly and Company, EnVivo Pharmaceuticals, Inc, Euthymics Bioscience, Inc, Forest Pharmaceuticals, Inc, Ganeden Biotech, Inc, GlaxoSmithKline, Harvard Clinical Research Institute, Hoffman-LaRoche, Icon Clinical Research, i3 Innovus/Ingenix, Janssen R&D, LLC, Jed Foundation, Johnson & Johnson Pharmaceutical Research & Development, Lichtwer Pharma GmbH, Lorex Pharmaceuticals, Lundbeck Inc, MedAvante, Methylation Sciences Inc, NARSAD, National Center for Complementary and

Alternative Medicine (NCCAM), National Institute of Drug Abuse (NIDA), National Institute of Mental Health (NIMH), Neuralstem, Inc, Novartis AG, Organon Pharmaceuticals, PamLab, LLC, Pfizer Inc, Pharmacia-Upjohn, Pharmaceutical Research Associates, Inc, Pharmavite LLC, PharmoRx Therapeutics, Photothera, Reckitt Benckiser, Roche Pharmaceuticals, RCT Logic, LLC (formerly Clinical Trials Solutions, LLC), Sanofi-Aventis US LLC, Shire, Solvay Pharmaceuticals, Inc, Stanley Medical Research Institute (SMRI), Synthelabo, and Wyeth-Ayerst Laboratories; has served on speakers or advisory boards for Adamed, Co, Advanced Meeting Partners, American Psychiatric Association, American Society of Clinical Psychopharmacology, AstraZeneca, Belvoir Media Group, Boehringer Ingelheim GmbH, Bristol-Myers Squibb, Cephalon, Inc, CME Institute/Physicians Postgraduate Press, Inc, Eli Lilly and Company, Forest Pharmaceuticals, Inc, GlaxoSmithKline, Imedex, LLC, MGH Psychiatry Academy/Primedia, MGH Psychiatry Academy/Reed Elsevier, Novartis AG, Organon Pharmaceuticals, Pfizer Inc, PharmaStar, United BioSource, Corp, and Wyeth-Ayerst Laboratories; has Equity holdings in Compellis, and PsyBrain, Inc; holds the patent for Sequential Parallel Comparison Design (SPCD), which is licensed by MGH to Pharmaceutical Product Development, LLC (PPD), and patent application for a combination of Ketamine plus Scopolamine in Major Depressive Disorder (MDD); and holds the copyright for the MGH Cognitive & Physical Functioning Questionnaire (CPFQ), Sexual Functioning Inventory (SFI), Antidepressant Treatment Response Questionnaire (ATRQ), Discontinuation-Emergent Signs & Symptoms (DESS), and SAFER; Lippincott, Williams & Wilkins, Wolkers Kluwer, and World Scientific Publishing Co, Pte, Ltd. **Dr Papakostas** has served as a consultant for Abbott Laboratories, AstraZeneca PLC, Avanir Pharmaceuticals, Brainsway Ltd, Bristol-Myers Squibb Company, Cephalon Inc, Dey Pharma, LP, Eli Lilly Co., Genentech, Inc, GlaxoSmithKline, Evotec AG, H. Lundbeck A/S, Inflabloc Pharmaceuticals, Janssen Global Services LLC, Jazz Pharmaceuticals, Johnson & Johnson Companies, Novartis Pharma AG, One Carbon Therapeutics, Inc, Otsuka Pharmaceuticals, PAMLAB LLC, Pfizer Inc, Pierre Fabre Laboratories, Ridge Diagnostics (formerly known as Precision Human Biolaboratories), Shire Pharmaceuticals, Sunovion Pharmaceuticals, Takeda Pharmaceutical Company LTD, Theracos, Inc, and Wyeth, Inc; has received grant/research support from AstraZeneca PLC, Bristol-Myers Squibb Company, Forest Pharmaceuticals, the National Institute of Mental Health, Neuralstem, Inc, Pamlab LLC, Pfizer Inc, Ridge Diagnostics (formerly known as Precision Human Biolaboratories), Sunovion Pharmaceuticals, Tal Medical, and Theracos, Inc; has received honoraria (for consulting or educational activities) from Abbott Laboratories, Astra Zeneca PLC, Avanir Pharmaceuticals, Bristol-Myers Squibb Company, Brainsway Ltd, Cephalon Inc, Dey Pharma, LP, Eli Lilly Co, Evotec AG, Forest Pharmaceuticals, GlaxoSmithKline, Inflabloc Pharmaceuticals, Jazz Pharmaceuticals, H. Lundbeck A/S, Medichem Pharmaceuticals, Inc, Novartis Pharma AG, Otsuka Pharmaceuticals, Pamlab LLC, Pfizer, Pierre Fabre Laboratories, Ridge Diagnostics, Shire Pharmaceuticals, Sunovion Pharmaceuticals, Takeda Pharmaceutical Company LTD, Theracos, Inc, Titan Pharmaceuticals, and Wyeth Inc.; and has served on speaker or advisory boards for Bristol-Myers Squibb Co, and Pfizer, Inc (previous). **Dr Baer** and **Ms Curren** have no conflicts of interest to report.

Funding/support: This study was supported by the National Institute for Mental Health (NIMH R01MH081235), Pfizer, Inc (providing free blinded ziprasidone/placebo pills), and Forest Laboratories, Inc. (providing free escitalopram).

Role of the sponsor: Only the authors were responsible for the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, and approval of the manuscript. The sponsors played no role in any of the preceding.

REFERENCES

1. Papakostas GI, Fava M. Monoamine-based pharmacotherapy for depression. In: Licinio J, Wong ML, eds. *Biology of Depression: From Novel Insights to Therapeutic Strategies*. 1st ed. Weinheim: Wiley-VCH Verlag; 2005:87–209.
2. Papakostas GI, Fava M. Does the probability of receiving placebo influence clinical trial outcome? a meta-regression of double-blind, randomized clinical trials in MDD. *Eur Neuropsychopharmacol*. 2009;19(1):34–40.
3. Papakostas GI. Managing partial response or nonresponse: switching, augmentation, and combination strategies for major depressive disorder. *J Clin Psychiatry*. 2009;70(suppl 6): 16–25.
4. Shelton RC, Papakostas GI. Augmentation of antidepressants with atypical antipsychotics for treatment-resistant major depressive disorder. *Acta Psychiatr Scand*. 2008;117(4):253–259.
5. Papakostas GI. Augmentation strategies in the treatment of major depressive disorder: examining the evidence on augmentation with atypical antipsychotics. *CNS Spectr*. 2007;12(suppl 22):10–12.
6. Papakostas GI. Augmentation of standard antidepressants with atypical antipsychotic agents for treatment-resistant major depressive disorder. *Essent Psychopharmacol*. 2005;6(4):209–220.
7. Papakostas GI, Shelton RC, Smith J, et al. Augmentation of antidepressants with atypical antipsychotic medications for treatment-resistant major depressive disorder: a meta-analysis. *J Clin Psychiatry*. 2007;68(6):826–831.
8. Nelson JC, Papakostas GI. Atypical antipsychotic augmentation in major depressive disorder: a meta-analysis of placebo-controlled randomized trials. *Am J Psychiatry*. 2009;166(9):980–991.
9. Richelson E, Souder T. Binding of antipsychotic drugs to human brain receptors: focus on newer generation compounds. *Life Sci*. 2000;68(1):29–39.
10. Tatsumi M, Jansen K, Blakely RD, et al. Pharmacological profile of neuroleptics at human monoamine transporters. *Eur J Pharmacol*. 1999;368(2–3):277–283.
11. Gartlehner G, Gaynes BN, Hansen RA, et al. Comparative benefits and harms of second-generation antidepressants: background paper for the American College of Physicians. *Ann Intern Med*. 2008;149(10):734–750.
12. Stahl SM, Shayegan DK. The psychopharmacology of ziprasidone: receptor-binding properties and real-world psychiatric practice. *J Clin Psychiatry*. 2003;64(suppl 19): 6–12.
13. Robinson DS, Rickels K, Feighner J, et al. Clinical effects of the 5-HT1A partial agonists in depression: a composite analysis of buspirone in the treatment of depression. *J Clin Psychopharmacol*. 1990;10(3 suppl):67S–76S.
14. Jordan S, Koprivica V, Chen R, et al. The antipsychotic aripiprazole is a potent, partial agonist at the human 5-HT1A receptor. *Eur J Pharmacol*. 2002;441(3):137–140.
15. Chessick CA, Allen MH, Thase M, et al. Azapirones for generalized anxiety disorder. *Cochrane Database Syst Rev*. 2006;(3):CD006115.
16. Kishi T, Meltzer HY, Matsuda Y, et al. Azapirone 5-HT1A receptor partial agonist treatment for major depressive disorder: systematic review and meta-analysis. *Psychol Med*. 2014;44(11):2255–2269.
17. Nelson JC, Thase ME, Bellocchio EE, et al. Efficacy of adjunctive aripiprazole in patients with major depressive disorder who showed minimal response to initial antidepressant therapy. *Int Clin Psychopharmacol*. 2012;27(3):125–133.
18. Schmidt AW, Lebel LA, Howard HR Jr, et al. Ziprasidone: a novel antipsychotic agent with a unique human receptor binding profile. *Eur J Pharmacol*. 2001;425(3):197–201.
19. Simpson GM, Glick ID, Weiden PJ, et al. Randomized, controlled, double-blind multicenter comparison of the efficacy and tolerability of ziprasidone and olanzapine in acutely ill inpatients with schizophrenia or schizoaffective disorder. *Am J Psychiatry*. 2004;161(10):1837–1847.
20. Simpson GM, Weiden P, Pigott T, et al. Six-month, blinded, multicenter continuation study of ziprasidone versus olanzapine in schizophrenia. *Am J Psychiatry*. 2005;162(8):1535–1538.
21. Breier A, Berg PH, Thakore JH, et al. Olanzapine versus ziprasidone: results of a 28-week double-blind study in patients with schizophrenia. *Am J Psychiatry*. 2005;162(10):1879–1887.
22. Lieberman JA, Stroup TS, McEvoy JP, et al; Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med*. 2005;353(12):1209–1223.
23. Kinon BJ, Lipkovich I, Edwards SB, et al. A 24-week randomized study of olanzapine versus ziprasidone in the treatment of schizophrenia or schizoaffective disorder in patients with prominent depressive symptoms. *J Clin Psychopharmacol*. 2006;26(2):157–162.
24. Addington DE, Pantelis C, Dineen M, et al. Efficacy and tolerability of ziprasidone versus risperidone in patients with acute exacerbation of schizophrenia or schizoaffective disorder: an 8-week, double-blind, multicenter trial. *J Clin Psychiatry*. 2004;65(12):1624–1633.
25. Allison DB, Mentore JL, Heo M, et al. Antipsychotic-induced weight gain: a comprehensive research synthesis. *Am J Psychiatry*. 1999;156(11):1686–1696.
26. Papakostas GI, Fava M, Baer L, et al. Ziprasidone augmentation of escitalopram for Major depressive disorder: efficacy results from a randomized, double-blind, placebo-controlled study. *Am J Psychiatry*. 2015;172(12):1251–1258.
27. First BM, Spitzer RL, Gibbon M, et al. *Structured Clinical Interview for DSM-IV Axis I Disorders - Patient Edition (SCID I/P)*. New York, NY: Biometrics Research, New York State Psychiatric Institute; 1995.
28. Trivedi MH, Rush AJ, Ibrahim HM, et al. The Inventory of Depressive Symptomatology, Clinician Rating (IDS-C) and Self-Report (IDS-SR), and the Quick Inventory of Depressive Symptomatology, Clinician Rating (QIDS-C) and Self-Report (QIDS-SR) in public sector patients with mood disorders: a psychometric evaluation. *Psychol Med*. 2004;34(1):73–82.
29. Barnes TR. A rating scale for drug-induced akathisia. *Br J Psychiatry*. 1989;154:672–676.
30. Guy W. *ECDEU Assessment Manual for Psychopharmacology*. Revised Edition. Washington, DC: US Department of Health, Education, and Welfare; 1976.
31. Greenberg WM, Citrome L. Ziprasidone for

schizophrenia and bipolar disorder: a review of the clinical trials. *CNS Drug Rev.* 2007;13(2):137–177.
32. Beach SR, Kostis WJ, Celano CM, et al. Meta-analysis of selective serotonin reuptake inhibitor-associated QTc prolongation. *J Clin Psychiatry.* 2014;75(5):e441–e449.
33. Musil R, Obermeier M, Russ P, et al. Weight gain and antipsychotics: a drug safety review. *Expert Opin Drug Saf.* 2015;14(1):73–96.
34. Kane JM, Carson WH, Saha AR, et al. Efficacy and safety of aripiprazole and haloperidol versus placebo in patients with schizophrenia and schizoaffective disorder. *J Clin Psychiatry.* 2002;63(9):763–771.
35. Berman RM, Thase ME, Trivedi MH, et al. Long-term safety and tolerability of open-label aripiprazole augmentation of antidepressant therapy in major depressive disorder. *Neuropsychiatr Dis Treat.* 2011;7:303–312.
36. Nelson JC, Thase ME, Trivedi MH, et al. Safety and tolerability of adjunctive aripiprazole in major depressive disorder: a pooled post hoc analysis (studies CN138-139 and CN138-163). *Prim Care Companion J Clin Psychiatry.* 2009;11(6):344–352.
37. McIntyre RS, Muzina DJ, Adams A, et al. Quetiapine XR efficacy and tolerability as monotherapy and as adjunctive treatment to conventional antidepressants in the acute and maintenance treatment of major depressive disorder: a review of registration trials. *Expert Opin Pharmacother.* 2009;10(18):3061–3075.
38. Bobo WV, Shelton RC. Fluoxetine and olanzapine combination therapy in treatment-resistant major depression: review of efficacy and safety data. *Expert Opin Pharmacother.* 2009;10(13):2145–2159.
39. Gao K, Kemp DE, Fein E, et al. Number needed to treat to harm for discontinuation due to adverse events in the treatment of bipolar depression, major depressive disorder, and generalized anxiety disorder with atypical antipsychotics. *J Clin Psychiatry.* 2011;72(8):1063–1071.