Ziprasidone Augmentation of Selective Serotonin Reuptake Inhibitors (SSRIs) for SSRI-Resistant Major Depressive Disorder

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Background: Due to their favorable side-effect profile, atypical antipsychotic agents offer important therapeutic advantages in mood disorders. Ziprasidone, an atypical antipsychotic agent with strong 5-HT_{1A} agonist activity, may be particularly useful when used in conjunction with standard antidepressants in treatment-resistant depression. The purpose of this study is to test this hypothesis in depressed outpatients who have not experienced significant clinical improvement following an adequate trial of a selective serotonin reuptake inhibitor (SSRI).

Method: Twenty patients with major depressive disorder (MDD) who had failed to experience a clinical response to an adequate trial of an SSRI were treated with open-label ziprasidone in addition to their SSRI for 6 weeks between February 2002 and December 2002. MDD was diagnosed with the Structured Clinical Interview for DSM-IV Axis I disorders. Clinical response was defined as a 50% or greater decrease in depressive symptoms during the course of the trial (baseline to endpoint), as measured by the HAM-D-17 total score.

Results: Thirteen of 20 patients (65.0%) completed the trial. Using a completer analysis, 8 patients (61.5%) were classified as responders. An intent-to-treat (ITT) analysis resulted in 10 responders (50.0%). The overall proportion of remitters was 5 of 13 (38.5%) using a completer analysis and 5 of 20 (25.0%) using the ITT analysis. Ziprasidone administration appeared to be safe, with no clinically significant QTc prolongation or severe adverse events observed in any of the study participants.

Conclusion: These results suggest a possible augmentation role for ziprasidone when used in conjunction with SSRIs in SSRI-resistant MDD.

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Studies suggest that 29% to 46% of depressed patients show only partial or no response to antidepressants, with most taking a selective serotonin reuptake inhibitor (SSRI) as an initial treatment.[1] Among responders to antidepressant treatment, residual symptoms are rather common[2] and have been shown to be associated with greater likelihood of relapsing and perhaps having a poorer long-term prognosis.[3] When one surveys psychiatrists to assess their perceptions of what works in refractory depression, it is clear that the most popular strategies, particularly newer ones, are not those that are best supported by evidence.[4]

Due to their favorable side-effect profile, atypical antipsychotic agents may offer important therapeutic advantages in mood disorders. Ziprasidone, in particular, due to its unique receptor-affinity profile, may be particularly useful when used in conjunction with standard antidepressants in the treatment of refractory depression. Specifically, in addition to an affinity for the dopamine-2 (D_2), serotonin-2A (5-HT_{2A}),[5–7] 5-HT_{2C},[6,8] and 5-HT_{1D} serotonergic receptors,[6,7] ziprasidone also acts as a strong 5-HT_{1A} receptor agonist,[7,9] a property that sets it aside

from the other atypical antipsychotics.[6,9] In fact, among the atypical agents, ziprasidone was found to possess the most potent affinity for the 5-HT_{1A}, 5-HT_{1D}, and 5-HT_2 receptors,[7,10] and the highest 5-HT_{2A}/D_2 affinity ratio compared with all marketed antipsychotics. Clinical evidence suggesting a potential role of the 5-HT_{1A} receptor in the treatment of major depressive disorder (MDD) comes from the antidepressant properties of selective 5-HT_{1A} receptor partial agonists. Ipsapirone,[11,12] buspirone,[13–16] and gepirone[17–21] have been shown to be effective in a number of clinical trials of MDD. Furthermore, it has been hypothesized that the strong 5-HT_{1A} agonist properties of ziprasidone are associated with the release of dopamine in rat prefrontal cortex.[9] Additionally, ziprasidone inhibits the neuronal uptake of 5-HT and norepinephrine, comparable to the antidepressant imipramine,[22] as well as the neuronal uptake of dopamine.[10]

In addition to the absence of controlled clinical trials, the main obstacles for the use of atypical antipsychotic agents while treating patients with refractory mood and/or anxiety disorders are the potential risks of extrapyramidal symptoms, neuroleptic malignant syndrome, and tardive dyskinesia. Such risks are markedly reduced compared with the typical antipsychotic agents[23,24] and the risk of developing side effects such as sedation, hyperprolactinemia, and weight gain.[25]

Ziprasidone, however, appears to be less likely to cause weight gain,[22,26–31] elevations in prolactin levels,[32–36] and extrapyramidal side effects[26,27,30,32,33,36–38] than the other agents in its class. In fact, short-term treatment with ziprasidone appears to lead to significant reduction in serum cholesterol and triglyceride levels,[39] while to date there have been no reports linking ziprasidone to any form of glucose dysregulation.[40] Although the U.S. Food and Drug Administration labeling for ziprasidone includes a warning about the potential for QTc prolongation, in clinical trials, ziprasidone was found to have a small effect on the QTc interval of approximately 6 to 10 ms, less than some of the standard antipsychotic agents.[41] More recent studies revealed no serious electrocardiographic changes or severe cardiac adverse events.[26,27,30,32,33,36,38] Finally, there are no reports to date of tardive dyskinesia associated with prolonged ziprasidone exposure, although there is a case report of ziprasidone being associated with the reemergence of tardive dyskinesia.[42]

In summary, ziprasidone appears to be safe and well tolerated, with a very low likelihood of sedation, weight gain, prolactin elevation, or extrapyramidal side effects. Due to the unique receptor-affinity profile, it has been hypothesized that ziprasidone may be particularly useful when used in conjunction with standard antidepressants in treatment-resistant MDD. The purpose of this study is to test this hypothesis in patients with MDD who have not experienced significant clinical improvement following treatment with SSRIs of adequate dose and duration.

METHOD

Subject Selection

Study subjects were recruited through general newspaper and radio advertisements that listed common symptoms of depression or through clinical referrals. Men and women, aged 18 to 65 years, with MDD diagnosed by the use of the Structured Clinical Interview for DSM-IV Axis I disorders (SCID I/P),[43] and with an initial 17-item Hamilton Rating Scale for Depression (HAM-D-17)[44] score ≥ 14, were eligible for the study. All patients had been treated with an adequate trial of an SSRI prior to study entry, defined as a minimum dose of 20 mg/day of fluoxetine, paroxetine, or citalopram or 50 mg/day of sertraline for a minimum duration of 6 weeks. All patients were taking an SSRI at the time of study enrollment and remained on that dose for at least 4 weeks. All patients continued their SSRI medication at the same dose throughout the study.

The following patients were excluded: pregnant women, patients who posed a serious suicidal or homicidal risk, and those with organic mental disorders, an active substance or alcohol use disorder within the last 3 months, schizophrenia, delusional disorder, mood congruent or incongruent psychosis, bipolar disorder, antisocial personality disorder, or a history of allergy to the study drug. Patients with significant cardiac conduction problems on screening electrocardiogram, electrolyte abnormalities, significant cardiovascular disease, a history of QTc prolongation, or those taking medications that prolong the QTc were also excluded. Finally, patients who had failed to respond to 4 or more adequate antidepressant trials during the course of their current major depressive episode (MDE) and patients who had had electroconvulsive therapy within 6 months of study enrollment were excluded.

Study Procedures

A total of 20 subjects were enrolled at the Depression Clinical and Research Program (DCRP) at Massachusetts General Hospital (Boston, Mass.). Written informed consent was obtained before any protocol-specified procedures, which were approved by the hospital's Institutional Review Board, were carried out. Patients were seen weekly for the first 4 weeks and at week 6 for the final visit. The following instruments were administered during each visit by experienced psychiatrists and psychologists who were trained in their use: the HAM-D-17[44] and the Clinical Global Impressions-Severity of Illness (CGI-S) and -Improvement (CGI-I) scales.[45] In our group, training in the use of instruments such as the HAM-D-28 and SCID I/P is done by peer review of videotaped interviews. Patients also completed the self-rated, 92-item Symptom Questionnaire (SQ)[46] during every study visit, which contains, among others, subscales for anxiety, de-

pression, hostility, somatic symptoms, and somatic well-being. During the first visit, all patients were instructed to take 1 tablet of the study medication (ziprasidone, 20 mg) twice daily. Starting with week 2, the medication dosage was increased by 20-mg/week increments, up to 80 mg b.i.d., until patients experienced a clinical response or significant side effects. At the conclusion of the trial, responders and nonresponders were offered the option of up to 3 months free follow-up at the DCRP.

Statistical Tests

The primary test of outcome was based on the assessment of the difference between baseline and endpoint in depression severity following ziprasidone treatment. Clinical response was defined as a 50% or greater reduction in HAM-D-17 score from baseline to endpoint. Remission was defined as a final HAM-D-17 score of ≤ 7. A paired t test was used to assess the changes in depression severity between the baseline HAM-D-17 score and the endpoint HAM-D-17 score. Two analyses were completed: (1) a completer analysis of all patients finishing the trial and (2) an intent-to-treat (ITT) analysis examining all patients enrolled in the trial, using the last recorded HAM-D-17 score as the endpoint. Appropriate parametric and nonparametric tests were used to compare differences in demographic and clinical variables between responders and nonresponders.

RESULTS

The mean ± SD age for all patients was 41.9 ± 10.1 years and 7 of 20 subjects (35.0%) were women. The mean duration of the current MDE was 32.9 ± 38.1 months. The mean number of lifetime MDEs was 2.9 ± 2.8. The mean age at onset of MDD was 23.6 ± 14.7 years. The mean number of adequate antidepressant trials failed during the current MDE was 1.9 ± 1.4. The mean total HAM-D-17 and CGI-S scores during the baseline visit were 21.8 ± 4.9 and 4.8 ± 0.9, respectively. Overall, 6 patients enrolled had an MDE resistant to fluoxetine; 5, to sertraline; 6, to citalopram; and 3, to paroxetine. The mean fluoxetine, sertraline, citalopram, and paroxetine doses during the present trial were 65.0 ± 10.0 mg, 215.0 ± 171.0 mg, 48.0 ± 22.8 mg, and 43.3 ± 15.3 mg, respectively. Of note, all but 1 patient failed to respond to SSRI doses higher than the required minimum to enroll in the study, all but 1 patient failed to respond to an SSRI trial longer than the required minimum to enroll, and all but 1 patient had a baseline HAM-D-17 score of ≥ 16.

Thirteen of 20 patients (65.0%) completed the 6-week trial. The reasons for premature discontinuation were intolerance (4/20 or 20.0%), discontinuation of the SSRI (1/20 or 5.0%), and lost to follow-up (2/20 or 10.0%). The most common adverse events (reported by 10% or more of the sample) are listed in Table 1. No patient experienced a severe adverse event. There was no change in QTc from baseline to week 6 (0.424 ms vs. 0.423 ms, respectively; $p > .05$). No patient had a QTc > 500 ms at week 6. Only 2 patients experienced a QTc increase greater than 10 ms (30 ms in both cases). Overall, there was a nonsignificant decrease in cholesterol levels from baseline to endpoint (208.7 mg/dL vs. 194.7 mg/dL, respectively; $p > .05$).

Table 1. Common Side Effects in Patients Treated With Ziprasidone Plus an SSRI[a]

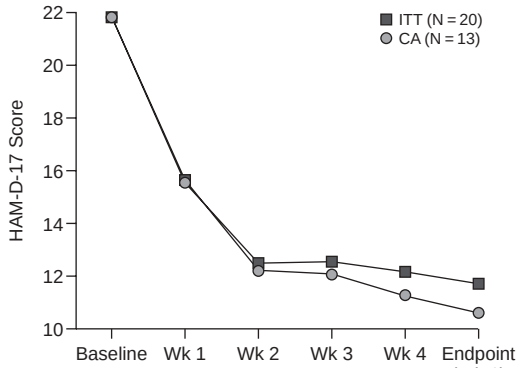
System Effect	%	N
Musculoskeletal/nervous		
Fatigue/sedation	50.0	10
Sleep disturbance	30.0	6
Restlessness	15.0	3
Tremor	15.0	3
Bruxism	15.0	3
Headaches	10.0	2
Gastrointestinal		
Dry mouth	20.0	4
Gastrointestinal distress	20.0	4
Urogenital		
Urinary frequency	10.0	2

[a]Reported by 10% or more of the sample (N = 20).
Abbreviation: SSRI = selective serotonin reuptake inhibitor.

Using a completer analysis, 8 patients (61.5%) were classified as responders. The proportion of remitters was 5 of 13 (38.5%). An ITT analysis revealed 10 (50.0%) responders. The overall proportion of remitters was 5 of 20 (25.0%). The mean daily ziprasidone dose was 82.1 ± 48.9 mg. The mean ziprasidone dose in the ITT sample was 92.0 ± 46.3 mg in nonresponders and 71.1 ± 52.0 mg in responders. Figure 1 presents mean HAM-D-17 scores by week for ITT and completer group samples. There was also a statistically significant improvement in SQ-depression scores (17.5 vs. 12.5, respectively; $p = .001$), SQ-anxiety scores (14.1 vs. 11.8, respectively; $p = .002$), and SQ-anger/hostility scores (10.4 vs. 6.9, respectively; $p = .021$), but not in SQ-somatic symptom scores (9.6 vs. 10.6, respectively; $p > .05$) or SQ-somatic well-being scores (1.5 vs. 1.5, respectively; $p > .05$) from baseline to endpoint in the ITT sample.

At the conclusion of the trial, 6 of 8 responders (75.0%) and 0 of 2 partial responders who completed the trial chose to continue to be followed at the DCRP free of charge and remained on their ziprasidone regimen. Two of the 6 responders chose to follow up with their psychiatrists. The mean duration of follow-up was 15.3 ± 6.9 weeks for these 6 responders. By the end of the free follow-up period, 2 responders who had not achieved remission by the last visit of the trial remitted, 1 relapsed, 1 maintained the response but never achieved remission, while the remaining 2 responders who had achieved remission maintained it during the free follow-up phase. Of note, 3 of the patients who responded during the trial had their ziprasidone regimen converted from 20 mg b.i.d. to

Figure 1. Change in Mean HAM-D-17 Scores in a 6-Week Trial of Ziprasidone Augmentation of SSRIs



% Responders					
ITT	25.0	40.0	40.0	50.0	50.0
CA	27.8	36.8	43.8	61.5	61.5

Abbreviations: CA = completer analysis, HAM-D-17 = 17-item Hamilton Rating Scale for Depression, ITT = intent to treat, SSRIs = selective serotonin reuptake inhibitors.

40 mg q.d. because once-daily administration was more convenient for them. These 3 patients had achieved remission status by the end of the free follow-up period.

DISCUSSION

The present findings suggest the potential usefulness of ziprasidone as an augmentation to SSRIs in treatment-resistant depression. Among 20 patients with an MDE resistant to an adequate trial of an SSRI, 10 (50.0%) responded, 5 of whom achieved remission, after 6 weeks of augmentation with ziprasidone. In addition, there was significant improvement in SQ scores for depressed mood, anxiety, and hostility/anger in the entire sample of patients treated with ziprasidone (N = 20). Furthermore, when we examined the rate of change of depressive symptoms over time, improvement with ziprasidone was robust and rapid, with a considerable proportion of overall improvement having occurred within 1 week of treatment (see Figure 1). This finding is in accordance with 2 other studies[47,48] reporting rapid improvement in depressive symptoms with olanzapine and risperidone augmentation of SSRIs. The reason for this rapid improvement remains unclear, but may be related to dopamine release in the prefrontal cortex seen when atypical antipsychotics are coadministered with SSRIs.[9,49] In fact, in view of this rapid response, questions have been raised about whether overall antidepressant efficacy of atypical antipsychotics persists. However, in the present study, 5 of 6 completers (83.3%) who had responded during the trial and chose to continue to receive free treatment with ziprasidone at the DCRP either maintained their improvement or improved further.

In the present study, ziprasidone augmentation appeared to be safe, with no patient experiencing a severe adverse event or a clinically significant increase in QTc. However, a significant number of patients (35% overall, 20% for intolerance) discontinued treatment, a rather high dropout rate for an open trial and similar to discontinuation rates reported in meta-analyses of tricyclic antidepressants.[50] It is also worthwhile to point out that even though the risk of neuroleptic malignant syndrome and tardive dyskinesia with atypical antipsychotics is as yet unknown, the present study supports the use of atypical antipsychotics in resistant MDD rather than as first-line treatment in MDD.

The major limitation of this study was the absence of placebo. Without the use of placebo, it is impossible to separate augmentation drug response from clinical response due to continued administration of the SSRI. It is important to keep in mind that the relatively short minimal adequate duration of 6 weeks for an SSRI trial as a criterion for study entry may have been responsible for considerable response to continued treatment with the SSRI. However, in reality, patients enrolled in the present trial had actually been treated with the "augmented" SSRI for much longer, as only 1 patient had been taking their SSRI for less than 10 weeks. Furthermore, given that the present sample consisted of patients with treatment-resistant depression, it is reasonable to assume that the placebo response rate would be much lower.[51] In this context, a response rate of 50.0% is likely to be clinically significant. An additional limitation is the definition of minimal adequate SSRI dose for study entry as an equivalent of 20 mg of fluoxetine or 50 mg of sertraline, although 17 of 20 enrolled patients had failed much higher doses. A further limitation is the definition of minimal severity for entry into the study as a baseline HAM-D-17 score of ≥ 14, although all patients enrolled but 1 had a HAM-D-17 score of ≥ 16 at baseline (mean HAM-D-17 score at baseline was 21.8 ± 4.9).

CONCLUSION

One in every 2 patients with depression resistant to an adequate trial of SSRIs responded when ziprasidone was added to their antidepressant regimen. Overall, 1 in every 4 patients experienced complete remission by the end of the trial. Ziprasidone augmentation should be among the options considered after a patient does not respond to an adequate SSRI trial.

Drug names: buspirone (BuSpar and others), citalopram (Celexa), fluoxetine (Prozac and others), imipramine (Tofranil, Surmontil, and others), olanzapine (Zyprexa), paroxetine (Paxil and others), sertraline (Zoloft), ziprasidone (Geodon).

REFERENCES

1. Fava M, Davidson KG. Definition and epidemiology of treatment-resistant depression. Psychiatr Clin North Am 1996;19:179–200

2. Nierenberg AA, Wright EC. Evolution of remission as the new standard in the treatment of depression. J Clin Psychiatry 1999;60(suppl 22):7–11
3. Fava M, Kaji J. Continuation and maintenance treatments of major depressive disorder. Psych Annals 1994;42:281–290
4. Mischoulon D, Fava M, Rosenbaum JF. Strategies for augmentation of SSRI treatment: a survey of an academic psychopharmacology practice. Harv Rev Psychiatry 1999;6:322–326
5. Seeger TF, Seymour PA, Schmidt AW, et al. Ziprasidone (CP-88,059): a new antipsychotic with combined dopamine and serotonin receptor antagonist activity. J Pharmacol Exp Ther 1995;275:101–113
6. Sprouse JS, Reynolds LS, Braselton JP, et al. Comparison of the novel antipsychotic ziprasidone with clozapine and olanzapine: inhibition of the dorsal raphe firing and the role of 5-HT1A receptor activation. Neuropsychopharmacology 1999;21:622–631
7. Richelson E, Souder T. Binding of antipsychotic drugs to human brain receptors, focus on newer generation compounds. Life Sci 2000;68: 29–39
8. Herrick-Davis K, Grinde E, Teitler M. Inverse agonist activity of atypical antipsychotic drugs at human 5-hydroxytryptamine2C receptors. J Pharmacol Exp Ther 2000;295:226–232
9. Rollema H, Lu Y, Schmidt AW, et al. 5-HT(1A) receptor activation contributes to ziprasidone-induced dopamine release in the rat prefrontal cortex. Biol Psychiatry 2000;48:229–237
10. Tatsumi M, Jansen K, Blakely RD, et al. Pharmacological profile of neuroleptics at human monoamine transporters. Eur J Pharmacol 1999;368:277–283
11. Lapierre YD, Silverstone P, Reesal R, et al. A Canadian multicenter study of three fixed doses of controlled-release ipsapirone in outpatients with moderate to severe major depression. J Clin Psychopharmacol 1998;18: 268–273
12. Heller AH, Beneke M, Kuemme B, et al. Ipsapirone evidence for efficacy in depression. Psychopharmacol Bull 1990;136:219–223
13. Robinson DS, Rickels K, Feighner J, et al. Clinical effects of the 5HT1a partial agonist in depression: a composite analysis of buspirone in the treatment of depression. J Clin Psychopharmacol 1990;10(suppl 3):67–76
14. Rickels K, Amsterdam JD, Clary C, et al. Buspirone in major depression: a controlled study. J Clin Psychiatry 1991;52:34–38
15. Schweizer EE, Amsterdam J, Rickels K, et al. Open trial of buspirone in the treatment of major depressive disorder. Psychopharmacol Bull 1986; 22:183–185
16. Dimitriou EC, Dimitriou CE. Buspirone augmentation of antidepressant therapy. J Clin Psychopharmacol 1998;18:465–469
17. Rausch JL, Ruegg R, Moeller FG. Gepirone as a 5HT1A agonist in the treatment of major depression. Psychopharmacol Bull 1990;26:169–173
18. Jenkins SW, Robinson DS, Fabre LF Jr, et al. Gepirone in the treatment of major depression. J Clin Psychopharmacol 1990;10(suppl 3):77–85
19. McGrath PJ, Stewart JW, Quitkin FM, et al. Gepirone treatment of atypical depression: preliminary evidence of serotonergic involvement. J Clin Psychopharmacol 1994;14:347–352
20. Wilcox CS, Ferguson JM, Dale JL, et al. A double-blind trial of low- and high-dose ranges of gepirone ER compared with placebo in the treatment of depressed outpatients. Psychopharmacol Bull 1996;32:335–342
21. Feiger AD. A double-blind comparison of gepirone extended release, imipramine, and placebo in the treatment of outpatient major depression. Psychopharmacol Bull 1996;32:659–665
22. Schmidt AW, Lebel A, Howard HR, et al. Ziprasidone: a novel antipsychotic agent with a unique human receptor binding profile. Eur J Pharmacol 2001;425:197–201
23. Tarsy D, Baldessarini RJ, Tarazi FI. Effects of newer antipsychotics on extrapyramidal function. CNS Drugs 2002;16:23–45
24. Thase ME. What role do atypical antipsychotic drugs have in treatment-resistant depression? J Clin Psychiatry 2002;63:95–103
25. Brown CS, Markowitz JS, Moore TR, et al. Atypical antipsychotics, pt 2: adverse effects, drug interactions, and costs. Ann Pharmacother 1999;33:210–217
26. Daniel DG, Zimbroff DL, Potkin SG, et al. Ziprasidone 80 mg/day and 160 mg/day in the acute exacerbation of schizophrenia and schizoaffective disorder: a 6-week placebo-controlled trial. Ziprasidone Study Group. Neuropsychopharmacology 1999;20:491–505
27. Allison DB, Fontaine KR, Heo M, et al. The distribution of body mass index among individuals with and without schizophrenia. J Clin Psychiatry 1999;60:215–220
28. Allison DB, Mentore JL, Heo M, et al. Antipsychotic induced weight gain: a comprehensive research synthesis. Am J Psychiatry 1999;156: 1686–1696
29. Taylor DM, McAskill R. Atypical antipsychotics and weight gain—a systematic review. Acta Psychiatr Scand 2000;101:416–432
30. Sallee FR, Kurlan R, Goetz CG, et al. Ziprasidone treatment of children and adolescents with Tourette's syndrome: a pilot study. J Am Acad Child Adolesc Psychiatry 2000;39:292–299
31. Wetterling T. Body weight gain with atypical antipsychotics: a comparative review. Drug Saf 2001;24:59–73
32. Keck P, Buffenstein A, Ferguson J, et al. Ziprasidone 40 and 120 mg/day in the acute exacerbation of schizophrenia and schizoaffective disorder: a 4-week placebo-controlled trial. Psychopharmacology (Berl) 1998;140: 173–184
33. Goff DC, Posever T, Herz L, et al. An exploratory haloperidol-controlled dose-finding study of ziprasidone in hospitalized patients with schizophrenia or schizoaffective disorder. J Clin Psychopharmacol 1998;18: 296–304
34. Micelli JJ, Wilner KD, Hansen RA, et al. Single and multiple dose pharmacokinetics of ziprasidone under non-fasting conditions in healthy male volunteers. Br J Clin Pharmacol 2000;49(suppl 1):5–13
35. Petty RG. Prolactin and antipsychotic medications: mechanism of action. Schizophr Res 1999;1(suppl 35):67–73
36. Keck PE, Reeves KR, Harrigan EP. Ziprasidone in the short-term treatment of patients with schizoaffective disorder: results from two double-blind, placebo-controlled, multicenter studies. J Clin Psychopharmacol 2001;21:27–35
37. Bagnall A, Lewis RA, Leitner ML. Ziprasidone for schizophrenia and severe mental illness (Cochrane Review). Cochrane Database Syst Rev 2000;4:CD001945
38. Brook S, Lucey JV, Gunn KP, for the Ziprasidone I.M. Study Group. Intramuscular ziprasidone compared with intramuscular haloperidol in the treatment of acute psychosis. J Clin Psychiatry 2000;61:933–941
39. Kingsbury SJ, Fayek M, Trufasiu D, et al. The apparent effects of ziprasidone on plasma lipids and glucose. J Clin Psychiatry 2001;62:347–349
40. Haupt DW, Newcomer JW. Hyperglycemia and antipsychotic medications. J Clin Psychiatry 2001;62(suppl 27):15–26
41. Glassman AH, Bigger TJ. Antipsychotic drugs: prolonged QTc interval, torsade de pointes, and sudden death. Am J Psychiatry 2001;158: 1774–1782
42. Rosenquist KJ, Walker SS, Ghaemi SN. Tardive dyskinesia and ziprasidone [letter]. Am J Psychiatry 2002;159:1436
43. 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
44. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62
45. Guy W. ECDEU Assessment Manual for Psychopharmacology, Revised. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health;1976:218–222
46. Kellner R. A symptom questionnaire. J Clin Psychiatry 1987;48:268–274
47. Shelton RC, Tollefson GD, Tohen M, et al. A novel augmentation strategy for treating resistant major depression. Am J Psychiatry 2001;158: 131–134
48. Rapaport M, Canuso C, Turkoz I, et al. Preliminary results from ARISe-RD (augmentation with risperidone in resistant depression) trial. Presented at the 43rd annual meeting of the New Clinical Drug Evaluation Unit; May 27–30, 2003; Boca Raton, Fla
49. Zhang W, Perry KW, Wong DT, et al. Synergistic effects of olanzapine and other antipsychotic agents in combination with fluoxetine on norepinephrine and dopamine release in rat prefrontal cortex. Neuropsychopharmacology 2000;23:250–262
50. Hotopf M, Hardy R, Lewis G. Discontinuation rates of SSRI and tricyclic antidepressants: a meta-analysis and investigation of heterogeneity. Br J Psychiatry 1997;170:120–127
51. Nierenberg A, Papakostas GI, Petersen T, et al. Lithium augmentation of nortriptyline for subjects resistant to multiple antidepressants. J Clin Psychopharmacol 2003;64:192–196