In the originally published article, Dr. Schweizer was incorrectly listed as an employee of Pfizer Inc in the acknowledgment statement.

Efficacy and Tolerability of Adjunctive Ziprasidone in Treatment-Resistant Depression: A Randomized, Open-Label, Pilot Study

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Objective: To evaluate the efficacy and tolerability of adjunctive ziprasidone in subjects with treatment-resistant major depressive disorder (DSM-IV criteria) without psychotic features.

Method: Subjects not responding to selective serotonin reuptake inhibitor (SSRI) monotherapy during a 6-week open-label trial were randomly assigned to continue monotherapy or receive adjunctive ziprasidone for 8 weeks in 1 of 3 groups: sertraline 100 to 200 mg/day, sertraline 100 to 200 mg/day plus ziprasidone 80 mg/day, or sertraline 100 to 200 mg/day plus ziprasidone 160 mg/day. The trial was conducted from May 2001 to October 2002. Ziprasidone was administered twice daily. Primary efficacy measure was the least squares mean change on the Montgomery-Asberg Depression Rating Scale (MADRS) total score from baseline of the 8-week phase to study end point.

Results: In total, 64 subjects were randomly assigned to sertraline monotherapy (N = 21), sertraline plus ziprasidone 80 mg/day (N = 23), or sertraline plus ziprasidone 160 mg/day (N = 20). Mean ± SE improvement in MADRS total score on adjunctive ziprasidone 80 mg/day and ziprasidone 160 mg/day versus monotherapy, respectively, was –5.98 ± 1.87 and –8.27 ± 2.17 versus –4.45 ± 2.03 (p = NS). Response rates for these groups were 19% (N = 4), 32% (N = 6), and 10% (N = 2), respectively (p = NS). No clinically significant changes were reported on physical examination, laboratory tests, or electrocardiogram on either adjunctive dose of ziprasidone.

Conclusions: In this preliminary study of antidepressant-resistant subjects with major depression, adjunctive ziprasidone was associated with greater clinical effect than was continued sertraline monotherapy and was generally well tolerated. These data suggest that further controlled study of ziprasidone in treatment-resistant depression is warranted.

(J Clin Psychiatry 2007;68:1071–1077)

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This research was funded by Pfizer Inc.

A preliminary report of this study was presented at the 43rd annual meeting of the American College of Neuropsychopharmacology, December 12–16, 2004, San Juan, Puerto Rico.

Assistance with data analysis was provided by Evan Batzar, M.S., an employee of Pfizer Inc. Edward Schweizer, M.D., of the Paladin Consulting Group provided editorial assistance in the preparation of the draft manuscript with funding from Pfizer Inc.

Financial disclosure appears at the end of the article.

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Treatment-resistant depression (TRD) continues to be a significant public health issue despite advances in the past 2 decades in the recognition of major depressive disorder (MDD) and despite a significant increase in the proportion of patients receiving an adequate course of treatment.[1,2]

The prevalence of TRD among patients presenting with uncomplicated MDD (i.e., without high levels of comorbidity or chronicity) is estimated to be ≈ 50% when response criteria are used to define treatment resistance and ≈ 70% when remission criteria are used.[3–5] The illness burden associated with TRD is substantial, even compared with treatment-responsive MDD, in terms of both indirect costs (lost work, decreased productivity) and direct (health care) costs.[6–9]

The high prevalence of TRD, especially using the gold-standard remission criterion, and the high degree of associated disability have led some researchers to recommend more aggressive treatment approaches, most notably, earlier use of augmentation strategies.[10] Lithium and triiodothyronine (liothyronine [T_3]) have been the most long-standing and widely used forms of augmentation. Recent meta-analyses[11–13] suggest that both agents may have benefit in TRD, but virtually all of the data come

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from studies that either were poorly designed and/or underpowered, or recruited patients whose TRD status was not well-established. A recent Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study found remission rates of 25% with T_3 augmentation and 16% with lithium augmentation of citalopram in patients with prospectively documented TRD.[14]

Another phase of the STAR*D program has also reported the largest clinical trial evaluating the efficacy of augmentation of a selective serotonin reuptake inhibitor (SSRI; citalopram) with another antidepressant (sustained-release bupropion).[15] The study found somewhat higher remission rates on bupropion treatment (39%) compared with buspirone treatment (33%). It is important to note that patients in the bupropion augmentation study were in an earlier stage of TRD than were patients in the lithium/T_3 augmentation study, which may account for the higher remission rates.

Multiple pilot studies have been reported in the past 5 years which suggest that atypical antipsychotics may be useful augmentation agents in TRD.[16–23] However, we are aware of only 1 large, double-blind study that has evaluated the acute efficacy of combination therapy with an SSRI and an atypical antipsychotic.[24] After 8 weeks, the response and remission rates, respectively, were similar for the combined olanzapine/fluoxetine treatment group (28% and 17%), compared with monotherapy with fluoxetine (29% and 13%) or nortriptyline (30% and 18%). Monotherapy with olanzapine yielded somewhat lower response (19%) and remission (13%) rates.

Ziprasidone is of interest as a potential augmentation agent in TRD because it has been reported to have higher affinity for monoamine transporter proteins than other atypicals, resulting in serotonin (5-HT) and norepinephrine reuptake inhibition that is in the range of imipramine.[25] In addition, ziprasidone has activity at 5-HT_{2A} and 5-HT_{1A} receptors, both of which have been suggested as antidepressant mechanisms.[26] Consistent with these promising central nervous system mechanisms, placebo-controlled trials of ziprasidone in patients with schizophrenia or schizoaffective disorder have demonstrated improvement in depressive symptoms.[27,28]

The objective of the current study was to extend these findings to nonpsychotic patients and obtain open-label pilot data on the efficacy of ziprasidone augmentation of sertraline in TRD patients who were nonresponders to at least 2 adequate trials of an SSRI or serotonin-norepinephrine reuptake inhibitor (SNRI) antidepressant, including a 6-week, prospective, open-label trial of sertraline. After completion of the 6-week lead-in study, nonresponders were randomized to open-label treatment with 8 weeks of additional sertraline monotherapy (Sert-mono) or ziprasidone augmentation of sertraline (Sert + Z) using 1 of 2 daily doses (Sert + Z80 mg or Sert + Z160 mg).

METHOD

Subjects

Adult outpatients aged 21 to 65 years were eligible for entry into the initial 6-week, open-label sertraline treatment period if they reported nonresponse to at least 1 course of treatment of at least 4 weeks' duration with a clinically appropriate dose of an SSRI or non-SSRI antidepressant and if their Montgomery-Asberg Depression Rating Scale (MADRS)[29] total score was ≥ 20 at screen. Subjects were excluded who met any of the following criteria: (1) a current DSM-IV diagnosis of any psychotic disorder, posttraumatic stress disorder, panic disorder, or obsessive-compulsive disorder; (2) a DSM-IV substance abuse or dependence disorder in the past 3 months; (3) a history of treatment with an atypical antipsychotic agent; (4) treatment with fluoxetine, a monoamine oxidase inhibitor, or electroconvulsive therapy during the 6 weeks prior to study entry; (5) any clinically significant abnormality on electrocardiogram (ECG); (6) current therapy with medications known to prolong the corrected QT (QTc) interval; and (7) any acute or unstable medical illness. Pregnant or breastfeeding women were also excluded, and those of childbearing potential were required to be using effective contraceptive methods.

Subjects were eligible for randomization to 8 weeks of open-label treatment with sertraline monotherapy (Sert-mono) or with Sert + Z80 mg or Sert + Z160 mg if they (1) failed to achieve at least a 30% decrease in MADRS score, (2) continued to have a Clinical Global Impressions-Severity of Illness (CGI-S)[30] score ≥ 4, (3) continued to meet DSM-IV criteria for MDD, and (4) continued not to meet all exclusion criteria.

The study protocol was approved by institutional review boards at each study site. All subjects provided written informed consent.

Study Design

Subjects were screened for 1 week for study eligibility, after which they were assigned to a prospective 6-week open-label lead-in treatment with sertraline 100 to 200 mg/day. Subjects were assessed by blinded clinician raters at the conclusion of 6 weeks of sertraline monotherapy. Subjects who continued to meet the above-specified inclusion criteria and avoid exclusion criteria were randomly assigned to 1 of the 3 treatment groups: Sert-mono, Sert + Z80, or Sert + Z160. The trial was conducted from May 2001 to October 2002.

Treatment

Sertraline was initiated at 50 mg/day during week 1, increased to 100 mg/day for week 2, and then increased, based on the investigator's judgment, to 150 mg/day for week 3 and a maximum of 200 mg/day for weeks 4 through 6. Subjects who could not tolerate the higher ser-

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traline doses were permitted dosage reductions in 50-mg increments, to a minimum of 100 mg/day, at any time during the study.

Subjects who continued to meet TRD criteria at the conclusion of the 6-week sertraline lead-in period were randomly assigned, in a 1:1:1 ratio, to 8 weeks of open-label treatment with Sert-mono versus Sert + Z80 versus Sert + Z160. Subjects in the Sert + Z80 group received ziprasidone 40 mg/day for 2 days and then 80 mg/day for the remainder of the study. Subjects in the Sert + Z160 group received ziprasidone 80 mg/day for 2 days and then 160 mg/day for the remainder of the study. Subjects unable to tolerate ziprasidone 160 mg/day could have their dosage decreased to a minimum of 80 mg/day.

Efficacy Assessments

The primary measure of efficacy was the mean change in the MADRS total score from baseline to study end point (unless otherwise specified, baseline refers to day 0 of the randomized phase of the study). The clinician who rated efficacy was blind to the subject's treatment assignment, and, whenever possible, the rater who conducted a subject's baseline assessments rated that subject at end point.

Secondary efficacy measures included the change from baseline to study end point in scores on the 17-item Hamilton Rating Scale for Depression (HAM-D-17),[31] the Hamilton Rating Scale for Anxiety (HAM-A),[32] the CGI-S scale, and the CGI-Improvement (CGI-I) scale[30] as well as MADRS responder rates. Post hoc analyses included individual MADRS item scores.

Safety Assessments

Routine safety assessments consisted of measurement of vital signs (blood pressure and heart rate) and monitoring of treatment-emergent adverse events (AEs). Investigators evaluated the severity of each AE and its possible relationship to the study drug and noted whether the AE necessitated a change in dose or withdrawal of the subject from treatment.

Additional safety assessments obtained at screening, randomization, and study end point included clinical laboratory tests (complete blood cell count with differential and platelet count, urinalysis, and blood chemistry) and electrocardiography. Physical examinations were carried out at screening and study end point. Movement disorders and extrapyramidal symptoms were rated at baseline and study end point by means of the Simpson-Angus Scale (SAS),[33] the Barnes Akathisia Scale (BAS),[34] and the Abnormal Involuntary Movement Scale (AIMS).[35]

Statistical Analyses

Study population. The intent-to-treat (ITT) population included randomized subjects who received at least 1 postbaseline efficacy assessment. Investigators recorded all observed or volunteered AEs, regardless of treatment group or suspected causal relationship to the study drug. Thus, the safety population consisted of all subjects who received at least 1 postbaseline dose of study medication.

Efficacy. Efficacy data were analyzed using last-observation-carried-forward (LOCF) analysis. Differences between treatment groups were estimated and tested (using least squares [LS] mean) based on an analysis of covariance (ANCOVA) model with terms for treatment and strata and with baseline values for response variable as covariates. Stratum 1 consisted of subjects who reported previous nonresponse to a non-SSRI antidepressant (either as monotherapy or in combination with an SSRI); stratum 2 consisted of subjects who reported previous nonresponse to an SSRI only. All statistical tests were 2-sided; statistical significance was established at .05.

Safety. The number and severity of AEs, regardless of whether they were related to treatment, were recorded. Physical examination results, vital signs, electrocardiogram results, and clinical laboratory data were summarized for each treatment group using descriptive statistics.

RESULTS

Subject Characteristics

The disposition of subjects throughout the study is summarized in Figure 1. Of the 90 subjects treated with sertraline in the open-label, 64 (71.1%) completed the 6 week lead-in phase, met protocol-defined criteria for nonresponse, and were therefore eligible to participate in the randomized open-label phase of the study. Three subjects discontinued without taking study medication assigned at randomization, resulting in an intent-to-treat (ITT) population of 61 subjects.

At the randomization baseline, the proportion of female subjects and the mean ± SD age were similar for the Sert + Z80 (54.5%; 43.1 ± 9.4 years), Sert + Z160 (47.4%; 42.6 ± 13.3 years), and Sert-mono (55.0%; 46.3 ± 10.4 years) groups. The majority of subjects were white in all 3 treatment groups: Sert + Z80, 91.0%; Sert + Z160, 94.7%, and Sert-mono, 80.0%. The mean ± SD weight (kg) and body mass index (kg/m^2) were also similar for all 3 treatment groups: Sert + Z80, 82.7 ± 19.0 and 28.0 ± 4.8; Sert + Z160, 77.4 ± 14.3 and 26.1 ± 4.5; and Sert-mono, 83.8 ± 21.8 and 28.8 ± 7.5. At randomization baseline, a similar proportion of patients in the Sert + Z80 (63.6%), Sert + Z160 (63.2%), and Sert-mono (65.0%) groups had failed to respond to at least 2 classes of antidepressants (an SSRI and a non-SSRI antidepressant).

Treatment Duration and Dosing

The median duration of treatment was somewhat lower for the 2 augmentation therapies (Sert + Z80, 52 days; Sert + Z160, 49 days) compared with Sert-mono

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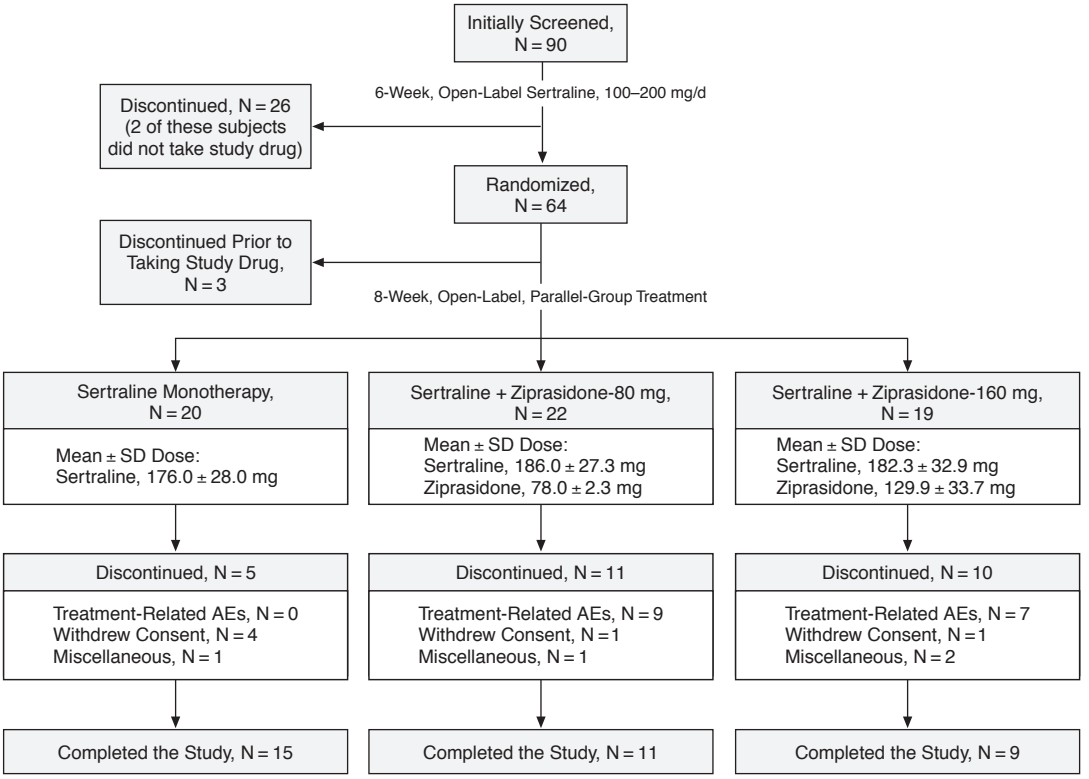
Figure 1. Patient Disposition



Abbreviation: AE = adverse event.

(56 days). The mean daily doses of sertraline were somewhat higher in the 2 augmentation groups (see Figure 1) compared with the Sert-mono group. The mean daily dose of ziprasidone (78 mg) was close to the prescribed dose in the Sert + Z80 treatment group and was somewhat lower (130 mg) than the prescribed dose in the Sert + Z160 treatment group.

Efficacy

Primary efficacy measurement. MADRS scores at randomization baseline were similar in all 3 treatment groups. There was no significant treatment-by-strata interaction, so the results are reported for each group as a whole. In each treatment group, the MADRS scores improved over the course of study treatment. At study end point, the effect size was greater for Sert + Z160 (0.41) than for Sert + Z80 (0.17), but the improvement in the MADRS score did not achieve significance for either treatment group relative to Sert-mono (Table 1).

Secondary efficacy measurements. No significant treatment-by-strata interactions were noted on any of the secondary efficacy measures (except the HAM-A scale, for which the interaction was not present at study end point), so these results are also reported for the groups as a whole.

There were no significant differences between Sert + Z80 or Sert + Z160 and Sert-mono in end point improvement in scores on the HAM-D-17, CGI-I, and HAM-A (Table 1), though effect sizes were in the 0.40 range for the higher-dose (Sert + Z160) treatment group. Improvement in the CGI-S score at study end point was significant ($p < .05$) for the Sert + Z160 treatment group (Table 1).

End point response rates (≥ 50% decrease from baseline MADRS score) and remission rates (MADRS score ≤ 10) were not significantly different between the 2 augmentation groups and the Sert-mono group (Figure 2).

Safety

Adverse events. The proportion of subjects experiencing at least 1 adverse event was higher in the Sert + Z80 group (100%) and Sert + Z160 group (84.2%) compared with the Sert-mono group (40.0%). No serious adverse events were reported, but a high proportion of subjects discontinued treatment due to an adverse event in both the Sert + Z80 group (40.9%) and the Sert + Z160 group (36.8%), while none discontinued in the Sert-mono group. In addition, 4 subjects (21.1%) in the Sert + Z160 group required a dose reduction or temporary discontinu-

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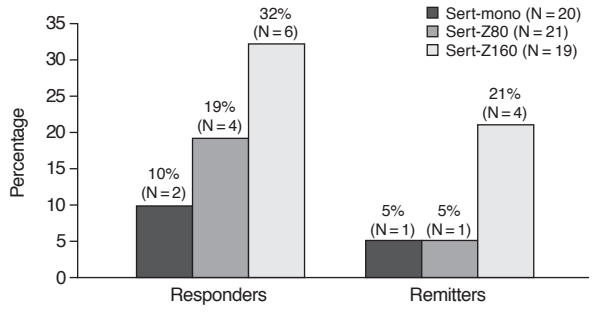
Table 1. Change in Efficacy Parameters at LOCF End Point

Parameter	N	Baseline Value, Mean (SD)	End Point Change, LS Mean (SE)	p Value (vs Sert-mono)	Cohen d Effect Size
MADRS total					
Sert-mono	20	30.7 (5.4)	–4.45 (2.03)	…	…
Sert + Z80	21	30.2 (5.7)	–5.98 (1.87)	.554	0.17
Sert + Z160	19	28.9 (5.4)	–8.27 (2.17)	.152	0.41
HAM-D-17 total					
Sert-mono	20	20.3 (3.6)	–2.48 (1.47)	…	…
Sert + Z80	21	19.1 (4.0)	–3.39 (1.36)	.630	0.14
Sert + Z160	19	19.7 (3.9)	–5.04 (1.53)	.180	0.39
CGI-S					
Sert-mono	20	4.3 (0.5)	–0.18 (0.28)	…	…
Sert + Z80	21	4.5 (0.5)	–0.46 (0.25)	.422	0.23
Sert + Z160	19	4.4 (0.7)	–1.01 (0.29)	.020	0.66
CGI-I					
Sert-mono	20	3.8 (0.4)	–0.21 (0.30)	…	…
Sert + Z80	21	3.7 (0.6)	–0.39 (0.27)	.647	0.14
Sert + Z160	19	3.4 (0.8)	–0.63 (0.32)	.293	0.31
HAM-A total					
Sert-mono	19	15.2 (5.8)	–1.06 (1.52)	…	…
Sert + Z80	18	16.5 (5.4)	–1.11 (1.46)	.981	0.01
Sert + Z160	17	15.2 (4.2)	–2.54 (1.61)	.443	0.21

Abbreviations: CGI-I = Clinical Global Impressions-Improvement, CGI-S = CGI-Severity of Illness, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D-17 = 17-item Hamilton Rating Scale for Depression, LOCF = last observation carried forward, LS = least squares, MADRS = Montgomery-Asberg Depression Rating Scale, Sert-mono = sertraline monotherapy group, Sert + Z80 = group receiving sertraline plus ziprasidone 80 mg/day, Sert + Z160 = group receiving sertraline plus ziprasidone 160 mg/day.
Symbol: … = not applicable.

Figure 2. Response and Remission Rates at Study End Point Based on MADRS Criteria[a]



[a]Response criteria: ≥ 50% reduction in MADRS total score at end point; remission criteria: MADRS total score ≤ 10 at end point.
Abbreviations: MADRS = Montgomery-Asberg Depression Rating Scale, Sert-mono = sertraline monotherapy group, Sert + Z80 = group receiving sertraline plus ziprasidone 80 mg/day, Sert + Z160 = group receiving sertraline plus ziprasidone 160 mg/day.

ation due to an adverse event. The most common all-causality adverse events are summarized in Table 2.

Vital signs, physical examinations, and clinical laboratory values. There were no clinically significant changes from baseline to study end point in any treatment group in sitting or standing blood pressure and pulse, physical examination parameters, or laboratory values.

Electrocardiograms. There were no treatment-emergent abnormalities on ECG in any of the 3 treatment groups. The mean change from baseline in QTc (Bazett's) was similar in the Sert + Z80 (+1.64 msec; N = 18), Sert + Z160 (+7.64 msec; N = 17), and Sert-mono (–2.19 msec; N = 19) groups. Only 1 subject, in the Sert + Z80 group, had a treatment-emergent QTc interval ≥ 450 msec: 454 msec on day 28, decreasing to 422 msec at end point.

Movement disorder evaluations. There were no clinically relevant changes from baseline to study end point in SAS, BAS, or AIMS scores for any treatment group. Small but statistically significant increases in BAS and AIMS scores ($p < .05$) were seen for the sertraline plus Sert + Z80 group, but not for the Sert + Z160 group.

DISCUSSION

The results of this randomized, open-label, parallel-group pilot study suggest that ziprasidone augmentation of an SSRI, using a daily dose of 160 mg, is a promising strategy for the treatment of TRD. The effect size of the Sert + Z160 group was 0.43 on the primary outcome measure, the MADRS, but was only 0.17 in the Sert + Z80 group, indicating that antidepressant benefit in a TRD population may require use of higher doses of ziprasidone. The effect sizes of the Sert + Z160 group were similarly higher on secondary measures (HAM-D, CGI-I, CGI-S). Response and remission rates, using MADRS criteria, were also higher in the Sert + Z80 treatment group than in the Sert-mono treatment group.

On the basis of these pilot data, it is estimated that a sample size of 124 per treatment group would be needed

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Table 2. Incidence of Treatment-Emergent Adverse Events During Augmentation Therapy (all causality, ≥ 10%).

Adverse Event	Sertraline Monotherapy (N = 20), % (N)	Sertraline + Ziprasidone 80 mg/d (N = 22), % (N)	Sertraline + Ziprasidone 160 mg/d (N = 19), % (N)
Insomnia	5.0 (1)	36.4 (8)	31.6 (6)
Asthenia	0	22.7 (5)	26.3 (5)
Agitation	0	22.7 (5)	26.3 (5)
Somnolence	10.0 (2)	22.7 (5)	15.8 (3)
Dizziness	0	18.2 (4)	21.1 (4)
Tremor	5.0 (1)	22.7 (5)	10.5 (2)
Dry mouth	0	9.1 (2)	21.1 (4)
Nausea	0	4.5 (1)	21.1 (4)
Headache	5.0 (1)	18.2 (4)	15.8 (3)
Akathisia	0	4.5 (1)	21.1 (4)
Abnormal vision	0	4.5 (1)	21.1 (4)
Respiratory infection	0	18.2 (4)	5.3 (1)
Constipation	0	13.6 (3)	5.3 (1)
Abnormal thinking	0	9.1 (2)	10.5 (2)

to have 90% power to demonstrate significance for augmentation with a 160-mg dose of ziprasidone versus SSRI monotherapy at an $\alpha = .05$. The initial number of patients randomized would have to be adjusted based on anticipated attrition rates. For reasons that are uncertain, the attrition rate in the current study was higher (50%) than has typically been reported in previous TRD trials, in which attrition has ranged from < 10% up to 47%.[16–23]

The estimated sample size of 124 per treatment group is similar to the sample size (N = 140) used in a large, double-blind trial in TRD.[24] In that 8-week study, the combined olanzapine/fluoxetine treatment group had an effect size of 0.39 at 4 weeks, and combined treatment was significantly superior to fluoxetine monotherapy on the MADRS at the 4-week time point. However, statistical significance was lost at week 8 (effect size, 0.03), primarily due to continued improvement in the fluoxetine monotherapy treatment group.

In the current study, improvement on the MADRS in the sertraline monotherapy group remained low at the 8-week end point. Without careful quantification of the number, and adequacy, of previous failed antidepressant trials, it is difficult to know whether this is attributable to a higher level of treatment resistance in the current patient sample. The low response rate (13.5%) among patients in the current study who completed 6 weeks of lead-in treatment with sertraline suggests that the sample was fairly treatment resistant. By comparison, the response rate among patients who had failed a previous SSRI trial was 26.7% with sertraline in the recently reported STAR*D trial.[36]

Safety results with ziprasidone in the present study are similar to those reported in clinical trials of schizophrenia, schizoaffective disorder, or acute mania,[27,28,37] though the incidence of adverse events was somewhat higher in the present study. This is likely attributable to use of higher doses of sertraline in this study. No clinically significant ECG or laboratory abnormalities emerged during the course of study treatment.

CONCLUSIONS

The results of this pilot study suggest that ziprasidone augmentation might be an efficacious strategy in the treatment of TRD, especially at a dose of 160 mg/day. A power calculation, based on the Sert + Z160 effect size of 0.41, indicates that a double-blind trial with a sample size of approximately 125 to 160 per treatment group should be sufficient to demonstrate significant efficacy for a ziprasidone augmentation strategy. Controlled studies to assess the efficacy of ziprasidone in patients with TRD are currently underway.

Drug names: bupropion (Wellbutrin and others), buspirone (BuSpar and others), citalopram (Celexa and others), fluoxetine (Prozac and others), imipramine (Tofranil and others), liothyronine (Triostat, Cytomel, and others), lithium (Lithobid, Eskalith, and others), nortriptyline (Pamelor and others), olanzapine (Zyprexa), sertraline (Zoloft and others), ziprasidone (Geodon).

Financial disclosure: Dr. Dunner has received recent grant support from Eli Lilly, Pfizer, GlaxoSmithKline, Wyeth, Bristol-Myers Squibb, Cyberonics, Janssen, and Novartis; has served as a consult and/or on advisory boards for Eli Lilly, Pfizer, GlaxoSmithKline, Wyeth, Bristol-Myers Squibb, Roche Diagnostics, Cypress, Corcept, Janssen, Novartis, Shire, Somerset, and Otsuka; and has served on the speakers bureau for Eli Lilly, Pfizer, GlaxoSmithKline, Wyeth, Bristol-Myers Squibb, Organon, and Forest. Dr. Amsterdam has received grant/research support from the National Institute of Mental Health, the National Institutes of Health/National Center for Complementary and Alternative Medicine, Eli Lilly, Pfizer, and Sanofi and has served on the speakers or advisory boards for Wyeth, Bristol-Myers Squibb, and Cephalon. Dr. Shelton has received grant/research support from Eli Lilly, GlaxoSmithKline, Janssen, Pfizer, Sanofi, Wyeth-Ayerst, AstraZeneca, and Abbott; has been a paid consultant to Pfizer and Janssen; and has served on the speakers bureau for Bristol-Myers Squibb, Eli Lilly, Janssen, Pfizer, GlaxoSmithKline, Solvay, Wyeth-Ayerst, and Abbott. Drs. Loebel and Romano are employees of Pfizer.

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Reprinted with correction (see page 1071).