Efficacy of Ziprasidone Augmentation of Escitalopram for Cognitive Symptoms of Major Depressive Disorder

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ABSTRACT

Objective: To examine the efficacy of adjunctive ziprasidone for cognitive symptoms in adult patients with major depressive disorder (MDD) experiencing persistent symptoms after 8 weeks of open-label escitalopram.

Methods: This post hoc analysis was conducted on a database derived from a previously published study. The parent study was a multicenter, parallel, randomized, double-blind, placebo-controlled trial conducted at 3 academic medical centers in the United States from July 2008 to October 2013. The participant pool consisted of 139 outpatients with persistent symptoms of MDD, according to *DSM-IV* criteria, following an 8-week open label, flexible-dose trial of escitalopram. Subjects were randomly assigned (1:1, N = 139) to adjunctive fixed-dose ziprasidone (escitalopram + ziprasidone, n = 71) or adjunctive placebo (escitalopram + placebo, n = 68) with 8 weekly follow-up assessments. Primary outcome was clinical response according to the 17-item Hamilton Depression Rating Scale, which was defined as a 50% or greater reduction in scale scores. The Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (CPFQ) was used to measure cognitive and executive dysfunction at each study visit. All statistical testing was conducted at the nominal, 2-sided, 0.05 level of significance.

Results: Adjunctive ziprasidone therapy did not result in significantly greater improvement in CPFQ scores compared to adjunctive placebo ($P > .05$). Residual cognitive symptoms were reported in a substantial number of patients who were considered responders to either adjunctive ziprasidone or placebo.

Conclusions: In the present study, ziprasidone used adjunctively with the selective serotonin reuptake inhibitor escitalopram did not demonstrate a greater efficacy for cognitive symptoms in patients with MDD compared with adjunctive placebo. Future, well-designed studies examining the role of atypical antipsychotics or other augmentation versus switch strategies for cognitive symptoms in MDD are warranted.

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In the 1930s, amphetamine was among the first drugs recommended for the treatment of depression.[1] Two decades later, the identification of antidepressant properties for both iproniazid and imipramine launched the modern era of antidepressant drug discovery.[2] Because these medications are thought to exert their antidepressant activity through the modulation of monoaminergic neurotransmission (whether selective[3] or nonselective[4,5]), antidepressant drug development over the past half-century has primarily focused on medications with mechanisms of action similar to that of imipramine,[2] with a few exceptions involving non-monoaminergic agents.[6,7] Regardless of mechanism, however, all of these agents have clear efficacy limitations.[8–10]

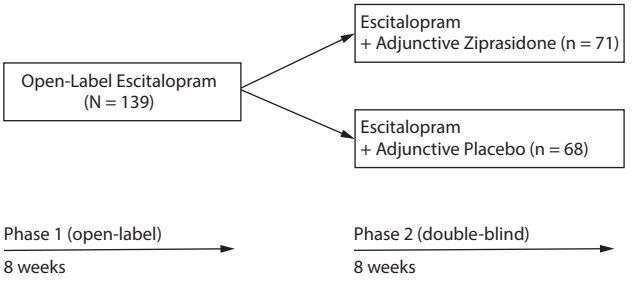
Cognitive deficits such as those in memory, attention, executive functioning, and psychomotor speed are common in depression and contribute to the burden of the disease. In 1 study[11] of 274 depressed patients, 71% ranked difficulty concentrating among the top 4 most troubling symptoms, while in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study,[12] only depressed mood and fatigue were reported more commonly. Cognitive impairments are common not only during depressive episodes but also between episodes. For example, in a large, cross-sectional study by Fava et al[13] of 117 patients with major depressive disorder (MDD), approximately 1 in 3 subjects who were considered treatment responders reported residual inattentiveness, forgetfulness, word-finding difficulty, apathy, and mental slowing. Similarly, a 3-year prospective study[14] of 267 patients found that cognitive problems were present 94% of the time during depressive episodes and as much as 44% of the time during remission. Moreover, in addition to being a symptom of the illness, cognitive dysfunction is also a functional outcome measure, as impaired cognition hinders the full restoration of psychosocial functioning, allowing for continued difficulty at work, at home, and in social settings.[8]

A growing body of literature suggests that cognitive dysfunction and, in particular, executive dysfunction are difficult to treat with traditional antidepressants.[13,15,16] A systematic review[17] of 30 studies, for example, assessed which cognitive domains were most likely to improve with treatment in patients with major depression. The authors concluded that verbal learning and memory and, to a lesser degree, psychomotor speed were most likely to improve alongside mood symptoms, while attention and executive function measures were less likely to improve. Randomized, placebo-controlled clinical trials investigating the effects of antidepressants on cognitive functioning have been scarce and, until recently, have focused exclusively on older

Clinical Points

- Augmentation with atypical antipsychotic agents for patients with treatment-resistant depression may not be the optimal choice for individuals with prominent cognitive symptoms.
- Some patients who experience improvement in depressive symptoms with augmentation with atypical antipsychotics may, nevertheless, experience a worsening of cognitive functioning.
- Other patients, however, may experience improvement in depressive symptoms with no corresponding worsening of cognitive functioning with this treatment strategy.

Figure 1. Design of Open-Label and Double-Blind Study[a]



[a]Original study by Papakostas et al.[25]

adults. Of agents tested thus far in placebo-controlled trials (citalopram, duloxetine, vortioxetine),[18–22] only vortioxetine has been studied in patients aged 18–65 years[20–22] and has been shown to be superior to placebo in improving measures of executive functioning and to do so across adult age groups. Even less is known regarding the impact of various adjunctive treatment strategies on cognition in MDD from randomized, double-blind studies. One study[23] that involved the use of *S*-adenosylmethionine (SAMe) as adjunctive for treatment-resistant depression reported significantly greater improvement in recall and word-finding scores for patients receiving adjunctive SAMe than placebo-treated patients. In another trial,[24] adjunctive therapy with modafinil, a dopamine reuptake inhibitor, improved scores on the Stroop interference test, a test measuring attention and executive functioning. Psychostimulants and other catecholaminergic agents are currently being investigated in clinical trials alone or in combination with antidepressants to determine their efficacy in improving cognitive symptoms of depression. Atypical antipsychotics are commonly used to augment the efficacy of antidepressants in treating MDD. To our knowledge, however, no study so far has investigated the effect of atypical antipsychotics on cognitive dysfunction in depression. The present work is the first to study the effects of augmentation of antidepressants with an atypical antipsychotic agent for treatment-resistant depression on cognitive symptoms in a randomized, double-blind, placebo-controlled trial.

METHODS

This analysis was conducted on a database derived from a previously published study; details of the trial are reported by Papakostas et al.[25] Briefly, IT was an 8-week multicenter, randomized, double-blind, parallel-group, placebo controlled trial, conducted at 3 academic medical centers in the United States from July 2008 to October 2013, of ziprasidone augmentation of escitalopram for patients with MDD experiencing the persistence of symptoms despite an 8-week, prospective, open-label, flexible-dose trial of escitalopram (Figure 1). Eligible participants for the open-label trial (phase 1) of the study were men and women 18–65 years of age with a primary diagnosis of current MDD according to *DSM-IV* criteria as determined with the Structured Clinical Interview for *DSM-IV* Axis I Disorders[26] and a 16-item Quick Inventory of Depressive Symptomatology-Self Rated scale (QIDS-SR)[27] total score ≥ 10 at screening. Escitalopram was initiated at a daily dose of 10 mg and could be increased by 10-mg increments per week to a maximum dose of 30 mg daily. The minimal acceptable escitalopram dose for the study was 10 mg. 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 abnormal serum potassium or magnesium levels, evidence of untreated hypothyroidism, a positive urine drug screen, or significant cardiac conduction problems were randomly assigned to receive adjunctive ziprasidone or placebo in a 1:1 fashion (phase 2). Ziprasidone (20 mg per capsule) and placebo were in capsule form and identical in appearance. All patients were instructed to take 1 capsule of study medication twice daily with a full meal in addition to continuing on the same dosage of escitalopram that they were on at the end of phase 1. Following the first phase 2 visit and throughout the 8 subsequent weekly visits, study clinicians could increase a subject's dose of the study drug in 1-capsule, twice-per-day, weekly increments, yielding a possible daily ziprasidone dosage range of 20–80 mg twice daily (40–160 mg total daily dose). When deemed appropriate, study clinicians could also lower the dosage of study medication to address intolerable or uncomfortable 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. Patients were permitted to take the following concomitant psychotropic medications, provided that daily doses remained stable throughout the randomized portion of the study and had been stable for at least 2 weeks prior to randomization: benzodiazepine or benzodiazepine-like agents, anticonvulsants, lithium, and buspirone. The study was approved by the institutional review board at each participating site.

The primary outcome measure for testing of the primary study hypothesis (antidepressant efficacy) was clinical response, defined as a 50% or greater reduction (improvement) from baseline to end point in 17-item Hamilton Depression Rating Scale ($HDRS_{17}$)[28] total score.

The Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (CPFQ)[29] was used to measure cognitive and executive dysfunction at each study visit. The CPFQ is a brief self-rating scale assessing the most common complaints of depressed patients reporting fatigue or cognitive/executive problems. The scale consists of 7 questions, each rated on a scale from 1 to 6, with 1 indicating greater than normal functioning, 2 indicating normal functioning, and higher numbers indicating poorer functioning. Symptoms assessed include motivation/interest/enthusiasm, wakefulness/alertness, energy, ability to focus/sustain attention, ability to remember/recall information, ability to find words, and sharpness/mental acuity. The CPFQ is a unifactorial scale and has been proved to have strong internal consistency, good temporal stability, and sensitivity to change with treatment, displaying convergent validity by significant correlations with other measures of sleepiness, fatigue, and neuropsychological functioning.[29]

All statistical testing was conducted at the nominal, 2-sided, 0.05 level of significance. An intent-to-treat analysis was used to define the study dataset. The last-observation-carried-forward method was used to define symptom severity at end point for patients who prematurely discontinued treatment. The analysis of covariance was used to compare CPFQ scores between patients assigned to adjunctive ziprasidone or placebo, adjusting for baseline CPFQ scores. STATA SE Version 13 statistical software was used for all analyses (StataCorp, College Station, Texas).

RESULTS

The overall results of the trial are reported in Papakostas et al.[25] In brief, 139 outpatients with persistent symptoms of MDD after an 8-week open-label trial of escitalopram were randomly assigned to receive adjunctive ziprasidone (escitalopram + ziprasidone, n = 71, mean [SD] age = 44.7 [13.8] years, 49% women) or adjunctive placebo (escitalopram + placebo, n = 68, mean [SD] age = 44.2 [11.9] years, 49% women), with 8 weekly follow-up assessments. The mean (SD) $HDRS_{17}$ score for these 139 patients at the initial study visit (corresponding to the open-label lead-in phase with escitalopram) was 20.0 (4.4). The mean (SD) number of historical trials of antidepressants failed during the current episode was 0.94 (0.76). There were no statistically significant differences between the 2 treatment groups for baseline (of the randomized phase) demographic and clinical data. Forty-nine adjunctive ziprasidone–treated patients (69.0%) and 53 placebo-treated patients (77.9%) completed the trial ($P = .23$).

Adjunctive ziprasidone therapy did not result in significantly greater improvement in CPFQ scores compared to adjunctive placebo. Baseline CPFQ scores, as well as change in scores from baseline for the 2 treatment groups in the randomized portion of the study, are reported in Table 1. Residual cognitive symptoms (assessed by a score on the CPFQ items at end point ≥ 4, corresponding to "moderately diminished," "markedly diminished," or "totally absent" function) were reported in a great number of patients who were considered responders to either adjunctive ziprasidone or placebo (50% or greater reduction from baseline to end point in $HDRS_{17}$ total score) (Table 2).

Table 1. Change in CPFQ Scores From Baseline for Patients Receiving Either Ziprasidone or Placebo Augmentation of Escitalopram[a]

	Ziprasidone + Escitalopram (n = 71)		Placebo + Escitalopram (n = 68)		
CPFQ Item	Baseline	Change From Baseline	Baseline	Change From Baseline	*P* Value
Motivation	4.4 (1.0)	−0.7 (1.3)	4.3 (1.0)	−0.6 (1.2)	.69
Wakefulness	3.9 (1.1)	−0.3 (1.1)	3.8 (1.0)	−0.4 (1.1)	.25
Energy	4.2 (1.2)	−0.3 (1.3)	4.4 (0.9)	−0.5 (1.0)	.70
Focus	4.0 (1.0)	−0.4 (1.2)	3.7 (0.9)	−0.4 (0.9)	.33
Recall	3.9 (1.1)	−0.3 (1.0)	3.6 (1.0)	−0.4 (0.7)	.36
Word finding	3.6 (1.1)	−0.3 (0.9)	3.2 (0.9)	−0.2 (0.8)	.65
Mental acuity	3.7 (1.1)	−0.1 (1.0)	3.3 (0.9)	−0.0 (0.9)	.49
Total	27.6 (5.9)	−2.4 (6.3)	26.3 (4.8)	−2.5 (5.0)	.57

[a]All values are mean (SD).
Abbreviation: CPFQ = Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire.

Table 2. Responders to Either Ziprasidone or Placebo Augmentation of Escitalopram With CPFQ Items Scores ≥ 4 at Study Endpoint

	Ziprasidone + Escitalopram (n = 25)		Placebo + Escitalopram (n = 14)		
CPFQ Item	n	%	n	%	*P* Value
Motivation	10	40	3	21.4	.65
Wakefulness	12	48	2	14.3	.09
Energy	17	68	5	35.7	.46
Focus	9	36	1	7.1	.08
Recall	8	32	0	0	.02
Word finding	7	28	1	7.1	.19
Mental acuity	13	52	3	21.4	.24

Abbreviation: CPFQ = Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire.

DISCUSSION

The present analysis is the first to examine the effects of augmentation of antidepressants with an atypical antipsychotic agent on cognitive symptoms in patients with persistent MDD symptoms despite selective serotonin reuptake inhibitor (SSRI) treatment. To conduct our analysis, we used an existing dataset from a randomized, double-blind, placebo-controlled trial that compared the efficacy of adjunctive ziprasidone with adjunctive placebo in outpatients with MDD who exhibited the persistence of depressive symptoms after an open-label, flexible-dose trial of escitalopram. The results of our study failed to demonstrate a significant effect of adjunctive ziprasidone on cognitive symptoms in patients with treatment-resistant depression compared to adjunctive placebo. A significant proportion of patients continued to show a high level of cognitive symptoms at the end of the

study; for example, more than 50% of patients reported a moderate or greater level of impairment in CPFQ items such as wakefulness, energy, and mental acuity. Thus, while the antidepressant and anxiolytic effect of this augmentation strategy was statistically and clinically significant,[25] a similar effect for cognitive symptoms of depression was not noted. Clinicians should keep these results in mind when selecting next-step treatments for antidepressant partial responders and nonresponders with MDD.

This study has several limitations, which should be taken into account when interpreting our findings. First, the analysis was carried out post hoc. A prospectively designed study with carefully selected and predefined primary and secondary outcome measures would have been better suited to specifically examine cognitive symptoms. In particular, the use of a comprehensive neuropsychological battery that allows an objective measurement to complement the results from the CPFQ, which is a self-administered 7-item scale, would give a more specific and complete assessment of cognitive functioning in this patient population. Moreover, the CPFQ was not used at the beginning of the open-label part of the trial (escitalopram lead-in) but only during the double-blind portion of the study. This lack may have missed a possible preexisting effect of escitalopram monotherapy on cognitive impairments. Furthermore, subjects enrolled into the ziprasidone and placebo arms may have had differences in the degree of cognitive impairment (ie, before treatment with escitalopram), although the randomized samples were similar with respect to this measure. Another limitation has to do with the generalizability of the study findings. Specifically, clinical trials typically use inclusion and exclusion criteria with regard to patient enrollment; whether adjunctive ziprasidone would be efficacious for cognitive symptoms in patients who are typically excluded from antidepressant clinical trials (eg, at imminent risk of suicide, with serious or unstable medical illness, the elderly) is unknown. Most importantly, the present analysis focuses on the use of a single atypical antipsychotic agent, namely, ziprasidone. Ziprasidone has a unique pharmacodynamic signature in the second-generation antipsychotic class. It is a weak serotonin-norepinephrine reuptake inhibitor as well as a weak 5-HT_{1D} antagonist, 5-HT_{1A} agonist, and 5-HT_{2C} antagonist. In particular, 5-HT_{1D} antagonism, combined with the absence of significant anticholinergic and antihistaminic effects, may have resulted in a relatively lower risk of cognitive side effects than is found with some of the other atypical antipsychotics. Whether results differ with other atypical antipsychotics when used as adjunctive therapy in MDD remains to be seen. Additionally, it is worthwhile to mention that the low dose of ziprasidone used in the study as augmentation treatment of escitalopram was chosen by clinicians via a flexible-dose design and not by a study algorithm. Whether results would have differed with the use of higher or lower doses is unclear.

In conclusion, in the present study, ziprasidone used adjunctively compared with adjunctive placebo with the SSRI escitalopram did not demonstrate a greater efficacy for cognitive symptoms in patients with MDD. A substantial number of patients continued to report a high level of residual cognitive symptoms at the end of the study, suggesting that cognitive dysfunction is a common and difficult-to-treat domain in depression that deserves more attention and research. Future studies specifically examining the role of atypical antipsychotics versus other augmentation versus switch strategies for cognitive symptoms in MDD are warranted.

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Pfizer, Pierre Fabre, Ridge Diagnostics (formerly known as Precision Human Biolaboratories), Shire, Sunovion, Taisho, Takeda, Theracos, and Wyeth; has received honoraria (for lectures or consultancy) from Abbott, Astra Zeneca, Avanir, Bristol-Myers Squibb, Brainsway, Cephalon, Dey, Eli Lilly, Evotec, Forest, GlaxoSmithKline, Inflabloc, Jazz, H. Lundbeck, Medichem, Meiji Seika, Novartis, Otsuka, Pamlab, Pfizer, Pharma Trade, Pierre Fabre, Ridge Diagnostics, Shire, Sunovion, Takeda, Theracos, Titan, and Wyeth; has received research support (paid to hospital) from AstraZeneca, Bristol-Myers Squibb, Forest, the National Institute of Mental Health (NIMH), Neuralstem, Pamlab, Pfizer, Ridge Diagnostics (formerly known as Precision Human Biolaboratories), Sunovion, Tal Medical, and Theracos; and has served (not currently) on the speaker's bureau for Bristol-Myers Squibb and Pfizer. (*Denotes activity undertaken on behalf of Massachusetts General Hospital.) **Drs Iovieno** and **Cusin** and **Mr Petrie** have no conflicts of interest to report.

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REFERENCES

1. Heal DJ, Smith SL, Gosden J, et al. Amphetamine, past and present—a pharmacological and clinical perspective. *J Psychopharmacol*. 2013;27(6):479–496.
2. López-Muñoz F, Alamo C. Monoaminergic neurotransmission: the history of the discovery of antidepressants from 1950s until today. *Curr Pharm Des*. 2009;15(14):1563–1586.
3. Papakostas GI, Nelson JC, Kasper S, et al. A meta-analysis of clinical trials comparing reboxetine, a norepinephrine reuptake inhibitor, with selective serotonin reuptake inhibitors for the treatment of major depressive disorder. *Eur Neuropsychopharmacol*. 2008;18(2):122–127.
4. Papakostas GI, Worthington JJ 3rd, Iosifescu DV, et al. The combination of duloxetine and bupropion for treatment-resistant major depressive disorder. *Depress Anxiety*. 2006;23(3):178–181.
5. Nierenberg AA, Papakostas GI, Petersen T, et al. Nortriptyline for treatment-resistant depression. *J Clin Psychiatry*. 2003;64(1):35–39.
6. Iosifescu DV, Bolo NR, Nierenberg AA, et al. Brain bioenergetics and response to triiodothyronine augmentation in major depressive disorder. *Biol Psychiatry*. 2008;63(12):1127–1134.
7. Mischoulon D, Best-Popescu C, Laposata M, et al. A double-blind dose-finding pilot study of docosahexaenoic acid (DHA) for major depressive disorder. *Eur Neuropsychopharmacol*. 2008;18(9):639–645.
8. Papakostas GI. Cognitive symptoms in patients with major depressive disorder and their implications for clinical practice. *J Clin Psychiatry*. 2014;75(1):8–14.
9. Papakostas GI. Antidepressants and their effect on cognition in major depressive disorder. *J Clin Psychiatry*. 2015;76(8):e1046.
10. Papakostas GI, Culpepper L. Understanding and managing cognition in the depressed patient. *J Clin Psychiatry*. 2015;76(4):418–425.
11. Pandina GJ, Revicki DA, Kleinman L, et al. Patient-rated troubling symptoms of depression instrument results correlate with traditional clinician- and patient-rated measures: a secondary analysis of a randomized, double-blind, placebo-controlled trial. *J Affect Disord*. 2009;118(1–3):139–146.
12. Hollon SD, Shelton RC, Wisniewski S, et al. Presenting characteristics of depressed outpatients as a function of recurrence: preliminary findings from the STAR*D clinical trial. *J Psychiatr Res*. 2006;40(1):59–69.
13. Fava M, Graves LM, Benazzi F, et al. A cross-sectional study of the prevalence of cognitive and physical symptoms during long-term antidepressant treatment. *J Clin Psychiatry*. 2006;67(11):1754–1759.
14. Conradi HJ, Ormel J, de Jonge P. Presence of individual (residual) symptoms during depressive episodes and periods of remission: a 3-year prospective study. *Psychol Med*. 2011;41(6):1165–1174.
15. Culang-Reinlieb ME, Sneed JR, Keilp JG, et al. Change in cognitive functioning in depressed older adults following treatment with sertraline or nortriptyline. *Int J Geriatr Psychiatry*. 2012;27(8):777–784.
16. Keefe RSE, McClintock SM, Roth RM, et al. Cognitive effects of pharmacotherapy for major depressive disorder: a systematic review. *J Clin Psychiatry*. 2014;75(8):864–876.
17. Douglas KM, Porter RJ. Longitudinal assessment of neuropsychological function in major depression. *Aust N Z J Psychiatry*. 2009;43(12):1105–1117.
18. Raskin J, Wiltse CG, Siegal A, et al. Efficacy of duloxetine on cognition, depression, and pain in elderly patients with major depressive disorder: an 8-week, double-blind, placebo-controlled trial. *Am J Psychiatry*. 2007;164(6):900–909.
19. Culang ME, Sneed JR, Keilp JG, et al. Change in cognitive functioning following acute antidepressant treatment in late-life depression. *Am J Geriatr Psychiatry*. 2009;17(10):881–888.
20. Katona C, Hansen T, Olsen CK. A randomized, double-blind, placebo-controlled, duloxetine-referenced, fixed-dose study comparing the efficacy and safety of Lu AA21004 in elderly patients with major depressive disorder. *Int Clin Psychopharmacol*. 2012;27(4):215–223.
21. McIntyre RS, Lophaven S, Olsen CK. A randomized, double-blind, placebo-controlled study of vortioxetine on cognitive function in depressed adults. *Int J Neuropsychopharmacol*. 2014;17(10):1557–1567.
22. Mahableshwarkar A, Zajecka J, Jacobson W, et al. Efficacy of vortioxetine on cognitive function in adult patients with major depressive disorder: results of a randomized, double-blind, active-referenced, placebo-controlled trial. Presented at the 29th CINP World Congress of Neuropsychopharmacology; June 24, 2014; Vancouver, British Columbia, Canada.
23. Levkovitz Y, Alpert JE, Brintz CE, et al. Effects of S-adenosylmethionine augmentation of serotonin-reuptake inhibitor antidepressants on cognitive symptoms of major depressive disorder. *J Affect Disord*. 2012;136(3):1174–1178.
24. DeBattista C, Lembke A, Solvason HB, et al. A prospective trial of modafinil as an adjunctive treatment of major depression. *J Clin Psychopharmacol*. 2004;24(1):87–90.
25. 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.
26. 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 Department, New York State Psychiatric Institute; 1995.
27. 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.
28. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;23:56–62.
29. Fava M, Iosifescu DV, Pedrelli P, et al. Reliability and validity of the Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire. *Psychother Psychosom*. 2009;78(2):91–97.