Real-world effectiveness and safety of aripiprazole augmentation therapy in patients with major depressive disorder

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ABSTRACT
Aims: Augmentation therapy is an option for patients with major depressive disorder who do not respond sufficiently to adequate dosages of selective serotonin reuptake inhibitors or serotonin–norepinephrine reuptake inhibitors, but little is known about application of this strategy in everyday practice.

Methods: This prospective, multi-center, observational study investigated the effectiveness and safety of aripiprazole augmentation in Japanese patients with inadequate response to conventional antidepressant therapy in real-world clinical practice. The primary endpoint was mean change in the (Japanese version) Montgomery-Åsberg Depression Rating Scale (MADRS) total score from baseline to study end. Safety was assessed by monitoring adverse events.

Results: There were 1103 patients in the safety population and 1090 patients in the effectiveness population. Mean change in the MADRS total score at study end was −14.9 ± 12.3 (p < .001 vs baseline). The remission rate increased from 34.5% at Month 6 to 43.3% at Month 12, suggesting additional benefit with continued treatment. The type of primary antidepressant (paroxetine, fluvoxamine, sertraline, milnacipran, duloxetine, mirtazapine, or escitalopram) had no influence on the effectiveness of aripiprazole augmentation therapy. A baseline MADRS total score of <33 points and an elapsed time of <176 days from an episode of depression to the start of aripiprazole treatment increased the likelihood of achieving remission; 24.8% of patients experienced at least one adverse event, but no new safety signals were identified.

Conclusions: Aripiprazole augmentation therapy appears to be effective and safe in Japanese patients with depression/depressive symptoms treated in everyday clinical practice, taking into account factors associated with achieving remission.

Introduction
Depression is a common psychiatric condition observed globally. In 2015, 4.4% of the world’s population, equivalent to more than 300 million people, was estimated to suffer from depression. The 4.2% prevalence of depression in Japan aligns with the global rate. Depression tends to be most prevalent in older adulthood (55–74 years), which is clinically relevant in light of global population aging. Major depressive disorder consistently ranks among the top five leading causes of disability worldwide, thus representing an enormous burden to individuals, healthcare systems, and society. Identifying effective treatment options must be viewed as a priority.

Clinical practice guidelines advocate use of selective serotonin reuptake inhibitors (SSRI) or serotonin–norepinephrine reuptake inhibitors (SNRIs) as first-line treatment for major depressive disorder. However, non-response to antidepressant therapy is common; approximately two-thirds of patients receiving their first course of antidepressant pharmacotherapy do not achieve full remission. Strategies for patients with inadequate response include switching, combining, or augmenting antidepressant therapy.

The anti-Parkinson medications ropinirole and pramipexole were reported to have an antidepressant effect, implying involvement of a dopamine D3 receptor agonistic mechanism. Aripiprazole, an antipsychotic drug indicated for treatment of schizophrenia, acts as a D3 receptor agonist and partial agonist at D2 and 5-HT1A receptors, a sub-type of the serotonin receptor. In 2007, aripiprazole was approved by the US Food and Drug Administration as adjunctive therapy for major depressive disorder. In Japan, aripiprazole was approved in 2013 as an adjunctive treatment for depression/depressive symptoms in case of insufficient response to other antidepressants.

The efficacy and safety of adjunctive aripiprazole in patients with inadequate response to antidepressant therapy, including patients with treatment-resistant depression in later life, have been confirmed in clinical studies conducted in Japan and other countries. However, results were attained under the usual constraints of randomized controlled trials, including strict inclusion and exclusion criteria,
and during relatively short double-blind treatment periods of 6 weeks\textsuperscript{10-13} or 12 weeks\textsuperscript{14}. As such, the results reported in clinical studies may not necessarily reflect the profile of aripiprazole augmentation therapy under everyday clinical practice conditions. Herein, we report results of a post-marketing surveillance study on the effectiveness and tolerability of aripiprazole in patients with depression/depressive symptoms in daily clinical practice.

**Methods**

**Study design and participants**

This was a prospective, multi-center, non-interventional, observational study conducted in compliance with the Japanese Ministry of Health, Labour & Welfare (MHLW)'s Ordinance on Good Post-marketing Study Practice: MHLW Ordinance Related to Standards for Conducting Post-Marketing Surveys and Studies on Drugs; MHLW Ordinance No. 171 issued by the MHLW on December 20, 2004. Although informed consent and ethics committee approval are not required in Japan for a non-interventional research study of this nature, all procedures were conducted in accordance with applicable legal and regulatory requirements of each participating medical institution.

Study sites were selected across Japan. All participating sites were medical centers experienced in the treatment of patients with major depression. Eligible patients were adults (\(\geq 18\) years) with a diagnosis of treatment-resistant depression/depressive symptoms who were eligible for treatment with aripiprazole and who were starting aripiprazole augmentation therapy for the first time (independent of study inclusion) beginning from January 2014. Patients were then enrolled into the study within 5 days of first administration of aripiprazole. Patients with contraindications for aripiprazole treatment were excluded from the study.

Patients were treated with aripiprazole according to local product label and prescription/reimbursement guidelines at a starting dose of 3 mg and a maintenance dose of 3–15 mg. Evaluations were conducted at enrollment (baseline), and at Month 1, Month 3, Month 6, and Month 12 of treatment or at discontinuation. The maximum duration of observation was 12 months.

**Study assessments**

At each study visit, data were collected using a designated questionnaire form.

Baseline documentation included: socio-demographic characteristics; disease severity; duration of illness; number of depressive episodes; day of occurrence of a depression episode (confirmed day); Montgomery-Åsberg Depression Rating Scale (MADRS) score; Clinical Global Impression–Severity of Illness (CGI-S) rating scale category; complications; family history of diabetes; drug sensitivity; medical history; history of attempted suicide; and history of adverse drug reactions.

At each study visit, details were collected on the status of aripiprazole administration: name of product; daily dose; number of daily administration; route of administration; administration period (start date and end date); reason for changing the daily dose (if reduced/increased); and reason for discontinuation (if discontinued).

At each study visit, details were collected on concomitant antidepressant treatment: name of product; route of administration; daily dose; administration period (start date and end date); and reason for use.

Effectiveness was evaluated using the Japanese version of the Montgomery-Åsberg Depression Rating Scale (MADRS-J), at baseline (day of first administration), Month 1, Month 3, Month 6, and Month 12, or at discontinuation. The MADRS includes 10 items and uses a 0–6 severity scale. The overall score ranges from 0–60, with higher scores indicating increasing depressive symptoms.

Safety was assessed based on adverse events reported during the observation period. Adverse events were defined as medically undesirable symptoms or diseases (including abnormal clinical laboratory values) which occurred or were aggravated after the start of aripiprazole treatment. Adverse events were classified using the Japanese translation of the Medical Dictionary for Regulatory Activities version 18.0 (MedDRA/J). Adverse events for which a causal relationship to aripiprazole could not be ruled out were considered adverse drug reactions. Serious adverse events were defined as any untoward medical occurrence that resulted in death, was life-threatening, required inpatient hospitalization, or caused prolongation of existing hospitalization.

**Study endpoints**

The primary endpoint was the mean change in the MADRS total score from baseline to study end.

Secondary endpoints measured from baseline to Month 12 were: percentage of patients in remission according to MADRS, where remission was defined as a \(\geq 50\%\) decrease from baseline in the MADRS total score, and a MADRS total score of \(\leq 10\) points; percentage of patients in remission stratified by baseline CGI-S category (mild: 1–3; moderate: 4; severe: 5–7); rate of change in MADRS individual scores; change in MADRS total score by concomitant antidepressant.

**Statistical analysis**

All statistical analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC). Results were summarized using descriptive statistics. Continuous variables were described as mean \(\pm\) standard deviation (SD). Categorical variables were described by absolute (n) and relative (%) frequency distributions. Analyses of MADRS scores were conducted using data from patients with at least one measurement before and after treatment with aripiprazole (i.e. minimum of two measurements). The last observation carried forward (LOCF) method was used with imputation of the latest observed values. An applicable \(t\)-test was applied to compare the pre-dose and post-dose effect. For analysis of the MADRS total score by type of underlying concomitant antidepressant, drugs administered at the start of aripiprazole treatment.
were introduced as stratification factors in the calculation. Analysis of covariance (ANCOVA) was performed to test for statistically significant differences in MADRS total scores between antidepressant types.

The remission rate was determined by calculating the percentage of patients who met the definition of remission at each study time point using the LOCF method. To determine factors influencing achievement of remission, univariate analysis was performed, and significant \( p < 0.05 \) variables were selected for use in logistic regression analysis. For each factor selected, cut-off points were determined according to sensitivity and specificity values obtained by the receiver operating characteristic (ROC) curve.

The target sample size was 1000 patients, which is the number required to ensure 99% power to detect an unexpected adverse drug reaction at an incidence of \( \geq 5\% \).

## Results

### Analyses sets and patient disposition

Patient disposition is shown in Figure 1. Of 1132 patients enrolled, 1121 patient surveys were collected during the period of January 2014 to January 2017. The safety analysis population consisted of 1103 patients. Among excluded patients, one patient was not treated with aripiprazole, one patient was treated with aripiprazole prior to establishment of a contract, and 16 patients were lost to follow-up. After excluding patients with major protocol deviations (treated with aripiprazole for an indication other than depression: \( n = 1 \); enrolled into the study outside the 5-day window from first administration of aripiprazole: \( n = 12 \)), the effectiveness analysis population consisted of 1090 patients.

A total of 599 patients discontinued aripiprazole treatment during the course of the study. The discontinuation rate at day 365 was 52% (574/1103), after excluding 25 patients who discontinued treatment after 365 days. The most common reasons for discontinuation (multiple responses were allowed) were: at the request of the patient or his/her family (23.5%), adverse events (23.4%), inadequate effect (18.2%), symptom improvement (16.7%), and no re-visit (i.e. loss to follow-up: 15.5%).

### Demographic characteristics and dose

The demographic and clinical characteristics of the safety analysis population are summarized in Table 1. The mean age of the patient population at baseline was 45.5 ± 15.2 years, and most participants (93.5%) were outpatients. The majority of patients had either moderate disease (63.9%) or severe disease with non-psychotic symptoms (22.9%). Duration of illness was less than 1 year in 32.5% of patients, and between 1–4 years in 35.9% of patients. Nearly half the population (47.9%) was experiencing a depressive episode for the first time. On the physician-rated CGI-S scale, most patients were assessed as being moderately (58.7%) or markedly (23.3%) ill. The mean MADRS total score at baseline was 29.6 ± 9.2.

Patients were treated with a mean daily aripiprazole dose of 3.5 ± 1.8 mg. The mean duration of treatment was 253.7 ± 169.8 days.

### Effectiveness

The change from baseline in the mean MADRS total score is shown in Figure 2. The mean MADRS total score showed...
continuous and statistically significant improvement at all time points (all $p < .001$ vs baseline) from Month 1 ($\Delta = -8.8 \pm 8.3$) to Month 12 ($\Delta = -14.9 \pm 12.3$).

Remission, defined as a MADRS total score $\leq 10$ points and $\geq 50\%$ reduction from baseline, increased over time and was achieved in 34.5% of patients at Month 6, and in 43.3% of patients at Month 12 (Figure 3).

The remission rate according to baseline CGI-S category increased over time in all three severity groups. At Month 12, remission rates were 50% in the mild depression group, 48% in the moderate depression group, and 35% in the severe depression group (Figure 4).

The rate of change in MADRS individual scores from baseline to final evaluation was between $-40.0\%$ and $-60.0\%$, and the differences were statistically significant for all 10 items (all $p < .001$ vs baseline) (Figure 5). The rate of change was highest for suicidal thoughts ($-55.7\%$) and reduced appetite ($-54.0\%)$.

Mean daily doses of paroxetine, fluvoxamine, sertraline, milnacipran, duloxetine, mirtazapine, and escitalopram were $31.4 \pm 13.5$ mg, $107.8 \pm 44.4$ mg, $75.9 \pm 28.4$ mg, $62.3 \pm 43.7$ mg, $47.7 \pm 15.3$ mg, $29.3 \pm 13.3$ mg, and $13.6 \pm 5.1$ mg, respectively. Analysis of change from baseline to final evaluation in the MADRS total score according to concomitant antidepressant treatment showed no statistical significance between medications ($p = 0.085$) (Figure 6).

Demographic and clinical characteristics of patients found to be significantly associated with achieving remission were: disease severity ($p = 0.017$); duration of illness ($p < .001$); baseline MADRS score ($p < .001$); CGI-S score ($p < .004$); mean/median duration of days from an episode of depression to the start of aripiprazole treatment ($p < .001$); and concomitant mirtazapine ($p = 0.017$) (Table 2). After logistic regression analysis, the “MADRS score” and “duration of days...
from an episode of depression to the start of aripiprazole treatment remained as factors significantly influencing remission, with p-values of .013 and <.001, respectively (Table 3). Optimal cut-off points for these two factors derived by ROC analysis were 33 points and 176 days, respectively. Incorporating these cut-off values into the analysis, odds ratios for achieving remission were 1.715 (95% confidence intervals [CI] = 1.320–2.228; p < .001) if the baseline MADRS total score was below 33 and 1.802 (95% CI = 1.403–2.316; p < .001) if there were fewer than 176 days from an episode of depression to the start of aripiprazole augmentation therapy (Table 4).

In a sub-analysis, outcomes were compared between patients experiencing a first-time episode of depression and those with one or more previous episodes of depression. No significant differences were found between groups for mean aripiprazole dose (3.4 ± 1.7 vs 3.6 ± 1.8 mg/day), change in the MADRS total score from baseline to final observation (−15.9 vs −14.9), or proportion of patients who achieved remission (46.5 vs 48.1%) (Supplementary Table S1).

In a second sub-analysis, logistic regression analysis was performed to identify factors in MADRS individual scores at Month 1 predictive for remission by 12 months. In this analysis, explanatory variables were per cent reductions from baseline to Month 1 in MADRS individual scores, and the response variable was the remission rate by 12 months. Items found to be statistically significant for predicting remission were inner tension (p = 0.043), the inability to feel (p = 0.010), and suicidal thought (p < .001) (Supplementary Table S2).

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**Table 2.** Comparison of demographic and clinical characteristics between patients who did or did not achieve remission.

| Characteristics                                      | Overall (n = 1090) | Remission (n = 472) | No remission (n = 618) | p-value |
|------------------------------------------------------|--------------------|---------------------|------------------------|---------|
| Age (years)                                          | 45.5 ± 15.2        | 45.3 ± 15.3         | 45.7 ± 15.1            | .659    |
| Female                                               | 52.0               | 51.3                | 52.6                   | .669    |
| Disease severity                                     |                    |                     |                        |         |
| Mild                                                 | 10.6               | 12.5                | 9.1                    | .017*   |
| Moderate                                             | 63.9               | 65.0                | 63.1                   |         |
| Severe (psychotic)                                   | 23.0               | 19.9                | 25.4                   |         |
| Severe (non-psychotic)                               | 2.5                | 2.5                 | 2.4                    |         |
| Duration of illness (years)                          |                    |                     |                        |         |
| <1                                                   | 32.6               | 37.1                | 29.1                   | <.001   |
| 1–4                                                  | 35.9               | 38.6                | 33.8                   |         |
| 5–9                                                  | 16.9               | 13.6                | 19.4                   |         |
| 10–19                                                | 9.2                | 6.4                 | 11.3                   |         |
| ≥20                                                  | 2.8                | 2.3                 | 3.1                    |         |
| Unknown/not reported                                 | 2.8                | 2.1                 | 3.2                    |         |
| Clinical Global Impression–Severity of Illness rating scale (CGI-S) | 4.2 ± 0.7          | 4.1 ± 0.7           | 4.2 ± 0.7              | .004**  |

**Table 3.** Logistic regression analysis of factors influencing remission.

| Characteristics                                      | Odds ratio | 95% CI     | p-value |
|------------------------------------------------------|------------|------------|---------|
| Disease severity                                     | 1.074      | 0.792–1.457| .644    |
| Duration of illness                                  | 0.880      | 0.772–1.003| .056    |
| MADRS total score (baseline)                         | 0.974      | 0.954–0.994| .013*   |
| Duration of days from an episode of depression to the start of aripiprazole treatment | 0.999 | 0.999–1.000 | <.001 |
| CGI-S score                                          | 0.944      | 0.694–1.285| .715    |
| Mirtazapine                                          | 0.758      | 0.555–1.035| .081    |

Abbreviations. CGI-S, Clinical Global Impression–Severity of Illness rating scale; MADRS, Montgomery-Åsberg Depression Rating Scale; SD, standard deviation. *< .05. **< .01.
This prospective, multi-center, non-interventional, observational study evaluated the effectiveness and tolerability of aripiprazole augmentation therapy in treatment-resistant patients in everyday clinical practice and over a treatment period longer than 6 or 12 weeks. Aripiprazole augmentation therapy was equally effective in patients with a first-episode of depression/depressive symptoms resistant to conventional therapies, this result contributes as evidence for the effectiveness of aripiprazole augmentation therapy as a strategy for managing treatment-resistant depression/depressive symptoms.

Overall, 274 patients (24.8%) in the safety analysis population experienced at least one adverse event (Table 5). The most commonly-reported event was akathisia (52 events), with an incidence of 4.7%. Other events with an incidence ≥1% were weight gain (44 events, 4.0%), insomnia (26 events, 2.4%), somnolence (21 events, 1.9%), malaise (15 events, 1.6%), and constipation (11 events, 1.0%). The majority of adverse events were considered to be adverse drug reactions based on investigator-assessed causality (i.e. definitely, probably, possibly related to treatment).

Ten serious adverse drug reactions were reported in nine patients. Abnormal hepatic function was reported in two patients, and there was one case each of pneumonia; mania; diabetes mellitus; decreased appetite and pain; completed suicide; cardiac failure; and death. Although a causal relationship between serious adverse events and aripiprazole could not be ruled out, except for one case of abnormal hepatic function there was insufficient information about the diagnosis/patient’s condition before the event and history to draw a definitive conclusion. A marked increase in hepatic enzymes was observed in a female patient 3 days after the start of aripiprazole treatment. Her hepatic function improved after discontinuation of aripiprazole, suggesting a probable causal relationship.

Discussion

In patients with depression/depressive symptoms resistant to pharmacological treatment, strategies include increasing the dose of the current antidepressant, switching to other antidepressant therapies, or using augmentation/combination therapies. Several randomized placebo-controlled trials have demonstrated that augmentation strategies involving aripiprazole, a drug with pharmacological activity distinct from SSRI or SNRI, can increase the proportion of patients who achieve remission. However, less is known about the effectiveness of aripiprazole augmentation therapy in treatment-resistant patients in everyday clinical practice and over a treatment period longer than 6 or 12 weeks.

This prospective, multi-center, non-interventional, observational study evaluated the effectiveness and tolerability of aripiprazole augmentation therapy over 12 months during routine use in ~1100 Japanese patients with depression/depressive symptoms non-responsive to usual therapy. Underlying antidepressant therapies included paroxetine, fluvoxamine, sertraline, milnacipran, duloxetine, mirtazapine, and escitalopram.

There was a rapid decrease in the MADRS total score from baseline to Month 1, followed by continuous improvement through to Month 12, indicating additional benefit with continued treatment. This finding was supported by the remission rate, defined as a MADRS total score of ≤10 points and ≥50% reduction from baseline, which increased from 24.4% of patients at Month 3 to 34.5% of patients at Month 6 and to 43.3% of patients at Month 12. Aripiprazole augmentation therapy was equally effective in patients with a first-time episode of depression and in those with one or more previous episodes of depression.

Although remission rates tended to be lower in line with higher baseline severity of depression, in relative terms, the increase in the remission rate from 5% at Month 1 to 35% at Month 12 in patients with severe depression (CGI-S: 5–7) was proportionately higher than corresponding increases in the mild and moderate severity groups. Given that the target population for the current study was patients who were unresponsive to conventional therapies, this result contributes as evidence for the effectiveness of aripiprazole augmentation therapy as a strategy for managing treatment-resistant depression/depressive symptoms.

Analyses of changes in MADRS individual scores from baseline to final evaluation showed statistically significant improvement (p < .001) in all 10 items. With respect to the items “inner tension”, “reduced sleep”, and “concentration difficulties”, a randomized controlled study of aripiprazole augmentation therapy in Japanese patients with major depressive disorder reported no significant difference in scores for these items between active treatment groups and the placebo group, although this may reflect the comparatively short treatment period of only 6 weeks. Our findings suggest that longer-term aripiprazole augmentation therapy in patients with depression/depressive symptoms may effectively alleviate symptoms measurable by the MADRS instrument.

Analyses of change in the MADRS total score according to specific concomitant antidepressant revealed no differences in the effectiveness of aripiprazole augmentation therapy, implying that the results were not confounded by the type of primary antidepressant. Aripiprazole augmentation therapy, thus, can be used in conjunction with a range of commonly prescribed antidepressant medications.

Univariate analysis of baseline demographic and clinical characteristics in patients achieving remission identified disease severity, duration of illness, MADRS total score, CGI-S score, duration of days from an episode of depression to

### Table 4. Odds ratios for remission based on cut-off values for factors significantly associated with achieving remission.

| Term                        | Odds ratio | 95% CI       | p-value |
|-----------------------------|------------|--------------|---------|
| Baseline MADRS total score  | 1.175      | 1.320–2.228  | <.001   |
| Duration of days from an    | 1.802      | 1.403–2.316  | <.001   |

All values are expressed as n (%) of patients.

| Term                        | Adverse events | Adverse drug reactions |
|-----------------------------|----------------|-----------------------|
| Akathisia                   | 52 (4.7)       | 52 (4.7)              |
| Weight gain                 | 44 (4.0)       | 39 (3.5)              |
| Insomnia                    | 26 (2.4)       | 23 (2.1)              |
| Somnolence                  | 21 (1.9)       | 21 (1.9)              |
| Malaise                     | 15 (1.4)       | 15 (1.4)              |
| Constipation                | 11 (1.0)       | 9 (0.9)               |

### Table 5. Adverse events and adverse drug reactions with an incidence of ≥1% reported in the safety analysis population (n = 1103).

Odds ratios for remission based on cut-off values for factors significantly associated with achieving remission.
start of aripiprazole treatment, and concomitant mirtazapine therapy as factors significantly affecting the remission rate. Following logistic regression analysis, only baseline MADRS total score ($p = 0.013$) and duration of days from an episode of depression to the start of aripiprazole treatment ($p < 0.001$) remained as significant effect factors. Application of cut-off points obtained from ROC analysis indicated that patients were 1.7-times more likely to achieve remission if their baseline MADRS score was less than 33 points and 1.8-times more likely to achieve remission if the length of time from an episode of depression to the start of aripiprazole treatment was less than 176 days. These findings are relevant in terms of managing treatment expectations (patients and physicians) and optimizing the timing of aripiprazole augmentation therapy during use in clinical practice.

Logistic regression analysis identified inner tension, the inability to feel, and suicidal thought as MADRS items significantly predictive for remission by Month 12. In other words, a clinician could expect a patient to achieve remission if improvement was observed in these three items at Month 1. However, as odds ratios for these items were not high, the result must be interpreted with caution.

In light of the low mean daily dose of aripiprazole used in this study (3.5 ± 1.8 mg), it is possible that the true effects of aripiprazole augmentation therapy were under-estimated. Conversely, the comparable efficacy of a fixed dose (3 mg/day) and flexible dose (3–15 mg/day) aripiprazole augmentation schedule during 6 weeks’ treatment reported in the phase 3 ADMIRE trial and a general desire by physicians to avoid aripiprazole augmentation therapy during use in clinical practice.

Following logistic regression analysis identified inner tension, the inability to feel, and suicidal thought as MADRS items significantly predictive for remission by Month 12. In other words, a clinician could expect a patient to achieve remission if improvement was observed in these three items at Month 1. However, as odds ratios for these items were not high, the result must be interpreted with caution.

Regarding the safety profile of aripiprazole, the most common adverse event was akathisia (52 events, 4.7% incidence), and all akathisic events, as well as all events of somnolence (21 events, 1.9%) and malaise (15 events, 1.4%), and most events of insomnia (23 of 26 events, 2.1%) and constipation (9 of 11 events, 0.9%), were deemed to be adverse drug reactions. Although aripiprazole is characterized as being low risk for weight gain, 44 events (4.0%) were reported and 39 events (3.5%) were assessed as adverse drug reactions. Upon further evaluation of the weight gain events, investigator reports indicated that the events were associated with improvement of symptoms and/or an adverse drug reaction of the primary antidepressant; in other words, a clear relationship with aripiprazole was not confirmed. For greater clarification, a sub-group analysis of patients experiencing weight gain events by type of primary antidepressant medication should be considered. Serious adverse drug reactions were rare (10 events in nine patients; 0.8% incidence) and all events except one case of elevated hepatic enzymes were unlikely to be related to aripiprazole treatment.

To our knowledge, this is the first study evaluating the effectiveness and tolerability of aripiprazole augmentation therapy over the long-term and under actual clinical practice conditions in Japanese patients with depression/depressive symptoms. Previously, a US study reported on the safety and tolerability of aripiprazole augmentation therapy in 1002 patients (previous study completers and de novo patients) receiving open-label treatment for up to 52 weeks. Similar to our results, the most frequent spontaneously reported adverse events were akathisia, fatigue, and weight gain, which were mainly mild-to-moderate in severity. In terms of efficacy as measured by the CGI-S, most improvement occurred during the first month of treatment and was maintained over the 12-month observation period, similar to the pattern we observed. Aligning with our finding that 52% of patients had discontinued aripiprazole augmentation therapy by Day 365, Berman et al. reported a treatment discontinuation rate of 68%, highlighting one of the major challenges of conducting research in patients with depression/depressive symptoms.

Three studies from Korea have reported use of aripiprazole augmentation therapy for major depressive disorder. A prospective open-label study documented a significant 11.6-point improvement in the MADRS total score and a remission rate of 41.3% after 12 weeks’ treatment, although the mean dose of aripiprazole at study end was 6.6 mg/day (i.e. nearly twice that of the mean dose in the current study). Similar to our findings, the most frequent adverse events were headache, akathisia, insomnia, and constipation. In a naturalistic setting, patients showed a clear preference for aripiprazole augmentation therapy over an antidepressant combination or switching to a different antidepressant and, overall, aripiprazole augmentation yielded greater clinical benefit than the other two strategies. Interestingly, low initial (3.4 mg/day), maximal (4.7 mg/day) and maintenance (4.4 mg/day) doses of aripiprazole were reported for patients receiving aripiprazole augmentation therapy in routine practice, aligning with our findings that, in the naturalistic setting, patients and clinicians tend to be cautious about using higher doses.

**Strengths and limitations**

The main limitation of the study is the observational design, which precluded comparing the effectiveness and tolerability of an aripiprazole augmentation strategy with a control group. Conversely, the study design permitted evaluation of the effect of aripiprazole augmentation therapy in a large group of patients with a broad variety of demographic characteristics in a naturalistic environment. Although the large sample size may have contributed to the statistical significance of some results (e.g. changes in individual MADRS scores), it is likely that the 40–60% improvement observed across all 10 items from baseline to study end represented clinically meaningful improvement in depressive symptoms. Overall, the results can be considered useful in supporting and promoting further investigation of aripiprazole augmentation therapy in clinical practice settings.

**Conclusion**

The findings suggest that aripiprazole augmentation therapy is an effective and safe option for Japanese patients with...
depression/depressive symptoms non-responsive to conventional antidepressant therapies, bearing in mind that the severity of the patient's initial condition can influence the level of benefit achieved. Symptom improvement was maintained during 12 months' treatment, suggesting longitudinal benefit with continued treatment. Aripiprazole augmentation therapy was well tolerated, without the emergence of any new safety signals.

**Transparency**

**Declaration of funding**

The study was funded by Otsuka Pharmaceuticals Co., Ltd., Japan. Otsuka Pharmaceuticals Co., Ltd. has provided oversight on the conduct of the study, including design, collection, compilation, and analysis of data.

**Declaration of financial/other interests**

KK has received consulting fees from Otsuka Pharmaceutical Co. Ltd. MY, KY, and YF are full-time employees of Otsuka Pharmaceuticals Co., Ltd. A CMRO peer reviewer on this manuscript declares consultancy for Eisai, Assurex, and Janssen. Other CMRO peer reviewers on this manuscript have no financial/other interests to disclose.

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