Optimizing the Use of Aripiprazole Augmentation in the Treatment of Major Depressive Disorder: From Clinical Trials to Clinical Practice

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INTRODUCTION: WHY DO WE NEED ANOTHER TREATMENT OPTION FOR MAJOR DEPRESSIVE DISORDER?

Major depressive disorder (MDD) is a recurrent, chronic, and devastating disorder leading to serious impairment in functional capacity as well as increasing public health care costs. In the previous decade, switching therapy and dose adjustment of ongoing antidepressants was the most frequently chosen subsequent treatment option for MDD. However, such recommendations were not based on firmly proven efficacy data from well-designed, placebo-controlled, randomized clinical trials (RCTs) but on practical grounds and clinical reasoning. Aripiprazole augmentation has been dramatically increasing in clinical practice owing to its unique action mechanisms as well as proven efficacy and safety from adequately powered and well-controlled RCTs. Despite the increased use of aripiprazole in depression, limited clinical information and knowledge interfere with proper and efficient use of aripiprazole augmentation for MDD. The objective of the present review was to enhance clinicians’ current understanding of aripiprazole augmentation and how to optimize the use of this therapy in the treatment of MDD.

Key Words: Antidepressive agents; Depressive disorder, Major; Aripiprazole

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Diverse antidepressants with different action mechanisms, such as selective serotonin reuptake inhibitors (SSRIs), dopamine-norepinephrine reuptake inhibitors (DNRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), and noradrenergic and specific serotonin antagonists (NaSSAs), are available as a monotherapy for initial biological treatment of MDD. These antidepressants have been developed mainly under the monoamine hypothesis.³⁵ Recently, newer antidepressants such as vilazodone, vortioxetine, desvenlafaxine, and agomelatine have also been introduced on the market.⁶⁻¹⁴ Despite the fact that the mainstay of treatment for MDD remains the use of antidepressants, the limited efficacy of contemporary anti-
depressants is well known. Thereby, the response and remission rates after antidepressant monotherapy are approximately 50-70% and 30%, respectively, in routine practice. These rates have been consistently reported in numerous sponsor-initiated and independent randomized clinical trials (RCTs) as well as in a few large practical clinical trials such as the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) and Combining Medications to Enhance Depression Outcomes (CO-MED) studies. In particular, the STAR*D trial showed that most MDD patients need additional treatment steps as the result of lower response and remission and higher relapse rates after initial treatment. In addition, large meta-analyses have also proven the limited efficacy of antidepressants. According to recent RCTs,18-21 significant functional impairment was clearly observed even in partial responders to citalopram at Level 1 exit, which was substantially different from the results in remitted patients in terms of quality of life, mental and physical functioning, and social and work-related impairment. That study clearly proposed the importance of controlling patients with partial response to achieve full remission and restoration of functioning.

WHICH STRATEGIES ARE POPULAR AS A SUBSEQUENT TREATMENT OPTION FOR MDD WHEN A PATIENT FAILS TO SHOW MEANINGFUL IMPROVEMENT AFTER ANTIDEPRESSANT MONOTHERAPY?

Most currently available treatment guidelines recommend that clinicians select a subsequent treatment option when patients do not respond or show only a partial response to initial antidepressant treatment (i.e., switch, combination, or augmentation therapy).18-21 Each treatment option has different pros and cons according to the patients' clinical status, and there is no clear evidence supporting the superiority of one treatment modality over another.22 Anecdotal data support the usefulness of switching or combining antidepressant strategies; however, few clinical trials of such therapies have been conducted and the results are inconsistent.23-26 A number of small RCTs have investigated the efficacy of switching therapy for depression (10 RCTs and 30 open-label studies).27-35 According to these controlled clinical trials, the remission rates after switching therapy ranged from 10% to 80%. In addition, switching to either a different class or within the same class of antidepressants is an intriguing clinical issue, but the number of high-quality studies that have investigated this issue remains limited. The results are also inconsistent, and thereby no clear evidence supports the superiority of either switching within a class or switching to a different class.

A handful of studies have tried to investigate the usefulness of antidepressant combination therapy.36 Since the clinical trial of mianserin,37,38 a few subsequent controlled trials were conducted mainly using the combination of mirtazapine with contemporary antidepressants.36,39,40 For instance, according to the two studies by Blier et al.,39,40 diverse combination therapy has better efficacy than monotherapy with a magnitude of difference of approximately 30% in the remission rate. However, the most recent large RCT of combination therapy conducted by Stewart et al.41 completely failed to show any superiority of combination therapy over monotherapy in terms of timing of remission or the remission rate. These findings were also replicated in a recent large practical clinical trial, the CO-MED.42 In the CO-MED, the remission and response rates as well as most secondary outcomes were not significantly different among treatment groups at the end of acute treatment. Such trends were also similar in the continuation phase, although remission and response rates were slightly increased in all treatment groups compared with the acute phase. In addition, combination therapy of mirtazapine and venlafaxine had a higher frequency of adverse events than did escitalopram monotherapy.

Non-antidepressant agents are also a popular subsequent treatment option for difficult-to-treat MDD patients. The available augmentation agents include mood stabilizers, T3, buspirone, and psychostimulants, but their utility is not supported by well-designed large RCTs. In addition, these agents have been used to augment only old formulations of antidepressants and not contemporary antidepressants.43 Table 1 summarizes the data regarding currently available augmentation agents. Recently, augmentation of antidepressants with atypical antipsychotics (AAs) has dramatically increased in clinical practice because AAs (particularly aripiprazole and quetiapine ex-

| Agent | Number of RCTs | Results |
|-------|----------------|---------|
| Lithium | 10 | OR for response: 3.3 |
| T3 | 3 | 2 trials positive, 1 trial negative |
| Stimulants | 2 | All failed |
| Modafinil | 4 | 2 trials positive, 2 trials negative |
| Buspirone | 3 | All failed |
| Pindolol | 12 | Only 2 trials showed superior efficacy to placebo |
| Folic acid | 2 | Positive |
| Omega-3 | 7 | 4 trials negative, 3 trials positive |
| SAMe | 1 | Positive |
| Creatine | 1 | Positive |
| Monohydrate Testosterone | 1 | Positive |
| Mecamylamine/ Celecoxib/ Pramipexole | 2/4/2 | Positive/All positive/All failed |
| Atypical antipsychotics | 26 | Most trials showed positive results |

OR: odds ratio, SAMe: S-adenosyl methionine.
Aripiprazole Augmentation for MDD

Tended release [XR]) have been officially approved by regulatory agencies owing to their proven efficacy and safety data from adequately powered and well-controlled RCTs.43-47 Table 2 presents dosages and side effects of the currently available AAs used in clinical trials for patients with nonpsychotic depression.

**WHICH STRATEGY IS MORE BENEFICIAL FOR TREATING PATIENTS WITH MDD?**

Limited studies have looked into the differential effects and preferences of the subsequent treatment option for MDD. As seen in surveys by clinicians and the preferred treatment strategy in the STAR*D trial, augmentation therapy is preferred for partial responders.48-53 Indeed, augmentation therapy may sustain the initial response from the first antidepressant and show additional effects with the augmented agent, whereas a switching strategy poses the risk of losing the benefits of the previously effective treatment.54 Combination of antidepressants is also common in clinical practice and has an advantage generally similar to that of augmentation therapy; however, RCTs are still very limited.

A recent European naturalistic study showed that augmentation was preferred by physicians over switching or antidepressant combination therapies. Furthermore, AA or lithium augmentation was more effective than combining or switching antidepressants. However, the small sample size (total n=98) is an important limitation of this study.28 In line with the findings by Köhler et al.,28 a recent Korean naturalistic study55 also found that patients have chosen AA therapy more than antidepressant combination and switching therapies when experiencing nonresponse to initial antidepressant treatment. In addition, AA therapy was shown to have more clinical benefit than antidepressant combination and switching. Recently, the first 6-week randomized study56 directly compared effectiveness and tolerability between AAs and switching therapy. An inadequate response to antidepressants was defined as a total score $\geq 14$ on the Hamilton Depression Rating Scale-item 17 (HDRS-17), although adequate antidepressant dosage for at least 6 weeks was used for treating the current depressive episode. The primary endpoint was change in the total score of the Montgomery-Åsberg Depression Rating Scale (MADRS) from baseline to the end of treatment. The study showed that the mean change in the MADRS score from baseline was significantly higher with AAs, with a difference in magnitude of $-8.7$, which was clinically very significant and already evident by week 2. The number of responders and remitters was also significantly higher with the AA treatment (60% and 54%, respectively) compared with switching (32.6% and 19.6%, respectively). AAs also showed better clinical outcomes compared with switching therapy for most secondary outcome measures. The tolerability profiles were comparable between the two groups. Despite the study’s methodological shortcomings, the results suggested that AAs might produce better clinical outcomes than switching therapy in the treatment of MDD patients with inadequate responses to antidepressants. Some evidence suggests that AA augmentation may be more efficient and beneficial for treating MDD than switching and antidepressant combination therapies; however, we will need more definite data based on well-controlled direct comparison studies.

**WHICH AUGMENTATION AGENT IS BETTER THAN OTHERS?**

Interestingly, a recent network meta-analysis investigated the differential effects of various augmentation

| Drug | Duration (week) | RCTs (n) | Dose Range | AEs |
|------|----------------|----------|------------|-----|
| Olanzapine<sup>a</sup> | 8-12 | 4 | 5-20 mg/d with various combinations, mean dose: 8-14 mg/d | Weight gain: 4 kg for 8 weeks |
| Risperidone<sup>b</sup> | 4-6 | 5 | 0.5-3.0 mg/d, mean dose: 1.2-1.6 mg/d, 1-1.5 mg/d with minimal risk to developing AEs | Hyperprolactinemia |
| Quetiapine<sup>c</sup> | 8-52 | 6 | 50-300 mg/d in flexible and fixed dose trials, mean dose: 180 mg/d | Sedation and weight gain |
| Aripiprazole<sup>a</sup> | 6-52 | 6 | 3-15 mg/d, mean dose: 3-12 mg/d | Akathisia |
| Ziprasidone<sup>b</sup> | 6 | 2 | 40-160 mg/d, mean dose in RCT was 96 mg/d | Most common AE was somnolence and fatigue in RCT |
| Amsulpride<sup>c</sup> | 8-24 | 7 | 50 mg/d in MDD and dysthymia | Sexual dysfunction and weight gain |
| Asenapine, iloperidone, sertindole, and lurasidone | NA | 0 | NA, lurasidone under investigation yet | NA |
| Brexpiprazole | 6 | 2 | Two positive phase III RCTs | Akathisia and weight gain |

MDD: major depressive disorder, EPS: extrapyramidal symptoms, NA: not available, *double-blind, randomized, (placebo)-controlled studies (RCTs), *monotherapy and augmentation therapy, *open-label and randomized controlled studies for MDD and dysthymia. From references 46, 47, 116-122. Aripiprazole and quetiapine XR have been officially approved by the US Food and Drug Administration.
agents by analyzing 18 RCTs (total n=4,422). In the study, quetiapine (odds ratio [OR]=1.92), aripiprazole (OR=1.85), thyroid hormone (OR=1.84), and lithium (OR=1.56) were significantly more effective than placebo. The meta-analysis also proved that the efficacy of aripiprazole and quetiapine was more robust than that for thyroid hormone and lithium in sensitivity analyses. Only quetiapine 250-350 mg/d showed superiority over placebo in terms of all-cause discontinuation (OR=1.89). As for quality of life (function), aripiprazole and risperidone proved to have benefit over placebo; additionally, risperidone showed greater efficacy than quetiapine. This network meta-analysis suggests that AAs may be more beneficial than other augmentation agents for treating patients with MDD. One interesting insurance claim data study (2006 through 2010) showed a recent usage trend for aripiprazole and quetiapine augmentation therapies in clinical practice. Those who took US Food and Drug Administration (FDA)-recommended doses proportionally increased among the aripiprazole-treated patients (86.3% in 2006 to 94.5% in 2010), whereas quetiapine prescription failed to show such a trend (21.3% in 2006 to 24.0% in 2010). The quetiapine doses were less than those recommended by the US FDA. The authors indicated that aripiprazole augmentation should be prescribed at therapeutic doses for treating MDD itself, whereas quetiapine augmentation might be more targeted for treating specific symptoms such as insomnia and anxiety owing to its side effects such as sedation and somnolence. In this context, the preferential use of aripiprazole compared to other AAs has been consistently reported in many different studies. According to a recent survey study, the rates of AAs used for MDD in Taiwan were aripiprazole (78.2%), quetiapine (62%), olanzapine (34.6%), risperidone (30.2%), and sulpiride (27.4%) which is in line with previous studies. However, no direct comparison studies have been conducted. Clinical considerations on the use of aripiprazole augmentation will be discussed in detail in the later section.

INTRODUCTION OF ARIPIPRAZOLE AUGMENTATION FOR MDD

A number of small open-label studies and well-designed RCTs have proved the antidepressant augmentation effects of AAs. Indeed, prescription of AAs has rapidly increased over the past decade and they are considered one of the most useful augmentation agents. Aripiprazole augmentation was approved by the US FDA in 2007. Aripiprazole augmentation has also been approved in a majority of Asian countries including Japan, the country which originally developed aripiprazole for the treatment of schizophrenia.

THE MECHANISM OF ACTION OF ARIPIPRAZOLE AUGMENTATION FOR MDD

We do not yet understand the clear mechanisms of action
of AAs as antidepressants. However, we can speculate on some potential action mechanisms (Table 3 and Fig. 1). Effects on the regulation of monoamine receptors and transporters leading to changes in monoamine transmission are a possible underlying mechanism of action of AA augmentation for treating MDD. These receptors and transporters include 5HT1A, 5HT2A/2B, 5HT2C, 5HT6, 5HT7, α-2 receptor, dopamine receptor, and norepinephrine transporter. Additional putative mechanisms are based on modification of hormones, the immune system, the sleep cycle, and neurotrophic factors.61

Likewise, the mechanism of action of aripiprazole augmentation for treating MDD may depend on diverse neurotransmitter receptors.46,62 Aripiprazole has a partial agonistic effect on 5-HT1A receptor, and it also imposes 5-HT2A receptor antagonist with a partial dopamine D2/D3 agonist effect. Activation of 5-HT1A receptors is considered to regulate serotonin and dopamine balance in the prefrontal cortex and other brain areas relevant to MDD. 5-HT1A receptor agonists were found to be effective in the preservation of neuronal cells from the hazardous effects of glutamate or ischemia. 5-HT1A receptor agonists are also effective in hippocampal cell survival, whereas such an effect is antagonized by WAY-100635.63,64 Blockage of 5-HT2A receptors elevates the extracellular levels of norepinephrine and leads to an antidepressant effect. Unlike other AAs, aripiprazole is a partial dopamine D2/D3 agonist with 30% intrinsic dopaminergic activity.48 In addition, aripiprazole has low to moderate affinity for dopamine D4, serotonin 5-HT2c and 5-HT7, alpha1-adrenergic, and histamine H1 receptors, which might also be involved in its antidepressant property.65 There is also an intriguing imaging study that investigated the action mechanism of aripiprazole augmentation for treating MDD.66 The effects of aripiprazole augmentation on the cerebral utilization of 6-[18F]-fluoro-3,4-dihydroxy-L-phenylalanine (FDOPA) was tested by using positron emission tomography (PET). Fourteen depressed patients who had failed 8 weeks of antidepressant therapy with SSRIs underwent FDOPA PET scans before and after aripiprazole augmentation. Eleven responded to aripiprazole augmentation. Interestingly, increased FDOPA trapping occurred in the right medial caudate in 10 of the 11 patients (91%) who showed a response to aripiprazole augmentation, whereas nonresponders demonstrated decreased right medial caudate FDOPA trapping.66 The study also showed that the two symptoms showing the greatest improvement in responders were dopaminergic neurotransmission-related depressive systems such as lassitude and inability to feel. These results may suggest that the effects of aripiprazole augmentation may occur via alteration in dopaminergic activity or that dopaminergic involvement may be a key component of the anti-depressant effects.66

**SUMMARY OF RCT EVIDENCE FOR ARIPIPRAZOLE AUGMENTATION THERAPY OF MDD**

The clinical efficacy and safety of aripiprazole augmentation for treating patients with MDD were clearly proven in three identically designed initial phase RCTs67-69 and three subsequent RCTs.70-72 Table 4 summarizes the RCTs of aripiprazole augmentation for MDD. The mean change from baseline for the MADRS total score was the primary endpoint. Decrease of the MADRS total score from baseline to endpoint of more than 50% was defined as response. A decrease of 50% or more of the MADRS score along with a total MADRS score of 10 or less at the endpoint was considered remission. The remission rates were also significantly higher with aripiprazole augmentation (25.4% to 36.8%).
tently proved in well-designed RCTs.67-69 When the three
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their mean MADRS total score (z:ole experienced significantly greater improvement in 
received either a low fixed dose or a flexible dose of aripipra-
over placebo.73 Recently, the first 6-week Asian RCT (low 
firmed the superior efficacy of aripiprazole augmentation 
Asian RCT by Kamijima and colleagues.72 In the study, dis-
These favorable AE profiles were also replicated in the first 
continuation due to AEs occurred in 2 patients (1.0%) in the 
In a pooled analysis, 75 the mean weight gain was signi-
mild to moderate akathisia was consistently the 
less between aripiprazole augmentation and placebo treatment in all short-term studies.67-69 These favorable AE profiles were also replicated in the first 

than with placebo (15.2% to 18.9%).67-69 In addition, sig-
ificantly more patients taking aripiprazole augmentation 
achieved remission than patients taking placebo as 
early as week 177 and week 2.67 A pooled analysis also con-
formed the superior efficacy of aripiprazole augmentation 
placebo group (20.5%). All those significant differences 
flexible-dose group. Patients who experienced AEs leading 
to dose reduction were 6 (3.1%) in the placebo group, 17 
(8.6%) in the aripiprazole fixed-dose group, and 33 (17.0%) 
in the aripiprazole flexible-dose group. The most common 
AEs in the aripiprazole groups were akathisia (37% vs 14%) 
and tremor (10% vs 7%), and the incidence was overall high-
er in the flexible-dose group than in the fixed-dose group. 
The majority of AEs were mild (aripiprazole flexible-dose 
59.3%, fixed-dose 54.8%, placebo 48.7%) or moderate 
(17.0%, 15.7%, and 10.8%, respectively) in severity. 

HOW TO OPTIMIZE THE USE OF ARIPIPRAZOLE 
AUGMENTATION IN CLINICAL PRACTICE 

1. When is the proper time to augment with aripiprazole 
for patients with MDD?

On the basis of the inclusion criteria of the registry RCTs 
of aripiprazole augmentation and the fact that 70% of pa-
tients had a history of use of at least one antidepressant and 
that remission rates were significantly increased after two 
sequential antidepressant treatments,17 aripiprazole aug-
mentation can be tried for those who have a poor response 
to two initial antidepressant treatments. However, one 
Taiwanese study found that 2.5 mg/d of aripiprazole aug-
mentation could be useful for treating drug-naïve MDD pa-
tients in combination with sertraline.76 Those results sug-
gested that aripiprazole augmentation could also be used 
in an earlier treatment stage for patients with MDD rather 
than wasting time until patients show an inadequate re-

2. How effective is aripiprazole augmentation in clinical 
practice?

The number needed to treat (NNT) and the number need-
ed to harm (NNH) are easy and intuitive alternatives for 
clinicians to use in understanding complex clinical trial 
results.78 In registry RCTs of aripiprazole augmentation, 
the NNTs for response and remission were 7 and 8, respec-

TABLE 4. Selected affinities of aripiprazole compared with antidepressants

| Target Ki (nM) | Aripiprazole | Duloxetine | Imipramine | Desipramine | Mianserin |
|---------------|--------------|------------|------------|-------------|-----------|
| D2            | 0.03         | 250        | 140        | 100         | 35        |
| NET           | 1,200        | 24         | 58         | 0.12        | 150       |
| SERT          | 1,400        | 0.02       | 0.36       | 42          | >10,000   |
| 5HT2A         | 0.74         | >10,000    | 350        | 480         | 1.3       |
| 5HT2C         | 33           | 3,000      | 330        | 630         | 1.4       |
| 5HT1A         | 12           | >10,000    | 760        | 730         | 2,300     |

NET: norepinephrine transporter, SERT: serotonin transporter, 5HT: serotonin, D: dopamine receptor.
tively. The results indicate that as many as 7 and 8 patients need to receive the aripiprazole augmentation for one additional patient to show response and remission.

Concerning long-term effects, aripiprazole sustained its efficacy in a 52-week study. Indeed, almost 70% of patients scored 1 or 2 on the CGI-S at the end of treatment. This clearly showed the maintenance efficacy of aripiprazole augmentation and also contradicted the previous two double-blind discontinuation studies showing that patients who achieved symptom remission after risperidone augmentation did not maintain remission in a long-term follow-up. However, data on more than 1 year of maintenance treatment are not yet available.

3. Is aripiprazole augmentation safe and tolerable regardless of duration of treatment for patients with MDD?

In a close look at the representative RCTs of AAs, aripiprazole is found to have a strong relation with akathisia (NNH=6), whereas weight gain (NNH=3) and somnolence (NNH=5 for 300 mg/d and NNH=6 for 150 mg/d) were more significantly related to olanzapine and quetiapine XR, respectively, compared with placebo. Careful consideration of the NNT and NNH for each AA can enable clinicians to practically weigh the benefit versus risk ratio and may help to select the best available AA in clinical practice. Serious AEs, such as tardive dyskinesia, did not occur in registry RCTs. According to a recent meta-analysis that included 18 clinical studies (n=5,531), the overall proportion with metabolic syndrome (MetS) was 31% by use of any standardized MetS criteria. Compared with age- and gender-matched control groups, patients with MDD had a higher MetS prevalence (OR=1.5). They also had a higher risk for hyperglycemia (OR 1.3) and hypertriglyceridemia (OR 1.2). AA use was also significantly correlated with higher MetS prevalence estimates in MDD, whereas the prevalence of MetS was not moderated by age, gender, geographical area, smoking, antidepressant use, presence of psychiatric comorbidity, or timing of the data collection. The results clearly favored aripiprazole over other AAs including olanzapine and quetiapine as an augmentation therapy in terms of the risk of developing MetS.

Overall, the AE profile in the 52-week long-term trial was reported to be consistent with the results from the registry RCTs, and the most common AEs reported included akathisia (26%), fatigue (18%), and weight gain (17%). Although there were four cases of probable tardive dyskinesia in the 52-week trial, the tardive dyskinesia spontaneously subsided after cessation of aripiprazole augmentation.

4. Are there differential effects of aripiprazole augmentation in accordance with disease characteristics such as subtype of MDD?

MDD patients with atypical or anxious features may have poorer clinical outcomes including higher baseline MDD severity and lower functional capacity than do those without such subsymptoms. Subanalyses of previous clinical trials also showed different response and remission rates in accordance with the subtypes of MDD, such as anxious depression or atypical depression. According to a pooled data set, aripiprazole was found to be an efficacious augmentation agent for patients with MDD regardless of subsymptoms, baseline severity of MDD, degree of prior treatment response, or a history of failure of initial antidepressant treatment. Traditionally, MAOIs have been considered to be more favorable over tricyclic antidepressants (TCAs) for treating atypical MDD. However, there were no such differences in response and remission rates by antidepressant class in a subanalysis of aripiprazole augmentation RCTs. The difference in mean reduction of the MADRS total score between the aripiprazole augmentation and placebo groups was −3 and −3.2, favoring aripiprazole augmentation over placebo for both between-class (p < 0.001) and within-class (p < 0.001) switching groups. Relative risks for response were 1.6 for those who switched between classes and 1.7 for those who switched within a class. According to a subanalysis by Stewart and colleagues, aripiprazole augmentation produced greater improvement over placebo in the MADRS total score regardless of baseline MDD severity; the changes in the MADRS total score from baseline were −2.5 in mild, −3.2 in moderate, and −4.5 in severe groups, without statistical differences between subgroups. In addition, compared with placebo, aripiprazole augmentation increased the likelihood of response and remission in all subgroups of baseline severity of MDD. No robust clinical factors predicting response to augmentation antipsychotics have been found in patients with MDD. However, one subanalysis revealed that the presence of early response to aripiprazole augmentation as early as week 2 may strongly predict significantly more remission rates than in those who did not show a response. Approximately 61% (44/72) of patients receiving aripiprazole augmentation who exhibited early response (week 2) achieved remission, whereas only 17% of non-early-responders showed remission at the study endpoint. The OR was almost 8 for prediction of early response to endpoint remission. Similarly, the recent Japanese RCT also showed that the superior efficacy of aripiprazole augmentation over placebo was not affected by numerous clinical factors (gender, age, number of previous antidepressant treatments, MDD diagnosis, number of past episodes, duration of illness, first onset age, type of antidepressants, or severity at the end of treatment).

5. Can we use aripiprazole augmentation to treat patients who are not partial responders to their current antidepressant?

Most treatment guidelines suggest that augmentation therapy be used to treat partial responders to a current antidepressant, whereas switching therapy may be more suitable for treating those presenting with no or worsening response or tolerability issues with the current antidepressant. However, some subanalyses have clearly challenged such a traditional viewpoint, arguing that those recom-
mendations were not actually based on data from well-designed RCTs. In fact, they were proposed merely from clinical reasoning or on practical grounds. According to Nelson and colleagues’ subanalysis of minimal responders to open-label antidepressant, the time to response was significantly shorter for minimal responders taking aripiprazole augmentation (32 days) than for the placebo group (35.7 days). The minimal responders showed significantly higher response rates (36% vs. 19%) and higher remission rates (24% vs. 12%) with aripiprazole augmentation. Such differences were also evident as early as week 1 or 2. These trends were similar to those from subanalysis of partial responders to a current antidepressant. According to another subanalysis regarding worsening cases based on changes in the MADRS total score, the efficacy of aripiprazole augmentation was maintained regardless of such clinical factors. According to the results, 15% of patients who completed the prospective treatment period were classified as having worsened MADRS, whereas 85% were considered not to have worsened MADRS. The difference in response rate between aripiprazole augmentation and placebo for patients who had worsened MADRS at the study endpoint was 14.1%, favoring aripiprazole augmentation over placebo. Similarly, the difference between aripiprazole augmentation and placebo was 15% at the study endpoint for patients whose symptoms did not worsen, also favoring aripiprazole augmentation over placebo. These trends were replicated in the remission rates (difference of 13% in patients whose symptoms worsened and 12.5% in those whose symptoms did not worsen). Therefore, the traditional preference in clinical practice for augmentation therapy only for partial responders and switching therapy for minimal or nonresponders should be revised, because aripiprazole augmentation may give a direct benefit and a more rapid response, which would improve clinical outcomes for both clinicians and patients. However, such findings must be replicated in prospectively well-designed and adequately powered RCTs before conclusions can be made.

6. What are the proper doses of aripiprazole for treating MDD?

Although the registry RCTs of aripiprazole augmentation did not specifically investigate the appropriate dosing strategy for aripiprazole augmentation, some generalizations can be made. The recommended dose of aripiprazole for MDD is 5-10 mg/d with a maximum dose of 15 mg/d according to the product label information. However, these recommendations were a consequence of design issues of the registry RCTs. In those trials, the initiation dose was 5 mg/d and it was up-titrated weekly within 2-20 mg/d. The mean daily dose of aripiprazole was approximately 11-12 mg/day. The median dose was 10 mg/d and the modal dose was 5 mg/d. Overall, a terminal dose was evident at week 3 and it was maintained until the end of the study period. The class of antidepressants did not have any impact on the dosing trend.

Despite the lack of a strong dose-response relationship in most of the AA augmentation studies, increased intolerance has been found in accordance with dose increments of AAs. Therefore, a low starting dose with slow titration to the target dose is prudent for achieving better efficacy and lesser AEs. A Japanese RCT with a low-dose fixed (3 mg/d) and flexible-dose (3-15 mg/d) design also proved the significant effects of 3 mg/d of aripiprazole augmentation for treatment of MDD (mean dose=11 mg/d). The fact that a low mean dose of aripiprazole (3.8 mg/d) yielded substantial benefits over switching therapy is also noteworthy. In the real-world setting the dose should be lower than what was originally believed to be necessary. Most experts now accept 1-3 mg as the initiation dose and 5-10 mg as the target dose. These new concepts for aripiprazole dosing are also supported by informative data from insurance claim studies and retrospective studies reflecting real-world clinical practice. Finally, we have to remember that aripiprazole augmentation shows a dose-response relationship in terms of the occurrence of akathisia. For instance, the akathisia rate was 37% in the dose range of 3-15 mg/d and 14% for the group receiving 3 mg/d, and this dose-response relationship for akathisia was also consistently observed in previous RCTs.

7. Are there differences in dosing patterns of aripiprazole augmentation between Asian and Western populations?

Given currently available data, 2-5 mg/d could be considered a low-dose aripiprazole augmentation, whereas 5-15 mg/d should be regarded a high dose. The low-dose data were mainly from Asian clinical trials, whereas the high-dose data were obtained from Western clinical trials. This difference may come from genetic differences in polymorphisms of cytochrome P450 2D6 (CYP2D6), which is the principal cause of pharmacokinetic variability in humans. Sufficient evidence suggests substantial racial differences in AA metabolism between Asians and Caucasians. The CYP2D6*10 allele, which decreases CYP2D6 enzyme activity, is known to be highly prevalent in Asian populations but rare in Caucasians, which may influence the pharmacokinetics of aripiprazole. This genetic difference may also lead to differential clinical outcomes and AEs by aripiprazole doses. Small-scale studies with Asians also proposed a potential difference in the proper doses of aripiprazole augmentation therapy. The mean daily doses of augmentation aripiprazole ranged from 2 to 8 mg/d in Asians, whereas they were estimated to range from 11 to 12 mg/d in Caucasians. Subsequent research is mandatory to confirm whether such racial differences may exist in aripiprazole augmentation therapy for the treatment of MDD.

8. Is there a proper duration of treatment or appropriate time of discontinuation of aripiprazole augmentation?

No well-designed discontinuation study investigating this intriguing clinical issue is yet available. Currently, no consensus or prescription guide exists for aripiprazole augmentation. All of the short-term RCTs were designed
to observe aripiprazole efficacy only until 6 weeks after treatment, and open-label acute studies lasted no longer than 12 weeks.\textsuperscript{103,104} Hence, clinicians may consider aripiprazole augmentation for at least 6 weeks and up to 12 weeks to see an acute response. However, when we consider the results from the 52-week maintenance trial, aripiprazole augmentation could be utilized for 1 year after achieving remission. Aripiprazole is basically an antipsychotic that can lead to unwanted AEs such as tardive dyskinesia. Indeed, tardive dyskinesia is one of the serious AEs that can be caused by any antipsychotic. Most treatment guidelines do not specifically address this clinical issue, but experts recommend that clinicians gradually taper aripiprazole augmentation within 3 to 6 months after achieving remission, although it is not mandatory. In our clinical practice, some patients who had already achieved remission experienced relapse or worsening of MDD symptoms immediately after early discontinuation of aripiprazole. The data regarding early termination of aripiprazole augmentation after achieving remission or response are still not sufficient. Therefore, adequately powered, controlled clinical trials should be conducted to address this issue in the near future.

9. What else can we expect from aripiprazole augmentation?
According to insurance data analysis of health care utilization and expenditures,\textsuperscript{105} the mean costs for aripiprazole were significantly lower than those for olanzapine and quetiapine for most service types, including all-cause medical care, mental health, and mental-health-related medical care. In addition, aripiprazole had significant effects in reducing the duration and chance of hospitalization and the use of the emergency department compared with quetiapine in patients having MDD. Clinicians may consider currently available pharmaco-economic vigilance data in clinical practice. Aripiprazole was also efficacious and safe for chronic and recurrent MDD,\textsuperscript{104} as well as for elderly populations.\textsuperscript{106} In the subanalysis by Steffens et al,\textsuperscript{106} elderly patients on aripiprazole showed significantly greater reduction (3.6 points more) in MADRS total score versus the placebo group at the endpoint, which was similar to the improvement observed in younger patients. Remission rates were also significantly higher with aripiprazole versus placebo in older (15.4\% difference) and younger (10.5\% difference) patients. Akathisia was the most common AE in both populations, but the incidence was higher in younger (26.0\%) than in elderly (17.1\%) patients. It is also notable that simultaneous aripiprazole augmentation with SNRI produced a huge response and remission rates in a previous study, indicating that clinicians may promptly use aripiprazole augmentation at the beginning of antidepressant treatment according to the patient’s clinical status.\textsuperscript{103} Well-controlled clinical trials or naturalistic studies of the role of aripiprazole augmentation for treating MDD patients with comorbid medical diseases are lacking, although some anecdotal data suggest that aripiprazole may be beneficial in the treatment of eating disorders, nicotine/alcohol dependence, behavioral disturbances due to neuropsychiatric diseases (brain injury, epilepsy, etc), and neurological motor disease.\textsuperscript{15,77,107-111} MDD is commonly comorbid with medical diseases such as diabetes mellitus and cardiovascular diseases in routine clinical practice. These comorbid conditions are known to negatively impact the clinical course and prognosis of patients with MDD.\textsuperscript{112} Hence, it will be intriguing and necessary for clinicians to investigate the potential role of aripiprazole in the treatment of MDD with comorbid medical diseases in the future.

10. What barriers to aripiprazole augmentation therapy exist?
The prescription pattern of clinicians in the selection of certain medications may be influenced by various factors, especially when the candidate medication is originally approved for different diseases and also when the candidate medication (antipsychotic) is in fact originally not for the specific disorder of interest (MDD). The level of evidence with medication, personal experience, knowledge about the medication, health insurance, and reimbursement and payment policies may also affect clinicians’ choice of certain medications in clinical practice.\textsuperscript{113-115} An interesting study used a survey to investigate the factors influencing the prescription of aripiprazole augmentation in Taiwan.\textsuperscript{29} Even though the most frequently used antipsychotic was aripiprazole, the study showed that the main reason psychiatrists did not choose aripiprazole was because of its higher price leading to insurance audit. In contrast to the American Psychiatric Association’s willingness to appeal the use of innovative treatments with insurance companies and regulatory agencies, these authors asserted that the Taiwanese Society of Psychiatry has taken little action against insurance audits.\textsuperscript{59} In fact, the prescribing behavior of psychiatrists may influence the outcomes of refractory MDD and may cause a delay in the use of adequate antipsychotic augmentation therapy.\textsuperscript{59} It is important, therefore, for health policy makers to understand the prescribing behaviors and modify the insurance policy accordingly if a newer agent is available on the market. Clinical factors other than the insurance issue that circumvent the use of aripiprazole augmentation may include clinicians being afraid to use antipsychotics for MDD patients. Theses prejudices could be reduced by continuing medical education (CME) or scientific symposiums by opinion leaders and clinical experts. Indeed, the pharmacodynamics profile of aripiprazole surpasses that of some of antidepressants.\textsuperscript{46} In addition, the use of generic formulations can reduce medical costs if bioequivalence is fully achieved compared with the original formulation.

CONCLUSIONS
Evidence supporting the beneficial effects and tolerability of AAs for the treatment of MDD as an augmentation therapy has been dramatically increasing in recent days, particularly for those patients who showed a partial re-
Aripiprazole augmentation has consistently shown its efficacy for MDD through adequately powered and well-controlled clinical trials. The efficacy of atypical antipsychotics as augmentation therapy has been found to be similar across such agents; however, safety and tolerability of atypicals may substantially differ. Metabolic syndrome is a raising clinical concern in treatment of patients with MDD; hence, the risk of metabolic side effects must be carefully weighed against clinical benefits when prescribing atypicals as augmenting agents. Evidence indicates that aripiprazole has a more favorable metabolic profile than others. Dose titration should be done carefully so as to minimize side effects and optimize therapeutic benefits. Initiation doses of aripiprazole augmentation should be 1-3 mg/d and 5-10 mg/d for target doses. Wait and increase the dose less than 5 mg/d by two weeks (i.e., 2 mg/d by a week) under consideration of its pharmacokinetic profile when observing partial or no improvement with good tolerability. Dose increase could be stopped for observation of maximal benefits at the current dose when observing meaningful improvement with good tolerability. Too rapid up-titration may result in transient gain and possibly cause loss of efficacy. When stopped aripiprazole augmentation for a while, reinstatement should resume the first use of aripiprazole augmentation not the last dose. Ethnic difference is clearly proposed in terms of dosing of aripiprazole due to different genetic polymorphism of CYP2D6 10 allele between Asian and Western populations. The effects of aripiprazole augmentation may be equally retained regardless of the subtypes of depression (i.e., anxious or atypical depression). Tapering issue may need more well controlled clinical trials. Gradual tapering off within 3 to 6 months should be proper after achieving remission. Data suggest that aripiprazole augmentation can be maintained up to 52 weeks; however, benefit/risk of long-term use of aripiprazole may need to await more high-quality data. Aripiprazole augmentation is beneficial not only for partial responders to current antidepressant but also for minimal responders and those who worsen with current antidepressants. The effect of aripiprazole augmentation is not influenced by diverse clinical factors such as gender, age, number of adequate antidepressant trials in the current episode, number of depressive episodes, duration of the MDD episode, age at first onset, duration of illness, antidepressant class (SSRI vs SNRI), or baseline severity of MDD. Early response to aripiprazole augmentation by 2 weeks may strongly predict the better response and remission at the end of short-term treatment (i.e 6 weeks). Augmentation, antidepressant switching and antidepressant combination therapies have differential pros/cons based on patients’ own clinical status and there had been no clear evidence supporting a superiority of one treatment modality over the other till today. Only limited naturalistic data propose more benefit of augmentation therapy over other strategies. Direct comparison studies between aripiprazole and other augmentation agents for MDD need more clear data. Some limited data suggest superiority of aripiprazole augmentation over other treatment option (i.e., antidepressant switching therapy). SSRI: selective serotonin reuptake inhibitor, SNRI: serotonin-norepinephrine reuptake inhibitor.

**TABLE 5. Clinical considerations in the use of aripiprazole augmentation for major depressive disorder (MDD)**

- Aripiprazole augmentation has consistently shown its efficacy for MDD through adequately powered and well-controlled clinical trials.
- The efficacy of atypical antipsychotics as augmentation therapy has been found to be similar across such agents; however, safety and tolerability of atypicals may substantially differ.
- Metabolic syndrome is a raising clinical concern in treatment of patients with MDD; hence, the risk of metabolic side effects must be carefully weighed against clinical benefits when prescribing atypicals as augmenting agents. Evidence indicates that aripiprazole has a more favorable metabolic profile than others.
- Dose titration should be done carefully so as to minimize side effects and optimize therapeutic benefits. Initiation doses of aripiprazole augmentation should be 1-3 mg/d and 5-10 mg/d for target doses.
- Wait and increase the dose less than 5 mg/d by two weeks (i.e., 2 mg/d by a week) under consideration of its pharmacokinetic profile when observing partial or no improvement with good tolerability.
- Dose increase could be stopped for observation of maximal benefits at the current dose when observing meaningful improvement with good tolerability. Too rapid up-titration may result in transient gain and possibly cause loss of efficacy.
- When stopped aripiprazole augmentation for a while, reinstatement should resume the first use of aripiprazole augmentation not the last dose.
- Ethnic difference is clearly proposed in terms of dosing of aripiprazole due to different genetic polymorphism of CYP2D6 10 allele between Asian and Western populations.
- The effects of aripiprazole augmentation may be equally retained regardless of the subtypes of depression (i.e., anxious or atypical depression).
- Tapering issue may need more well controlled clinical trials. Gradual tapering off within 3 to 6 months should be proper after achieving remission.
- Data suggest that aripiprazole augmentation can be maintained up to 52 weeks; however, benefit/risk of long-term use of aripiprazole may need to await more high-quality data.
- Aripiprazole augmentation is beneficial not only for partial responders to current antidepressant but also for minimal responders and those who worsen with current antidepressants.
- The effect of aripiprazole augmentation is not influenced by diverse clinical factors such as gender, age, number of adequate antidepressant trials in the current episode, number of depressive episodes, duration of the MDD episode, age at first onset, duration of illness, antidepressant class (SSRI vs SNRI), or baseline severity of MDD.
- Early response to aripiprazole augmentation by 2 weeks may strongly predict the better response and remission at the end of short-term treatment (i.e 6 weeks).
- Augmentation, antidepressant switching and antidepressant combination therapies have differential pros/cons based on patients’ own clinical status and there had been no clear evidence supporting a superiority of one treatment modality over the other till today. Only limited naturalistic data propose more benefit of augmentation therapy over other strategies.
- Direct comparison studies between aripiprazole and other augmentation agents for MDD need more clear data. Some limited data suggest superiority of aripiprazole augmentation over other treatment option (i.e., antidepressant switching therapy).

Sponsor to initial antidepressants despite adequate dosing and treatment duration. Aripiprazole was the first AA approved as an augmentation agent for the treatment of MDD. However, differential effects among the AAs used as augmentation agents for treating MDD have not been fully studied. Such studies may be difficult to conduct because of sponsorship issues. Therefore, naturalistic studies concerning this issue may be helpful for clinicians to address whether one specific AA may have more benefit over other AAs for treating MDD. In fact, some insurance claim data have suggested that aripiprazole may have been used for MDD itself, whereas quetiapine XR was used to control specific symptoms of MDD (i.e, sleep and anxiety).

Which augmentation agent is more beneficial or harmful for specific groups of patients? Comparison among AAs, lithium, thyroid medications, and other augmentation agents have not been sufficiently conducted. However, studies have indicated that aripiprazole augmentation may be more beneficial compared with other augmentation agents (i.e, lithium and T3) and other treatment options (i.e, switch and combination). Hence, subsequent large RCTs or practical clinical trials should be conducted to address a clear benefit-to-risk ratio of aripiprazole augmentation for treating patients with MDD compared with other augmentation agents in routine clinical practice.

Informative clinical considerations based on various findings from RCTs for the prudent use of aripiprazole augmentation for treating MDD in clinical practice are listed in Table 5. These recommendations will be helpful for clinicians who may want to use aripiprazole for the first time for treating their MDD patients or for those who have some issues with the use of aripiprazole augmentation. Future studies of aripiprazole augmentation should have more specific and targeted designs to address the many clinical issues about real-world, optimal utilization of AA augmentation therapy in the treatment of MDD.

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CONFLICT OF INTEREST STATEMENT

None declared.

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