Analysis of Suicidality in Pooled Data From 2 Double-Blind, Placebo-Controlled Aripiprazole Adjunctive Therapy Trials in Major Depressive Disorder

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Objective: To assess the impact of adjunctive aripiprazole versus adjunctive placebo treatment on suicidality in patients with major depressive disorder.

Method: Data were pooled from 2 identical aripiprazole augmentation studies. Patients with *DSM-IV-TR*–diagnosed major depressive disorder with an inadequate response to 8 weeks of prospective antidepressant treatment were randomly assigned to adjunctive placebo or adjunctive aripiprazole (2–20 mg/d) treatment for 6 weeks. Adverse events related to suicidality were identified in the adverse event database using the Medical Dictionary for Regulatory Activities–preferred term. Treatment-emergent suicidal ideation was defined using item 10 (suicidality) of the Montgomery-Åsberg Depression Rating Scale (MADRS) and item 18 (suicidality) of the Inventory of Depressive Symptomatology (IDS).

Results: In total, 737 patients were included in the safety database (aripiprazole n = 371; placebo n = 366). No suicides were reported. There were no treatment-emergent, suicide-related adverse events in the aripiprazole group; 2 patients in the placebo group had ≥ 1 adverse event related to suicide (both suicidal ideation). More placebo than aripiprazole patients > 25 years old experienced a 2-point ($P < .01$) or 1-point ($P < .05$) worsening of MADRS item 10 scores. For this age group, 2-point improvement in MADRS item 10 scores and 1-point improvement of IDS item 18 scores were significantly more common in aripiprazole patients than placebo patients (both $P < .05$).

Conclusions: This post hoc analysis demonstrated that adjunctive aripiprazole treatment in patients with depression with a history of an inadequate response to antidepressant medication is associated with a decreased rate of suicidality in a group of subjects not at significant risk. Prospective trials directly assessing suicidality are needed to further understand the benefits of an adjunctive antipsychotic in an at-risk population.

Trial Registration: clinicaltrials.gov Identifiers: NCT00095823 and NCT00095758

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Suicidal ideation and suicide attempts are common in major depressive disorder (MDD). Over half of patients with MDD report suicidal ideation,[1–4] and the incidence of attempted suicide is approximately 15% in patients with MDD.[4,5] In a study in adults aged 18 years or older who had experienced a major depressive episode in the past year, 56.3% thought, during their worst or most recent episode, that it would be better if they were dead; 40.3% thought about committing suicide; 14.5% made a suicide plan; and 10.4% made a suicide attempt.[6] Moreover, more than 300,000 adults attempt to harm themselves every year and are treated in emergency rooms.[7] Suicide is also the 11th leading cause of death in adults,[8] and a recent review suggests that 90% of suicide victims have diagnosable psychological disorders—predominantly mood disorders, such as depression and bipolar disorders.[9] As suicide is the worst outcome of MDD, suicide risk should be monitored in all patients, even though suicide attempts or death by suicide occur in only a fraction of those who have thought about or attempted suicide. Suicide risk assessment and prevention efforts need to be a focus of clinician attention when starting or changing treatment, as risk may fluctuate with variations in depressive symptoms.

There has been growing controversy regarding the risk of suicidal behaviors after initiation of antidepressant treatment with selective serotonin reuptake inhibitors (SSRIs), and the US Food and Drug Administration has issued a black box warning regarding this risk in children, adolescents, and young adults (< 25 years old). However, there is limited evidence of an increase in completed suicides in this population, and the subject is a matter of ongoing debate. Analysis of US Food and Drug Administration reports has failed to support an overall difference in suicide risk between antidepressant- and placebo-treated subjects with depression in controlled trials.[10] Furthermore, increases in prescription rates for SSRIs, as well as newer non-SSRI antidepressants, are associated with a decrease in suicide rates in both adults[11] and older adolecents,[12] suggesting an overall protective effect of medication. This is further supported by recent studies that have shown that effective treatment of MDD with antidepressants, antipsychotics, and lithium can reduce suicide rates and suicidality in patients with MDD.[13,14] It has also been shown that combination treatment may be more effective than monotherapy in reducing overall mortality from suicidality.[14]

The efficacy and safety of adjunctive aripiprazole treatment in patients with an inadequate response to standard

antidepressant treatment have been demonstrated in 3 randomized, double-blind, placebo-controlled studies.[15–17] Pooled analyses of data from the first 2 studies[15,16] have shown that adjunctive aripiprazole treatment demonstrated improvements in depressive symptoms as early as week 1, as compared with patients in the adjunctive placebo treatment group,[18] and that adjunctive aripiprazole is safe and generally well tolerated as an augmentation strategy[19]; the third study was consistent with these findings.[17] Here, we report findings from analysis of the pooled dataset from the first 2 studies to assess the impact of adjunctive aripiprazole treatment on suicidality in patients with MDD and a history of an inadequate response to antidepressant medication.

METHOD

Study Design and Patients

This analysis used pooled data from 2 identically designed, multicenter, randomized, double-blind studies conducted in the United States evaluating the efficacy, safety, and tolerability of aripiprazole compared with placebo as adjunctive treatment to standard antidepressant treatment in patients who demonstrated an inadequate response to a prospective 8-week trial of the same antidepressant agent and at least 1 historical antidepressant treatment.[15,16] Full details of the study methods have been described previously.[15,16] Briefly, subjects included outpatients aged 18–65 years who met the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision (*DSM-IV-TR*) criteria for a major depressive episode[20] that had lasted ≥ 8 weeks. Inadequate response to at least 1 historical antidepressant treatment was determined by the Antidepressant Treatment Response Questionnaire. Specifically, inadequate response was defined as the patients' reporting of < 50% reduction in severity of depression to at least 1 and no more than 3 antidepressant treatment trials of > 6 weeks' duration (> 3 weeks for combination treatments) at the minimum acceptable dose specified in the Antidepressant Treatment Response Questionnaire. Additional inclusion and exclusion criteria have been reported elsewhere[15,16]; of note, patients who represented a significant risk of committing suicide during the course of the trial were excluded.

Eligible patients entered an 8-week prospective antidepressant treatment phase followed by a 6-week randomized treatment phase. During the prospective treatment phase, patients received 8 weeks of therapy with escitalopram, fluoxetine, paroxetine CR, sertraline, or venlafaxine XR, per investigator choice, and single-blind, adjunctive placebo. Patients with an inadequate response (< 50% reduction in the 17-item Hamilton Depression Rating Scale [HDRS-17] total score; HDRS-17 score ≥ 14; and the Clinical Global Impressions-Improvement scale [CGI-I] score ≥ 3 at the end of the antidepressant treatment phase) were randomly assigned (1:1) to continue the same antidepressant treatment (no dose adjustment was permitted) plus either adjunctive placebo or adjunctive aripiprazole treatment (2–20 mg/d) for 6 weeks. Aripiprazole was started at 5 mg/d and increased by 5 mg on a weekly basis to a maximum of 15 mg/d (patients receiving paroxetine or fluoxetine) or 20 mg/d (all other patients) on the basis of assessment of efficacy and clinical response. Aripiprazole doses could be decreased at any visit, on the basis of tolerability, except in the last week of double-blind treatment.

Assessment of Suicide-Related Adverse Events

Adverse events related to suicidality were identified in the adverse event database using the text term or Medical Dictionary for Regulatory Activities–preferred term. Both serious and nonserious adverse events were included. Reported events were classified into the following 3 groups: (1) completed suicide, (2) suicide attempt (intentional overdose, intentional self-injury, multiple drug overdose intentional, poisoning deliberate, self-injurious behavior, self-mutilation, suicide attempt, intentional misuse), or (3) suicidal ideation (depression, suicidal self-injurious ideation, suicidal ideation).

Treatment-Emergent Suicidal Ideation

The effects of aripiprazole on treatment-emergent suicidal ideation were investigated using item 10 (suicidality) of the clinician-rated Montgomery-Åsberg Depression Rating Scale (MADRS)[21] and item 18 (suicidality) of the subject-rated Inventory of Depressive Symptomatology (IDS).[22] The MADRS item 10 is rated on a 7-point scale ranging from 0 (enjoys life and takes it as it comes) to 6 (explicit plans for suicide when there is an opportunity/active preparation for suicide), whereas the IDS item 18 is rated on a 4-point scale: 0 (I do not think of suicide or death), 1 (I feel that life is empty or wonder if it's worth living), 2 (I think of suicide or death several times a week for several minutes), 3 (I think of suicide or death several times a day in some detail, or I have made specific plans for suicide or have actually tried taking my life).

Analyses

Analyses were conducted on pooled data from patients who participated in the 2 aripiprazole studies in patients with MDD. The safety sample included all randomly assigned patients who received at least 1 dose of study medication (adjunctive aripiprazole or adjunctive placebo) during the 6-week, double-blind treatment phase. The efficacy sample included all patients in the safety sample who had at least 1 efficacy assessment during the 6-week, double-blind treatment phase. Mean change in MADRS item 10 scores and IDS item 18 scores were evaluated using analysis of covariance, with randomized treatment and protocol as main effects and the baseline item score as the covariate. Analysis was performed on the efficacy sample using the last observation carried forward (LOCF) dataset. The Spearman correlation was used to evaluate the correlation between change in MADRS item 10 scores and change in MADRS total scores using the observed case dataset stratified by treatment. Similar analysis was conducted to assess the correlation between change in IDS item 18 score and change in IDS total score.

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P values were used to test the null hypothesis of no correlation ($r = 0$).

Changes in suicidality during treatment were assessed using the frequency of patients with a 1- or 2-point increase (worsening) or a 1- or 2-point decrease (improvement) in MADRS item 10 or IDS item 18 scores from baseline to endpoint. Analyses were performed on the safety sample using the LOCF dataset. For the purpose of this analysis, the following subgroups were also defined: MADRS responders—patients with a ≥ 50% decrease in MADRS total score from week 8 to week 14; MADRS remitters—patients with a ≥ 50% decrease in MADRS total score from week 8 to week 14 and a MADRS total score ≤ 10 at week 14; patients with an age ≤ 25 years and patients with an age > 25 years; and patients with and without akathisia reported as an adverse event during double-blind treatment. Relative risks (RRs) and the 95% confidence intervals (CIs) for relative risk were calculated for each category point change for patients > 25 years old. For MADRS responders and remitters, distribution of MADRS item 10 scores and IDS item 18 scores were calculated. Treatment differences in distribution were assessed using the Cochran-Mantel-Haenszel test for general association. Akathisia severity was also assessed using the Akathisia Global Clinical Assessment of the Barnes Akathisia Rating Scale (BARS)[23] (scores range from 0 to 5: 0 = absent, 1 = questionable, 2 = mild akathisia, 3 = moderate akathisia, 4 = marked akathisia, 5 = severe akathisia). Mean MADRS item 10 and IDS item 18 scores were calculated for patients with a BARS score ≥ 2.

RESULTS

Patient Disposition and Baseline Characteristics

In total, 741 patients (adjunctive aripiprazole n = 373; adjunctive placebo n = 368) were randomly assigned to treatment in these 2 studies. The percentage of randomly assigned patients completing the studies was similar between adjunctive aripiprazole– (n = 322; 86%) and placebo–treated (n = 322; 88%) patients. Reasons for discontinuation (adjunctive aripiprazole vs adjunctive placebo) in patients randomly assigned to treatment included lack of efficacy (1.6% vs 1.4%), adverse events (3.5% vs 1.6%), consent withdrawn (2.1% vs 3.8%), lost to follow-up (2.7% vs 3.0%), or other reasons (3.8% vs 2.7%). A total of 737 patients (adjunctive aripiprazole n = 371; adjunctive placebo n = 366) were included in the safety sample; 4 patients did not receive study medication and were not included in the safety analysis (adjunctive aripiprazole n = 2; adjunctive placebo n = 2). Baseline demographic characteristics were similar between treatment groups.[18]

Baseline MADRS item 10 scores and IDS item 18 scores for the total population, as well as by age and akathisia status, are shown in Table 1. The majority of patients were > 25 years of age in both treatment groups.

Table 1. Baseline MADRS Item 10 and IDS Item 18 Scores (safety sample)

	Placebo	Aripiprazole
MADRS item 10 score [a]	n = 356	n = 366
Total population		
Baseline, mean (SD)	1.1 (1.1)	1.1 (1.2)
Distribution, n (%)[b]		
0	140 (39.3)	146 (39.9)
1	81 (22.8)	78 (21.3)
2	98 (27.5)	101 (27.6)
3	27 (7.6)	26 (7.1)
4	10 (2.8)	15 (4.1)
By age		
Patients aged ≤ 25 y	n = 19	n = 16
Baseline, mean (SD)	1.32 (1.00)	0.94 (0.85)
Patients aged > 25 y	n = 337	n = 350
Baseline, mean (SD)	1.11 (1.11)	1.15 (1.16)
By akathisia status		
With akathisia	n = 16	n = 91
Baseline, mean (SD)	1.06 (1.48)	1.11 (1.12)
Without akathisia	n = 340	n = 275
Baseline, mean (SD)	1.12 (1.08)	1.15 (1.16)
IDS item 18 score[a]	n = 347	n = 356
Total population		
Baseline, mean (SD)	0.42 (0.64)	0.47 (0.65)
Distribution, n (%)[b]		
0	228 (65.7)	217 (61.0)
1	91 (26.2)	114 (32.0)
2	28 (8.1)	22 (6.2)
3	0 (0.0)	3 (0.8)
By age		
Patients aged ≤ 25 y	n = 19	n = 15
Baseline, mean (SD)	0.42 (0.61)	0.47 (0.74)
Patients aged > 25 y	n = 328	n = 341
Baseline, mean (SD)	0.42 (0.64)	0.47 (0.65)
By akathisia status		
With akathisia	n = 16	n = 89
Baseline, mean (SD)	0.50 (0.73)	0.40 (0.60)
Without akathisia	n = 331	n = 267
Baseline, mean (SD)	0.42 (0.63)	0.49 (0.67)

[a]N numbers represent the number of patients in the safety sample with MADRS item 10 or IDS item 18 scores at baseline.
[b]No patients had a baseline MADRS item 10 score > 4.
Abbreviations: IDS = Inventory of Depressive Symptomatology, MADRS = Montogmery-Åsberg Depression Rating Scale.

Suicide-Related Adverse Events

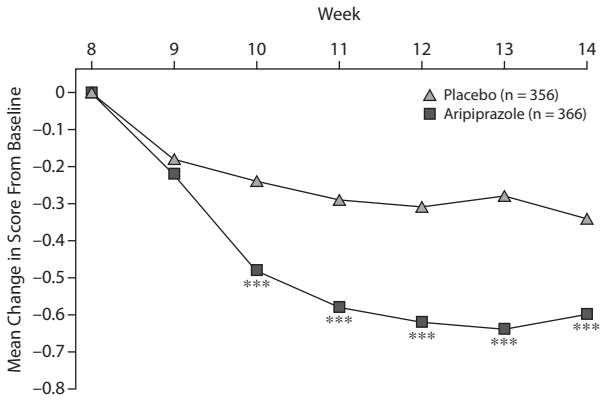
The number of patients per number of patient-years screened for adverse events was 366/39.1 for the placebo group and 371/39.9 for the adjunctive aripiprazole group. For males, the number of patients per number of patient-years screened was placebo = 125/13.1 and adjunctive aripiprazole = 134/14.1, and for females, the number of patients per number of patient-years screened was placebo = 241/26.0 and adjunctive aripiprazole = 237/25.7.

No suicides were reported in these 2 studies, and no adjunctive aripiprazole–treated patients reported treatment-emergent, suicide-related adverse events. Two patients (0.55%) in the adjunctive placebo group reported ≥ 1 adverse event related to suicide; both were suicidal ideation. This equates to an incidence rate for suicidal ideation of 0.051 per patient exposure year.

Total Population

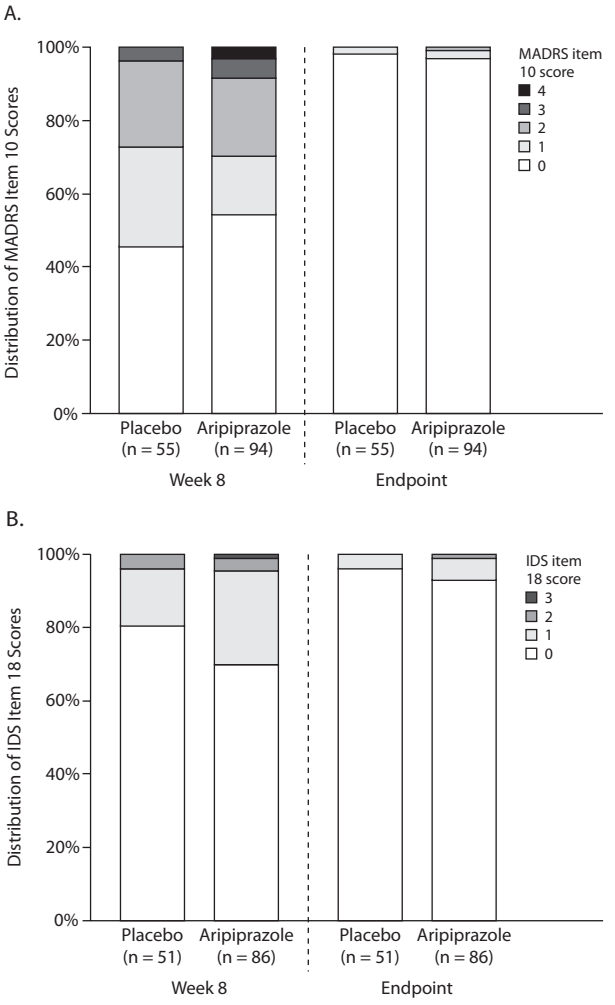
MADRS item 10 scores. At baseline, mean MADRS item 10 scores were low and comparable between treatment groups, and a large proportion of patients had a baseline MADRS item 10 score of 0 or 1 (adjunctive aripiprazole = 61.2%; adjunctive placebo = 62.1%). The effects

Figure 1. Mean Change in MADRS Item 10 Scores During Double-Blind Treatment (LOCF, efficacy sample)[a]



[a]Patients were randomly assigned to double-blind treatment (adjunctive aripiprazole or adjunctive placebo) at week 8.
***$P < .001$ versus placebo.
Abbreviations: LOCF = last observation carried forward, MADRS = Montgomery-Åsberg Depression Rating Scale.

Figure 2. Distribution of (A) MADRS Item 10 Scores and (B) IDS Item 18 Scores at Baseline and Endpoint in Remitters (efficacy sample)[a,b]



[a]Remission was defined as ≥ 50% decrease in MADRS total score from week 8 to week 14 and a MADRS total score ≤ 10 at week 14. [b]Patients were randomly assigned to double-blind treatment (adjunctive aripiprazole or adjunctive placebo) at week 8.
Abbreviations: IDS = Inventory of Depressive Symptomatology, MADRS = Montgomery-Åsberg Depression Rating Scale.

of treatment on suicidal thought, as measured by the mean changes in MADRS item 10 scores during treatment, are shown in Figure 1. Mean reduction in the MADRS suicidality line-item scores was significantly greater in patients receiving adjunctive aripiprazole than in those receiving adjunctive placebo from the second week of double-blind treatment onwards.

In addition, the distribution of MADRS item 10 scores showed improvement in patients achieving remission; the pattern was similar between treatment groups (Figure 2A). At endpoint, the majority of patients (~95%) had a score of 0 on the MADRS item 10 score; no item 10 scores were > 3. A similar distribution of data was observed in MADRS responders (data not shown).

Spearman correlation analysis showed a positive correlation between change in MADRS item 10 scores and change in MADRS total scores for both treatments (adjunctive aripiprazole $r = 0.36$, $P < .001$; adjunctive placebo $r = 0.39$, $P < .001$).

IDS item 18 scores. Similar to mean MADRS item 10 scores, mean IDS item 18 scores were low and comparable between treatment groups at baseline. The majority of patients had a baseline IDS item 18 score of 0 or 1 (adjunctive aripiprazole = 93.0%; adjunctive placebo = 91.9%). The effects of treatment on suicidal thought, measured by mean changes in IDS item 18 scores during treatment, are shown in Figure 3 and indicated that there was a reduction in suicidal thought by patient self-report with adjunctive aripiprazole treatment. Mean decreases in the IDS item scores were significantly greater in the patients receiving adjunctive aripiprazole than in those receiving adjunctive placebo from the second week of double-blind treatment onwards.

The distribution of IDS item 18 scores in treatment remitters also showed improvement in suicidal thoughts during treatment and was similar between treatment groups at baseline and endpoint (Figure 2B). At endpoint, the majority of the patients (~95%) had a score of 0 on the IDS item 18 score; only 1 patient had a score > 2 (in the aripiprazole arm). A similar distribution of data was observed in IDS responders (data not shown).

Spearman correlation analysis showed a positive correlation between change in IDS item 18 scores and change in IDS total scores for both treatments (adjunctive aripiprazole $r = 0.32$, $P < .001$; adjunctive placebo $r = 0.37$, $P < .001$).

Patients Aged ≤ 25 Years

MADRS item 10 scores. Few patients (n = 35) were ≤ 25 years of age in this study, precluding statistical analysis of suicidality in this patient group. Only 3 patients ≤ 25 years of age experienced an increase (worsening) in MADRS item 10 scores; 1 adjunctive placebo–treated patient and 1 adjunctive aripiprazole–treated patient experienced a 2-point increase in MADRS item 10 scores (both with baseline score 0–2), and 1 adjunctive placebo–treated patient experienced a

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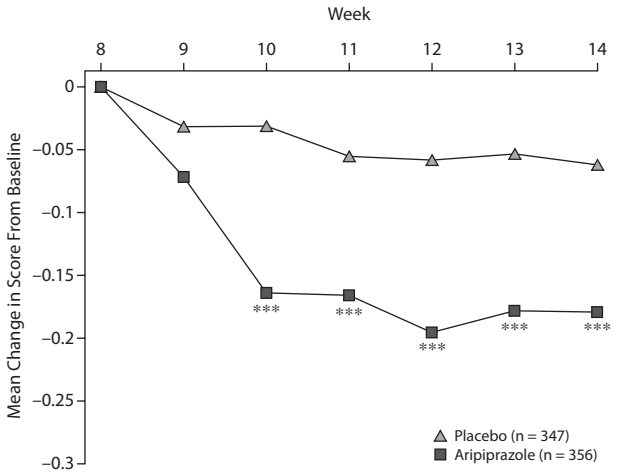
Figure 3. Mean Change in IDS Item 18 Scores During Double-Blind Treatment (efficacy sample, LOCF)[a]



[a]Patients were randomly assigned to double-blind treatment (adjunctive aripiprazole or adjunctive placebo) at week 8.
***$P \leq .001$ versus placebo.
Abbreviations: IDS = Inventory of Depressive Symptomatology, LOCF = last observation carried forward.

1-point increase (baseline score 0–1). By comparison, 14 patients ≤ 25 years of age experienced a decrease (improvement) in MADRS item 10 scores. Five adjunctive placebo–treated patients and 1 adjunctive aripiprazole–treated patient experienced a 2-point decrease (both with baseline score 2–0), and 2 adjunctive placebo–treated patients and 6 adjunctive aripiprazole–treated patients experienced a 1-point decrease (placebo baseline score 2–1; aripiprazole baseline score 1–0 [n = 5] and baseline score 2–1 [n = 1]).

IDS item 18 scores. No placebo patients experienced an increase (worsening) in the patient-rated IDS item 18 score, whereas 1 adjunctive aripiprazole–treated patient experienced a 1-point increase (worsening) in IDS item 18 scores. By comparison, 6 patients experienced a decrease (improvement) in IDS item 18 scores; 3 adjunctive placebo–treated patients and 2 adjunctive aripiprazole–treated patients experienced a 1-point decrease, and 1 adjunctive aripiprazole–treated patient experienced a 2-point decrease. No patients demonstrated a 2-point increase in this age group.

Patients Aged > 25 Years

MADRS item 10 scores. The proportion of patients > 25 years of age with a worsening (increase) in MADRS item 10 scores and the proportion of patients with an improvement (decrease) in MADRS item 10 scores is shown in Table 2A. More adjunctive placebo–treated patients than adjunctive aripiprazole–treated patients experienced a 2-point ($P < .01$; RR = 0.14; 95% CI, 0.03–0.60) or 1-point ($P < .05$; RR = 0.54; 95% CI, 0.31–0.95) worsening of MADRS item 10 scores. Conversely, more adjunctive aripiprazole–treated patients than adjunctive placebo–treated patients experienced a 2-point improvement of MADRS item 10 scores ($P < .05$; RR = 1.52; 95% CI, 1.01–2.29). The difference in the proportion of patients with a 1-point improvement in MADRS item 10 scores was not significant between treatment groups (RR = 0.93; 95% CI, 0.70–1.23).

Table 2. Proportion of Patients With a Change in Suicidality Scores From Baseline in Patients Aged > 25 Years (LOCF, safety sample)

Direction of Change	Magnitude of Change, n (%)	Adjunctive Placebo	Adjunctive Aripiprazole
A. MADRS Suicidal Thought (item 10)			
Worsening	2-point increase	n = 14	n = 2
	Baseline 0–2	11 (78.6)	0 (0.0)
	Baseline 1–3	1 (7.1)	2 (100.0)
	Baseline 2–4	2 (14.3)	0 (0.0)
	1-point increase	n = 32	n = 18
	Baseline 0–1	18 (56.3)	12 (66.7)
	Baseline 1–2	10 (31.3)	4 (22.2)
	Baseline 2–3	4 (12.5)	1 (5.6)
	Baseline 3–4	0 (0.0)	1 (5.6)
Improvement	2-point decrease	n = 33	n = 52
	Baseline 2–0	29 (87.9)	44 (84.6)
	Baseline 3–1	2 (6.1)	2 (3.8)
	Baseline 4–2	2 (6.1)	6 (11.5)
	1-point decrease	n = 78	n = 74
	Baseline 1–0	40 (51.3)	43 (58.1)
	Baseline 2–1	22 (28.2)	24 (32.4)
	Baseline 3–2	12 (15.4)	3 (4.1)
	Baseline 4–3	4 (5.1)	4 (5.4)
B. IDS Thoughts of Death or Suicide (item 18)			
Direction of Change	Magnitude of Change, n (%)	Adjunctive Placebo	Adjunctive Aripiprazole
Worsening	2-point increase	n = 1	n = 1
	Baseline 0–2	1 (100.0)	0 (0.0)
	Baseline 1–3	0 (0.0)	1 (100.0)
	1-point increase	n = 19	n = 15
	Baseline 0–1	15 (78.9)	10 (66.7)
	Baseline 1–2	1 (5.3)	4 (26.7)
	Baseline 2–3	3 (15.8)	1 (6.7)
Improvement	2-point decrease	n = 5	n = 9
	Baseline 2–0	5 (100.0)	9 (100.0)
	1-point decrease	n = 26	n = 56
	Baseline 1–0	21 (80.8)	48 (85.7)
	Baseline 2–1	5 (19.2)	8 (14.3)

Abbreviations: IDS = Inventory of Depressive Symptomatology, LOCF = last observation carried forward, MADRS = Montgomery-Åsberg Depression Rating Scale.

IDS item 18 scores. The proportions of patients with a worsening (increase) and an improvement (decrease) in IDS item 18 scores are shown in Table 2B. There was no significant difference between groups in 1-point worsening of IDS item 18 scores (RR = 0.75; 95% CI, 0.39–1.45), whereas more adjunctive aripiprazole–treated patients than adjunctive placebo–treated patients experienced a 1-point improvement of IDS item 18 scores ($P < .001$; RR = 2.04; 95% CI, 1.32–3.17). One patient in each treatment arm demonstrated a 2-point increase (RR = 0.95; 95% CI, 0.06–15.12). In the adjunctive aripiprazole arm, 9 patients demonstrated a 2-point decrease, and 5 placebo patients showed a 2-point decrease, although this difference was not significant (RR = 1.71; 95% CI, 0.58–5.04).

Akathisia Analyses

Table 3 shows the proportion of patients with a 1-point worsening (increase) or 1-point improvement (decrease) in suicidality scores from baseline by akathisia status. For both MADRS item 10 and IDS item 18, more patients with akathisia

Table 3. Proportion of Patients With a 1-Point Change in Suicidality Score From Baseline by Akathisia Status (LOCF, safety sample)

A. MADRS Suicidal Thought (item 10)

		With Akathisia		Without Akathisia	
Direction of Change	Magnitude of Change, n (%)	Adjunctive Placebo (n = 16)	Adjunctive Aripiprazole (n = 91)	Adjunctive Placebo (n = 340)	Adjunctive Aripiprazole (n = 275)
Worsening	1-point increase	n = 1	n = 8	n = 32	n = 10
	Baseline 0–1	1 (100.0)	7 (87.5)	18 (56.3)	5 (50.0)
	Baseline 1–2	0 (0.0)	0 (0.0)	10 (31.3)	4 (40.0)
	Baseline 2–3	0 (0.0)	0 (0.0)	4 (12.5)	1 (1.0)
	Baseline 3–4	0 (0.0)	1 (12.5)	0 (0.0)	0 (0.0)
Improvement	1-point decrease	n = 2	n = 22	n = 78	n = 58
	Baseline 1–0	1 (50.0)	13 (59.1)	39 (50.0)	35 (60.3)
	Baseline 2–1	0 (0.0)	7 (31.8)	24 (30.8)	18 (31.0)
	Baseline 3–2	0 (0.0)	0 (0.0)	12 (15.4)	3 (5.2)
	Baseline 4–3	1 (50.0)	2 (9.1)	3 (3.9)	2 (3.4)

B. IDS Thoughts of Death or Suicide (item 18)

		With Akathisia		Without Akathisia	
Direction of Change	Magnitude of Change, n (%)	Adjunctive Placebo (n = 16)	Adjunctive Aripiprazole (n = 89)	Adjunctive Placebo (n = 331)	Adjunctive Aripiprazole (n = 267)
Worsening	1-point increase	n = 1	n = 4	n = 18	n = 11
	Baseline 0–1	1 (100.0)	2 (50.0)	14 (77.8)	8 (72.7)
	Baseline 1–2	0 (0.0)	2 (50.0)	1 (5.6)	2 (18.2)
	Baseline 2–3	0 (0.0)	0 (0.0)	3 (16.7)	1 (9.1)
Improvement	1-point decrease	n = 1	n = 17	n = 28	n = 40
	Baseline 1–0	1 (100.0)	17 (100.0)	23 (82.1)	32 (80.0)
	Baseline 2–1	0 (0.0)	0 (0.0)	5 (17.9)	8 (20.0)
	Baseline 3–2	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: IDS = Inventory of Depressive Symptomatology, LOCF = last observation carried forward, MADRS = Montogmery-Åsberg Depression Rating Scale.

experienced improvement than worsening in scores. Eight patients with akathisia in the adjunctive aripiprazole treatment arm (n = 91) experienced a 1-point worsening, and 22 patients experienced a 1-point improvement in MADRS item 10 scores. For IDS item 18 scores, 4 patients with akathisia in the adjunctive aripiprazole treatment arm (n = 89; 2 patients did not have IDS scores) experienced a 1-point worsening, and 17 patients experienced a 1-point improvement.

Mean MADRS item 10 scores and IDS item 18 scores in aripiprazole-treated patients with a BARS Akathisia Global Clinical Assessment score of ≥ 2 at any time during double-blind treatment are shown in Figure 4. During the double-blind treatment phase, 7 adjunctive aripiprazole–treated patients had a BARS Akathisia Global Clinical Assessment score of 4 (marked akathisia), at its highest severity. For these patients, 2 had MADRS item 10 scores of 2 (ie, weary of life, only fleeting suicidal thoughts), and 5 had MADRS item 10 scores of 0 (ie, enjoys life or takes it as it comes). All 7 patients with a BARS Akathisia Global Clinical Assessment score of 4 (marked akathisia) had an IDS item 18 score of 0 (ie, I do not think of suicide or death).

DISCUSSION

The results of this post hoc pooled analysis showed that aripiprazole augmentation to antidepressant treatment in patients with MDD who had shown an inadequate response to previous antidepressant therapy was associated with a decreased risk of suicidality. There were no treatment-emergent, suicide-related adverse events in the adjunctive aripiprazole treatment group, and a low rate of treatment-emergent suicidality was observed following adjunctive aripiprazole therapy. Also, more adjunctive aripiprazole–treated patients showed improvement in their suicidality ratings than those in the adjunctive placebo group, when assessed by both the clinician and the patient. Furthermore, treatment with adjunctive aripiprazole was associated with a significantly greater decrease in the depressive symptoms of suicidality, measured by mean change in MADRS item 10 and IDS item 18 scores, compared with adjunctive placebo—an improvement that was evident from the second week of therapy and maintained to the end of treatment. Taken together, these findings indicate there is no evidence that use of adjunctive aripiprazole is associated with an increased rate of suicidal ideation in this population.

Importantly, the majority of patients who achieved symptom remission or response demonstrated no suicidality symptoms at endpoint. Consistent with this, Spearman correlation analyses indicated that mean improvements in suicidality items in both treatment arms corresponded to the overall mean improvement in depressive symptoms.

It is widely acknowledged that individuals with MDD are at increased risk of suicide, yet the ability to predict suicidal behavior is poor, and patients at the greatest risk often deny suicidal thoughts. For this reason, suicide risk should be closely monitored in all patients with MDD, especially at-risk populations, such as individuals < 25 years of age,[24,25] elderly patients, individuals with a history of previous suicide attempts, individuals with alcohol or other substance use or severe anxiety and/or agitation, those with a family history of suicide, and war veterans. Although this study had only a few patients ≤ 25 years of age, adjunctive aripiprazole did not appear to increase suicidality in this younger, at-risk patient group. As a history of past suicide attempts is a well-known risk factor for completed suicide, clinicians should be aware that the process from initial suicidal thought to suicide attempt is generally short—fewer than 10 minutes for approximately half of suicidal patients.[26] Therefore, educating patients and their families about suicidality and interventional measures is important when initiating antidepressant treatment or treating depression. Efforts to increase knowledge and awareness of health professionals and the general public about this issue may also be helpful in reducing suicidality and completed suicides.

It should be noted that all patients in these studies had received antidepressant treatment for a minimum of 8 weeks prior to randomization to adjunctive aripiprazole or adjunctive placebo treatment. Although treatment with SSRIs can be associated with activation of mania/hypomania, there was no evidence of hypomania in either treatment.

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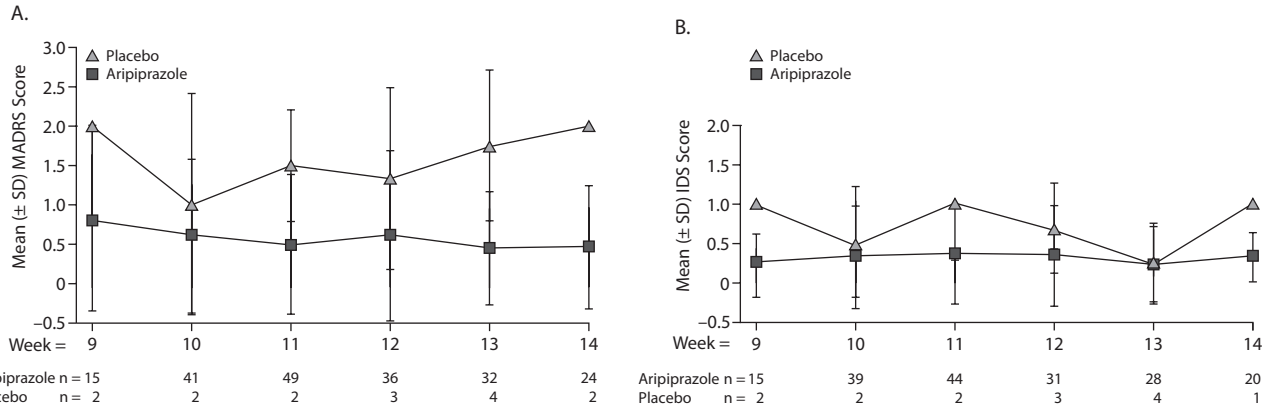
Figure 4. Mean (± SD) (A) MADRS Item 10 Scores and (B) IDS Item 18 Scores for Patients With Akathisia (BARS Akathisia Global Clinical Assessment score ≥ 2)[a]



[a]Note that SDs for weeks 9 and 14 MADRS and IDS mean scores were 0.
Abbreviations: BARS = Barnes Akathisia Rating Scale, IDS = Inventory of Depressive Symptomatology, MADRS = Montgomery-Åsberg Depression Rating Scale.

It has been suggested that akathisia may be a risk factor for suicidal behavior, despite a lack of categorical evidence for an association,[27] and it has been proposed that SSRIs may induce akathisia with associated self-destructive or aggressive impulses.[28] As such, this analysis included an investigation of the effects of akathisia on suicidality. Akathisia did not appear to increase the risk of suicidality in this study; adjunctive aripiprazole–treated patients with akathisia showed low suicidality scores during the trial, and even patients with akathisia at its highest severity were judged by both clinicians and patients to have low suicidality scores. Furthermore, shift analyses using clinician- and patient-reported scales indicated that the majority of subjects with akathisia did not experience a change from their baseline status, and more patients experienced improvement than worsening of suicidality scores. These data suggest that, for these patients, treatment-emergent akathisia is not accompanied by extreme changes in suicidality.

The findings reported here are strengthened by the relatively large numbers of patients with MDD included in this pooled analysis. However, the results should be considered preliminary in light of several limitations. This was a post hoc analysis, and the study was not specifically designed to assess the impact of treatment on suicidality. As such, suicidal ideation was measured using a single item on 2 separate symptom rating scales. However, the use of both a clinician- (MADRS) and patient-reported (IDS) scale may strengthen the study findings. Furthermore, patients with a significant risk of suicide, at screening or in the prospective treatment phase, were excluded from this study, and baseline MADRS item 10 and IDS item 18 scores were low, thus preventing conclusions about the effects of treatment on active suicidal behavior. It should also be considered that the design (placebo vs active control) and duration of randomized controlled trials of antidepressant medications can have a significant impact on study outcome.[29] The original studies used in this post hoc analysis implemented a modified sequential parallel comparison design aimed at ensuring careful characterization of the inadequate response to antidepressant monotherapy.[30] This design also attempts to reduce the placebo response, which is common in affective disorder clinical trials.[30] Using this methodological innovation, very consistent findings were reported across the aripiprazole augmentation studies. However, the extent to which the modified sequential parallel comparison design used in this study may have influenced the findings of this post hoc analysis is unknown. Finally, the short duration of this study does not allow for conclusions regarding the long-term effects of adjunctive aripiprazole on suicidality in this population. Longer-term studies are warranted.

Adjunctive aripiprazole treatment represents a generally safe and relatively well-tolerated and efficacious treatment option for patients with MDD who have had an inadequate response to standard antidepressant medication. All subjects enrolled in the aripiprazole MDD augmentation trials were not judged by investigators to be a significant suicide risk at screening and baseline study visits. Nevertheless, results from this post hoc analysis demonstrate that adjunctive aripiprazole treatment decreased the risk of suicidality in a variety of subpopulations defined in this analysis, although careful monitoring of patients for the potential development of suicidality remains clinically appropriate.

Drug names: aripiprazole (Abilify), escitalopram (Lexapro and others), fluoxetine (Prozac and others), lithium (Lithobid and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others), venlafaxine (Effexor and others).

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Potential conflicts of interest: **Dr Weisler**, in his career, is or has been a consultant to the following: Abbott, the Agency for Toxic Substances and Disease Registry/Centers for Disease Control and Prevention, AstraZeneca, Biovail, Bristol-Myers Squibb, Cephalon, Corcept, Eli Lilly,

Forest, GlaxoSmithKline, Johnson and Johnson, Merck, the National Institute of Mental Health (NIMH), Organon, Otsuka, Pfizer, ProPhase, sanofi, sanofi synthelabo, Shire, Solvay, Takeda, Validus, and Wyeth; is or has been on the speakers' bureaus for the following: Abbott, AstraZeneca, Biovail, Bristol-Myers Squibb, Burroughs Wellcome, Cephalon, Ciba-Geigy, Eli Lilly, Forest, GlaxoSmithKline, Janssen, Johnson and Johnson, Merck, Novartis, Organon, Pfizer, Pharmacia, sanofi, sanofi synthelabo, Schering-Plough, Shire, Solvay, Validus, and Wyeth; is receiving or has received research support from the following: Abbott, AstraZeneca, Biovail, Bristol-Myers Squibb, Burroughs Wellcome, Cenerx, Cephalon, Ciba-Geigy, Comentis, Dainippon Sumitomo Pharma America, Eisai, Eli Lilly, Forest, GlaxoSmithKline, Janssen, Johnson and Johnson, Lundbeck, McNeil, MediciNova, Merck, NIMH, Neurochem, New River, Novartis, Organon, Pfizer, Pharmacia, Repligen, Saegis, Sandoz, sanofi, sanofi synthelabo, Schwabe/Ingenix, Sepracor, Shire, Synaptic, Takeda, TAP, UCB Pharma, Vela, and Wyeth; and has held or holds stocks from the following: Bristol-Myers Squibb, Cortex, Merck, and Pfizer. **Dr Khan**, principal investigator of more than 330 clinical trials sponsored by more than 55 pharmaceutical companies and 30 clinical research organizations, has done no compensated consulting or speaking on their behalf. Dr Khan was a principal investigator during 9 Bristol-Myers Squibb–sponsored aripiprazole studies involving 477 patients. **Dr Trivedi** has received research support from, has served as a consultant to, or has been on the speakers' boards of the following: Abdi Brahim; Abbott Laboratories, Inc; Agency for Healthcare Research and Quality; Akzo (Organon Pharmaceuticals, Inc); AstraZeneca; Bayer; Bristol-Myers Squibb; Cephalon, Inc; Corcept Therapeutics, Inc; Cyberonics, Inc; Eli Lilly; Fabre-Kramer Pharmaceuticals, Inc; Forest Pharmaceuticals; GlaxoSmithKline; Janssen; Johnson & Johnson Pharmaceutical Research and Development; Meade Johnson; Merck; National Alliance for Research in Schizophrenia and Depression; National Institute of Mental Health; National Institute on Drug Abuse; Neuronetics; Novartis; Parke-Davis Pharmaceuticals, Inc; Pfizer, Inc; Pharmacia & Upjohn; Predix Pharmaceuticals; Sepracor; Solvay Pharmaceuticals, Inc; Targacept; VantagePoint; and Wyeth-Ayerst Laboratories. **Dr Yang** is a former consulting statistician at Bristol-Myers Squibb. **Drs Pikalov** and **Tran** were employees of Otsuka America Pharmaceutical, Inc, at the time of the study and submission, but they are no longer employed by Otsuka. **Drs Berman** and **Carlson** and **Mr Eudicone** are employees of Bristol-Myers Squibb.

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REFERENCES

1. Asnis GM, Friedman TA, Sanderson WC, et al. Suicidal behaviors in adult psychiatric outpatients, part I: description and prevalence. *Am J Psychiatry*. 1993;150(1):108–112.
2. Gladstone GL, Mitchell PB, Parker G, et al. Indicators of suicide over 10 years in a specialist mood disorders unit sample. *J Clin Psychiatry*. 2001; 62(12):945–951.
3. Oquendo MA, Galfalvy H, Russo S, et al. Prospective study of clinical predictors of suicidal acts after a major depressive episode in patients with major depressive disorder or bipolar disorder. *Am J Psychiatry*. 2004;161(8):1433–1441.
4. Sokero TP, Melartin TK, Rytsälä HJ, et al. Suicidal ideation and attempts among psychiatric patients with major depressive disorder. *J Clin Psychiatry*. 2003;64(9):1094–1100.
5. Chen YW, Dilsaver SC. Lifetime rates of suicide attempts among subjects with bipolar and unipolar disorders relative to subjects with other Axis I disorders. *Biol Psychiatry*. 1996;39(10):896–899.
6. The Office of Applied Studies Report. Suicidal thoughts, suicide attempts, major depressive episode, and substance use among adults. Substance Abuse and Mental Health Services Administration (SAMHSA) 2006; Issue 34. http://www.oas.samhsa.gov/2k6/suicide/suicide.htm. Accessed 30 June 2009.
7. Centers for Disease Control and Prevention Office of Statistics and Programming. National Center for Injury Prevention and Control Web-based Injury Statistics Query and Reporting System (WISQARS): nonfatal injury reports 2007. http://webappa.cdc.gov/sasweb/ncipc/nfirates2001.html. Accessed 30 June 2009.
8. Centers for Disease Control and Prevention Office of Statistics and Programming. National Center for Injury Prevention and Control Web-Based Injury Statistics Query and Reporting System (WISQARS): leading causes of death, United States 2006. http://webappa.cdc.gov/sasweb/ncipc/leadcaus10.html. Accessed 30 June 2009.
9. Joiner TE Jr, Brown JS, Wingate LR. The psychology and neurobiology of suicidal behavior. *Annu Rev Psychol*. 2005;56(1):287–314.
10. Khan A, Khan S, Kolts R, et al. Suicide rates in clinical trials of SSRIs, other antidepressants, and placebo: analysis of FDA reports. *Am J Psychiatry*. 2003;160(4):790–792.
11. Gibbons RD, Hur K, Bhaumik DK, et al. The relationship between antidepressant medication use and rate of suicide. *Arch Gen Psychiatry*. 2005; 62(2):165–172.
12. Olfson M, Shaffer D, Marcus SC, et al. Relationship between antidepressant medication treatment and suicide in adolescents. *Arch Gen Psychiatry*. 2003;60(10):978–982.
13. Gibbons RD, Brown CH, Hur K, et al. Relationship between antidepressants and suicide attempts: an analysis of the Veterans Health Administration data sets. *Am J Psychiatry*. 2007;164(7):1044–1049.
14. Angst J, Angst F, Gerber-Werder R, et al. Suicide in 406 mood-disorder patients with and without long-term medication: a 40 to 44 years' follow-up. *Arch Suicide Res*. 2005;9(3):279–300.
15. Berman RM, Marcus RN, Swanink R, et al. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a multicenter, randomized, double-blind, placebo-controlled study. *J Clin Psychiatry*. 2007;68(6):843–853.
16. Marcus RN, McQuade RD, Carson WH, et al. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a second multicenter, randomized, double-blind, placebo-controlled study. *J Clin Psychopharmacol*. 2008;28(2):156–165.
17. Berman RM, Fava M, Thase ME, et al. Aripiprazole augmentation in major depressive disorder: a double-blind, placebo-controlled study in patients with inadequate response to antidepressants. *CNS Spectr*. 2009; 14(4):197–206.
18. Thase ME, Trivedi MH, Nelson JC, et al. Examining the efficacy of adjunctive aripiprazole in major depressive disorder: a pooled analysis of 2 studies. *Prim Care Companion J Clin Psychiatry*. 2008;10(6):440–447.
19. 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.
20. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders,* Fourth Edition, Text Revision. Washington, DC: American Psychiatric Association; 2000.
21. Montgomery SA, Åsberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979;134(4):382–389.
22. Rush AJ, Gullion CM, Basco MR, et al. The Inventory of Depressive Symptomatology (IDS): psychometric properties. *Psychol Med*. 1996; 26(3):477–486.
23. Barnes TR. A rating scale for drug-induced akathisia. *Br J Psychiatry.* 1989;154(5):672–676.
24. Friedman RA, Leon AC. Expanding the black box—depression, antidepressants, and the risk of suicide. *N Engl J Med*. 2007;356(23):2343–2346.
25. Olfson M, Marcus SC. A case-control study of antidepressants and attempted suicide during early phase treatment of major depressive episodes. *J Clin Psychiatry*. 2008;69(3):425–432.
26. Deisenhammer EA, Ing CM, Strauss R, et al. The duration of the suicidal process: how much time is left for intervention between consideration and accomplishment of a suicide attempt? *J Clin Psychiatry*. 2009;70(1): 19–24.
27. Hansen L. A critical review of akathisia, and its possible association with suicidal behaviour. *Hum Psychopharmacol*. 2001;16(7):495–505.
28. Müller-Oerlinghausen B, Berghöfer A. Antidepressants and suicidal risk. *J Clin Psychiatry*. 1999;60(suppl 2):94–99, discussion 111–116.
29. Rutherford BR, Sneed JR, Roose SP. Does study design influence outcome? the effects of placebo control and treatment duration in antidepressant trials. *Psychother Psychosom*. 2009;78(3):172–181.
30. Fava M, Evins AE, Dorer DJ, et al. The problem of the placebo response in clinical trials for psychiatric disorders: culprits, possible remedies, and a novel study design approach. *Psychother Psychosom*. 2003;72(3):115–127.