Whether to Increase or Maintain Dosage of Mirtazapine in Early Nonimprovers With Depression

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ABSTRACT

Objective: To compare outcomes between increasing versus maintaining the dose of mirtazapine in patients with depression without initial improvement.

Method: Data from a 6-week double-blind randomized placebo-controlled trial of mirtazapine in major depressive disorder (*DSM-IV*) conducted from November 2004 to December 2005 were used. Percentages of remitters (ie, a score of ≤ 7 in the 17-item Hamilton Depression Rating Scale [HDRS-17]) and HDRS-17 score changes from baseline to week 6 were compared in the following 2 pairs, using Fisher exact test or mixed-effects model for repeated measures: (1) subjects who failed to show a ≥ 20% decrease in the HDRS-17 total scores at week 1 but were assigned to continue 15 mg/d ($stay_{15}$ group) versus those who were assigned to increase the dose to 30 mg/d ($increase_{30}$ group) and (2) subjects who failed to show a ≥ 20% decrease in the HDRS-17 total scores with 30 mg/d at week 2 but were assigned to continue 30 mg/d ($stay_{30}$ group) versus those who were assigned to increase the dose to 45 mg/d ($increase_{45}$ group).

Results: The $increase_{30}$ group showed a numerically but not significantly higher remission rate and a significantly greater decrease in the HDRS-17 total score at week 6 than the $stay_{15}$ group (34.7% [8 of 23 patients] vs 14.3% [3 of 21 patients], $P = .2$; least squares mean, −15.8 vs −10.9, $P = .003$). No significant differences were found between the $increase_{45}$ and $stay_{30}$ groups.

Conclusions: Dose increase of mirtazapine from 15 mg/d to 30 mg/d may be effective for patients with depression without initial improvement. However, effectiveness may not be the case beyond 30 mg/d.

Trial Registration: JapicCTI identifier: 152830

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Antidepressant medications have played an important role in the treatment of depression for many decades[1,2] and are endorsed as one of the first-line treatments.[3–5] Although some of the available guidelines for the treatment of depression recommend increasing the dose of antidepressants in patients with depression who fail to show initial treatment response,[6–8] a positive relationship between higher antidepressant dose and better clinical response has not been a robust finding.[9] For example, while tricyclic antidepressant drugs (TCAs), such as imipramine and clomipramine, have been shown to demonstrate such dose-dependent therapeutic efficacy,[10,11] the same may not hold true with respect to serotonin reuptake inhibitors (SSRIs), including fluoxetine and sertraline.[12,13] These inconsistent findings raise the possibility that such a dose–efficacy relationship may differ among antidepressants with different pharmacologic classes and characteristics.

Mirtazapine is an antidepressant with a unique pharmacologic profile, including potent antagonism of central α_2-adrenergic autoreceptors and heteroreceptors and antagonism of both serotonin 5-hydroxytryptamine-2 ($5\text{-}HT_2$) and 5-hydroxytryptamine-3 ($5\text{-}HT_3$) receptors[14]; thus, mirtazapine is classified as a noradrenergic and specific serotonergic antidepressant (NaSSA). In detail, putative mechanisms include antagonism of α_2-adrenergic receptors that leads to blockade of presynaptic autoreceptors and thus enhances norepinephrine release, while blockade of heteroreceptors on serotonergic neurons increases serotonin release. In addition, blockade of $5\text{-}HT_2$ and $5\text{-}HT_3$ receptors enhances serotonin release, which, in turn, results in a net increase in 5-hydroxytryptamine-1 ($5\text{-}HT_1$)–mediated neurotransmission.[15,16] According to the recent Cochrane Database Systematic Review, mirtazapine was found to be superior to other antidepressants in the acute-phase treatment of major depressive disorder and likely to have a faster onset of action than SSRIs.[17] In light of the unique pharmacologic profile of mirtazapine, the dose–response relationship in individual patients may differ from that in SSRIs and other antidepressants.[12,13]

To generate a hypothesis regarding the dose–response relationship in individual patients receiving mirtazapine, we conducted a post hoc analysis of the data from a 6-week double-blind placebo-controlled randomized trial of this drug in order to examine the effects of dose increase of mirtazapine in patients with depression who showed and failed to show initial improvement with this drug.

METHOD

Study Design

We used the data from a 6-week double-blind placebo-controlled randomized Phase II trial of mirtazapine that was conducted from November 2004 to December 2005 at 45 hospitals and clinics in Japan.[18] Inpatients and outpatients who fulfilled the following criteria were included: (1) 20 to 75 years of age, (2) primary diagnosis of major depressive disorder according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*), and (3) a baseline score of 18 or higher on the 17-item Hamilton Depression Rating Scale (HDRS-17).[19] Patients were excluded if they were

Clinical Points

- Increasing the dose of mirtazapine from 15 mg/d to 30 mg/d may be effective for patients with depression without initial improvement on 15 mg/d; however, effectiveness may not be the case beyond 30 mg/d.
- There may be no benefit in increasing the dose of mirtazapine in those who derived early benefit at 15 mg/d or 30 mg/d.
- In light of the small sample size, preliminary findings are not robust enough to influence clinical practice recommendations with regard to mirtazapine dosage.

treated by another drug that was effective or were treated with electroconvulsive therapy before this trial. Patients were also excluded if they received mirtazapine for the current episode, had a psychiatric comorbidity, showed a significant suicidal ideation (ie, a score of 3 or higher on item 11 of the HDRS-17), had a history of treatment with a mood stabilizer for the previous 2 weeks, or had a significant neurologic or general medical condition.

The subjects were randomized to 1 of the following 4 treatment arms of mirtazapine: 15 mg/d (15 mg/d for 6 weeks), 30 mg/d (15 mg/d for the first week and 30 mg/d for another 5 weeks), 45 mg/d (15 mg/d for the first week, 30 mg/d for the second week, and 45 mg/d for another 4 weeks), and placebo. The severity of depression was assessed at baseline and weekly thereafter, using the HDRS-17.

Following a complete description of the study, participants provided written informed consent at study enrollment in the original studies, and this post hoc analysis used data that were made completely anonymous. The parent clinical trial was approved by the institutional review board at each of the participating sites.

Statistical Analysis

In order to examine the effects of dose increase in subjects who failed to show initial improvement with mirtazapine at week 1, we classified the subjects in the original randomized clinical trial[18] into the following categories for our post hoc analyses (Figure 1): (1a) subjects who failed to show a ≥ 20% decrease in the HDRS-17 total score from baseline at week 1 but were assigned to continue 15 mg/d, (1b) those who failed to show a ≥ 20% decrease in the HDRS-17 total score from baseline at week 1 and were assigned to increase the dose to 30 mg/d for another 5 weeks, (2a) subjects who were treated at 30 mg/d for the second week and failed to show a ≥ 20% decrease in the HDRS-17 total score from baseline at week 2 but were assigned to continue 30 mg/d, and (2b) those who were treated at 30 mg/d for the second week and failed to show a ≥ 20% decrease in the HDRS-17 total score from baseline at week 2 and were assigned to increase the dose to 45 mg/d for another 4 weeks. Likewise, to evaluate the effects of a dose increase in subjects who showed initial response to mirtazapine, the following subjects were identified: (3a) subjects who showed a ≥ 20% decrease in the HDRS-17 total score from baseline at week 1 and were assigned to continue 15 mg/d, (3b) those who showed a ≥ 20% decrease in the HDRS-17 total scores from baseline at week 1 and were assigned to increase the dose to 30 mg/d for another 5 weeks, (4a) subjects who were treated at 30 mg/d for the second week and showed a ≥ 20% decrease in the HDRS-17 total score from baseline at week 2 and were assigned to continue 30 mg/d, and (4b) those who were treated at 30 mg/d for the second week and showed a ≥ 20% decrease from baseline at week 2 and were assigned to increase the dose to 45 mg/d for another 4 weeks.

Percentages of subjects who achieved remission (ie, a HDRS-17 score of ≤ 7)[20] at week 6 were compared between the 2 groups of interest, using Fisher exact test. In the analysis, subjects who failed to complete the study were treated as nonremitters. Changes in the HDRS-17 scores from baseline to week 6 were compared between the 2 groups of interest, using the mixed-effects model for repeated measures (MMRM) that contained treatment group, week, and group-by-week interaction as factors with autoregressiveAR(1) correlation matrix among time points. Least squares (LS) means for each group and their between-group differences at each time point were estimated by means of the MMRM in which degrees of freedom were approximated with the Kenward-Roger method. A P value of < .05 was considered statistically significant (2-tailed). Statistical analyses were performed with the SPSS Version 21.0 (IBM, New York, New York) and SAS Version 9.2 (SAS, Cary, North Carolina).

RESULTS

Study Sample

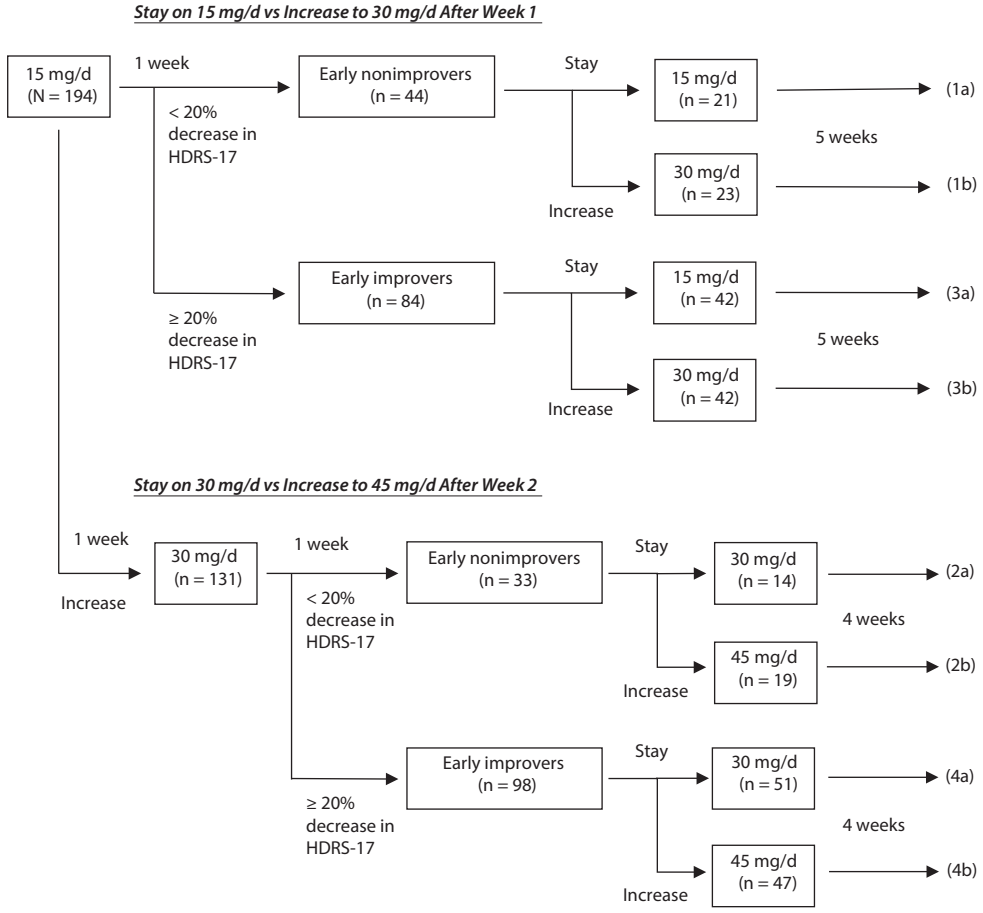
A total of 194 subjects were identified for the present study. Their demographic and clinical characteristics are summarized in Table 1.

Dose Increase in Early Nonimprovers

Stay on 15 mg/d versus increase to 30 mg/d after week 1 (1a vs 1b comparison). The remission rate at week 6 in subjects who failed to show a ≥ 20% decrease in the HDRS-17 total score at week 1 and experienced a dose increase to 30 mg/d was numerically higher than that in those who continued the dose of 15 mg/d, although the difference did not reach statistical significance (34.7% [8 of 23 patients] vs 14.3% [3 of 21 patients], $P = .2$). On the other hand, the 30-mg/d group experienced a significantly greater decrease (ie, improvement) in the HDRS-17 total score than the 15-mg/d group at weeks 5 and 6 (LS mean [95% confidence interval (CI)], −14.7 [−12.4 to −17.0] vs −10.4 [−8.2 to −12.6], $P = .01$ at week 5 and −15.8 [−13.5 to −18.1] vs −10.9 [−8.6 to −13.2], $P = .003$ at week 6) (Figure 2A), although the effect of the group-by-week interaction was not statistically significant ($P = .2$).

Stay on 30 mg/d versus increase to 45 mg/d after week 2 (2a vs 2b comparison). No significant difference was observed in the remission rate between the subjects who failed to show a ≥ 20% decrease in the HDRS-17 total score at week 2 and stayed on the same dose of 30 mg/d versus

Figure 1. Sorting of Subjects Based on Presence of Early Improvement or Nonimprovement and Assigned Dosage



Abbreviation: HDRS-17 = 17-item Hamilton Depression Rating Scale.

Table 1. Demographic and Clinical Characteristics of the Sample

	Early Nonimprovers				Early Improvers			
Characteristic	Stay on 15 mg/d (n = 21)	Increase to 30 mg/d (n = 23)	Stay on 30 mg/d (n = 14)	Increase to 45 mg/d (n = 19)	Stay on 15 mg/d (n = 42)	Increase to 30 mg/d (n = 42)	Stay on 30 mg/d (n = 51)	Increase to 45 mg/d (n = 47)
Age, mean ± SD (range), y	37.2 ± 11.2 (22–67)	36.3 ± 9.4 (21–65)	38.7 ± 10.51 (23–65)	43.9 ± 12.1 (23–65)	40.4 ± 11.0 (24–64)	38.6 ± 11.6 (21–72)	37.5 ± 11.0 (21–72)	40.2 ± 12.6 (20–66)
Women, n (%)	9 (42.9)	9 (39.1)	5 (35.7)	11 (57.9)	24 (57.1)	23 (54.8)	27 (52.9)	25 (53.2)
Outpatients, n (%)	21 (100.0)	22 (95.7)	14 (100.0)	18 (94.7)	41 (97.6)	42 (100.0)	50 (98.0)	47 (100.0)
Patients with multiple episodes, n (%)	6 (28.6)	9 (39.1)	5 (35.7)	6 (31.6)	11 (26.2)	14 (33.3)	18 (35.3)	17 (36.2)
Duration of illness, mean ± SD (range), mo	36.4 ± 54.8 (2–228)	28.8 ± 30.0 (0–120)	25.9 ± 25.4 (2–60)	49.8 ± 63.6 (1–192)	35.3 ± 53.2 (1–264)	53.4 ± 92.5 (1–360)	49.8 ± 85.1 (0–360)	38.4 ± 48.07 (1–180)
Duration of current episode, mean ± SD (range), mo	17.4 ± 28.11 (0–132)	10.4 ± 15.04 (0–60)	12.1 ± 16.5 (2–60)	21.3 ± 33.9 (0–122)	11.3 ± 12.0 (1–48)	10.8 ± 14.4 (1–72)	10.2 ± 14.0 (0–2)	13.7 ± 22.3 (0–114)
Baseline of HDRS-17 score, mean ± SD (range)	23.76 ± 5.02 (18–34)	23.17 ± 3.17 (18–29)	21.43 ± 2.50 (18–26)	23.63 ± 3.90 (18–32)	23.00 ± 4.18 (18–36)	22.62 ± 3.37 (18–32)	22.90 ± 3.45 (18–32)	21.66 ± 2.66 (18–28)
Dropout by week 6, n (%)	2 (9.5)	6 (26.1)	5 (35.7)	8 (42.1)	6 (14.3)	7 (16.7)	8 (15.7)	4 (8.5)

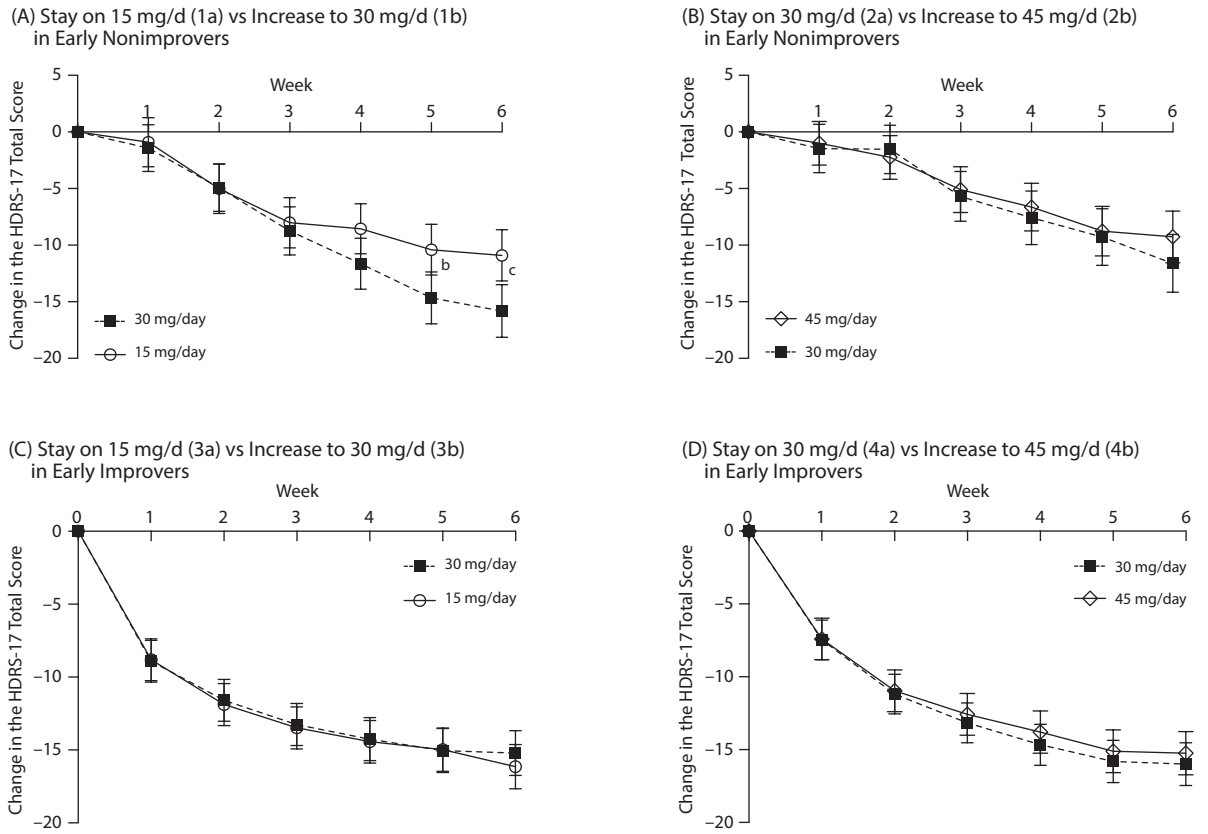
Abbreviations: HDRS-17 = 17-item Hamilton Depression Rating Scale, SD = standard deviation.

those who experienced a dose increase from 30 mg/d to 45 mg/d (7.1% [1 of 14 patients] vs 0.0% [0 of 19 patients], $P = .4$). There was no significant difference in the decrease in the HDRS-17 total score at week 6 between the 30-mg/d and 45-mg/d groups (LS mean [95% CI], −11.6 [−9.1 to −14.2] vs −9.3 [−7.0 to −11.5], $P = .2$) (Figure 2B).

Dose Increase in Early Improvers

Stay on 15 mg/d versus increase to 30 mg/d after week 1 (3a vs 3b comparison). The remission rate in the subjects who showed a ≥ 20% decrease in the HDRS-17 total score at week 1 and continued the initial dose (15 mg/d) was not statistically significantly different from the rate in those who

Figure 2. Changes in the HDRS-17 Total Scores in 8 Subgroups[a]



[a]Closed squares, open circles, and open squares represent least squares means. Bars represent 95% confidence intervals.
[b]$P = .01$ by the mixed-effects model for repeated measures.
[c]$P = .003$ by the mixed-effects model for repeated measures.
Abbreviation: HDRS-17 = 17-item Hamilton Depression Rating Scale.

experienced a dose increase to 30 mg/d (61.9% [26 of 42 patients] vs 54.8% [23 of 42 patients], $P = .7$). In addition, the decreases in the HDRS-17 total score at week 6 were comparable between the 2 groups (LS mean [95% CI], −16.1 [−14.6 to −17.7] vs −15.2 [−13.7 to −16.7], $P = .4$) (Figure 2C).

Stay on 30 mg/d versus increase to 45 mg/d after week 2 (4a vs 4b comparison). No significant difference was found in the remission rate between the subjects who demonstrated a ≥ 20% decrease in the HDRS-17 total score at week 2 and stayed on the same dose of 30 mg/d versus those who experienced a dose increase to 45 mg/d (58.8% [30 of 51 patients] vs 61.7% [29 of 47 patients], $P = .8$). Likewise, there was no significant difference in the decrease in the HDRS-17 total score at week 6 between the 30-mg/d and 45-mg/d groups (LS mean [95% CI], −16.0 [−14.5 to −17.5] vs −15.2 [−13.8 to −16.7], $P = .5$) (Figure 2D).

DISCUSSION

To our knowledge, the present post hoc analysis is the first study to examine the effects of dose response of mirtazapine in patients with depression who failed to show initial improvement with this drug. The dose increase to 30 mg/d in early nonimprovers failed to result in significantly better treatment outcomes in terms of remission than staying on the same dose of 15 mg/d, although the former group was found to be numerically superior. On the other hand, the increase group showed a significantly greater decrease in the HDRS-17 total score at weeks 5 and 6 than the other group. As such, increasing the dose among those without initial improvement may warrant clinical consideration with mirtazapine. Possible implications of our observations are discussed below.

In the present study, the dose increase from 15 mg/d to 30 mg/d in early nonimprovers resulted in a numerically higher remission rate and a numerically greater reduction in the HDRS-17 scores when compared to staying on the same dose, although the differences were not statistically significant. In addition, clinical outcomes were comparable between early nonimprovers who experienced a dose increase to 45 mg/d and those who continued the same dose of 30 mg/d. Thus, our results point to the possibility that the dose increase of mirtazapine to 30 mg/d after 1 week may be effective in early nonimprovers taking 15 mg/d; however, such a dose increase may not yield any additional therapeutic gains beyond 30 mg/d after 2 weeks if patients continue to show no improvement, exemplified as a < 20% decrease in the HDRS-17 scores in this study. For such patients, an antidepressant switch could be considered as an alternative option; our previous clinical trial indicated

that more patients with depression who failed to show early improvement with sertraline 50 mg/d at week 2 remitted by switching to paroxetine instead of increasing the dose of sertraline up to 100 mg/d.[21] More comparative studies are necessary to compare the stay, increase, or switch paradigms.

No additional therapeutic benefits of a dose increase of mirtazapine were observed in the subjects who responded to either 15 mg/d at week 1 or 30 mg/d at week 2. This result is consistent with the previous finding that the recovery process continues once patients get on the right track, without needing further dosage. In fact, Stassen et al[22] examined the time course of improvement among responders who were receiving placebo, oxaprotiline, and amitriptyline in a meta-analysis of double-blind randomized controlled trials. They found that the time course of improvement among responders was independent of the treatment modality, indicating that the course of improvement, once triggered, was identical, irrespective of the types of drugs. These findings suggest the usefulness of a conservative approach of sticking to the dose without increasing it once patients show initial improvement with mirtazapine; more investigations with other antidepressants are clearly warranted to confirm this contention.

There are several limitations to be noted with this study. First, the parent investigation was not designed to assess the effects of dose increase of mirtazapine among early nonimprovers or improvers, and this is a post hoc analysis. Second, the sample size in the present analysis was relatively small, which very likely limits the statistical power to detect statistically significant differences. Moreover, the study period of 6 weeks was too short to evaluate the long-term effects. Finally, all participants were Japanese, and most were outpatients receiving mirtazapine, a drug with a unique pharmacologic profile, which limits the extrapolation of our results to other populations receiving other antidepressant drugs.

In conclusion, the dose increase to 30 mg/d in early nonimprovers at week 1 showed better treatment outcomes than staying on the same dose (ie, 15 mg/d), although the results were mixed in terms of statistical significance, suggesting the possible clinical utility of a dose increase in patients with depression who failed to show some gains at this treatment dosage. However, such a dose increase may not yield any additional therapeutic benefit beyond 30 mg/d. In addition, a dose increase may not be necessary once patients show initial improvement with mirtazapine. In light of the small sample size of the present analysis, the findings are not robust enough to influence clinical practice recommendations. Further investigations are clearly warranted to confirm or negate whether increasing the dose of mirtazapine is of benefit in patients with depression who show no initial improvement.

Drug names: clomipramine (Anafranil and others), fluoxetine (Prozac and others), imipramine (Tofranil and others), mirtazapine (Remeron and others), paroxetine (Paxil, Pexeva, and others), sertraline (Zoloft and others).

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Author contributions: Drs Mimura and Uchida contributed equally to the study.

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