REVIEW ARTICLE

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Aripiprazole as Adjunctive Therapy for Patients with Major Depressive Disorder

Overview and Implications of Clinical Trial Data

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Abstract

Aripiprazole was initially approved to treat schizophrenia and later approved for bipolar mania, as a monotherapy and an adjunctive therapy (manic or mixed episodes), and for irritability associated with autism. Aripiprazole is a partial agonist at dopamine D_2 and D_3 and serotonin 5-HT_{1A} receptors, and is an antagonist at 5-HT_{2A} receptors. This profile, and convincing preliminary data from small-scale studies, provided the rationale for the large-scale exploration of aripiprazole for unipolar depression. Recently,

three 6-week, large-scale, randomized, double-blind, placebo-controlled clinical trials demonstrated clinically meaningful efficacy for aripiprazole as an adjunctive therapy to antidepressants for treating major depressive disorder (MDD). In November 2007, aripiprazole was approved by the US FDA as an adjunctive therapy to antidepressants for treating MDD, with support from two of the above-mentioned trials. In the trials, aripiprazole was demonstrated to be safe and well tolerated, and showed a minimal trend for weight gain over the course of a 6-week treatment. The incidence of akathisia was higher than that reported in studies of patients with schizophrenia; however, most cases were mild to moderate and infrequently lead to discontinuation (5/1090 from all three trials).

This comprehensive review provides an overview of the data from all three 6-week studies (including a pooled analysis) and from an unpublished 52-week, open-label extension study, to inform physicians and facilitate reasonable treatment decisions. In addition, specific issues associated with the use of aripiprazole as an adjunctive therapy in patients with MDD, including possible early treatment effect, appropriate timing of therapy initiation, appropriate dosing and duration of treatment, possible differential effect on depressive subgroups and long-term tolerability, are also discussed.

1. Introduction

Major depressive disorder (MDD) is a common and debilitating psychiatric condition.[1] According to the National Comorbidity Survey Replication, the prevalence of MDD in the US as reported by the WHO Composite International Diagnostic Interview was 16.2% during a lifetime and 6.6% over a 12-month period.[1] With the advent of the monoamine hypothesis of MDD, described in the 1960s, monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs) became a mainstay of treatment for MDD. However, since 1980, selective serotonin reuptake inhibitors (SSRIs) have been considered the first-line treatment for the disorder. Since the development of these medications, newer antidepressants such as serotonin-noradrenaline (norepinephrine) reuptake inhibitors (SNRIs) and noradrenergic and specific serotonergic antidepressant (NaSSA) medications have been introduced into clinical practice. Despite sufficient availability of different classes of antidepressants, currently, only 30% of patients show symptomatic remission after treatment with the first antidepressant chosen, and the majority continue to experience significant functional impairment.[2,3]

While the ultimate goal of antidepressant treatment is to achieve full resolution of symptoms and restoration of psychosocial and occupational functioning (i.e. recovery), a very small percentage of patients achieve this goal. According to the STAR*D (Sequenced Treatment Alternatives to Relieve Depression) trial, in which remission was identified as the most desirable and realistic outcome, lower remission and response rates and higher relapse rates were observed among those who required additional treatment steps (i.e. did not respond adequately to the first antidepressant prescribed) during the naturalistic follow-up phase.[4] Suboptimal long-term outcomes were observed in participants who required additional steps, independent of whether or not they were in remission at entry into the follow-up phase of the STAR*D trial.[4] These findings were replicated in large independent studies that investigated relevant antidepressant treatment algorithms.[5,6] In addition, incomplete remission with residual depressive symptoms is associated with less likelihood of long-term recovery, more residual psychosocial function impairment and increased relapse and recurrence.[7] The most recent report from the STAR*D trial has suggested that more than 90% of remitters

had at least one residual depressive symptom, and patients who remitted before 6 weeks had fewer residual symptoms at the end of the study than did later remitters, suggesting a critical relationship between residual symptoms and an early treatment effect.[8]

Most guidelines have suggested that non-responders or partial responders should be considered for switch, combination or augmentation treatment.[9-12] Traditional augmentation agents such as lithium, triiodothyronine (T3), buspirone,[13] azapirone,[14] dopamine agonists (including pramipexole and ropinirole),[15,16] modafinil[17-23] and stimulants (including methylphenidate)[12,24] have been commonly used for this patient population, but with limited supporting data. Recently, augmentation of antidepressant therapy with atypical antipsychotics has become a more commonly accepted treatment practice. This strategy has proven useful for enhancing the antidepressant effect, showing increased remission rates and early treatment effects on core depressive symptoms and co-morbid symptoms, as well as minimizing antidepressant-mediated side effects (e.g. sexual dysfunction).[9-12] Atypical antipsychotics, including aripiprazole, risperidone, olanzapine and quetiapine,[25] have demonstrated a positive antidepressant effect when used as augmentation agents in a number of small-scale, open-label studies or randomized, placebo-controlled trials (RCTs). Indeed, with its approval in late 2007, aripiprazole became the first drug to be approved by the US FDA as an augmentation therapy to antidepressants for treating patients with MDD. Recently, a series of RCTs[26-28] and open-label studies[29] demonstrated that adjunctive therapy and monotherapy with quetiapine extended release (XR) [150 mg/day and 300 mg/day] was effective in patients with MDD who had provided historical evidence of an inadequate response to antidepressant treatment, although another placebo-controlled clinical trial[30] failed to demonstrate the efficacy of augmentation with the drug for treating MDD. The drug has recently been approved as an adjunctive therapy for treating MDD by the FDA and the European Medicines Agency (EMA).[31] In addition, an olanzapine-fluoxetine combination has also been approved in the US to treat treatment-resistant depression.[32]

This review provides an overview of the efficacy and safety outcomes and clinical implications for adjunctive aripiprazole in the treatment of patients with MDD.

2. Pharmacology of Aripiprazole

2.1 Pharmacokinetics

The mean time to peak plasma concentration for aripiprazole is 3 hours following multiple-dose administration of 10 or 15 mg.[33] The bioavailability of the parent drug is approximately 85%, and the mean elimination half-life of a single dose of aripiprazole is approximately 80 hours.[34] Based on the half-life, steady state is expected to be achieved by day 14.[33,34]

Elimination of the drug is mainly by the hepatic cytochrome P450 (CYP) 3A4 and CYP2D6 enzyme systems. Hence, a dosage adjustment is recommended when aripiprazole is coadministered with CYP3A4 and CYP2D6 inhibitors (half-dose) and with CYP3A4 inducers (twice the normally prescribed dose).

There appears to be no clear ethnic difference between Asian and Western subjects in terms of mean plasma pharmacokinetics of oral formulations.[35,36] There are limited data on the correlation between dose, plasma concentration and efficacy response, which may be partially accounted for by the pharmacokinetic variability of aripiprazole. The variability of aripiprazole pharmacokinetics may be explained by individual variability in the metabolism of the parent drug to dehydroaripiprazole, which is pharmacologically active.[34] The variability of plasma aripiprazole concentrations appears to be unrelated to dose or sex differences.[34]

2.2 Pharmacodynamics

Studies have demonstrated the efficacy and safety of aripiprazole across a broad spectrum of psychiatric disorders for which non-homeostatic dopaminergic- and serotonergic-mediated neurotransmission is implicated.[37] More specifically, the therapeutic benefit of aripiprazole in patients

with MDD who are incomplete responders to SSRIs/SNRIs may manifest as a result of enhanced dopamine agonism at D_2 and/or D_3 receptors (partial agonist = agonism/antagonism). As suggested by the use of dopamine receptor agonists such as bromocriptine to promote improvement in motivation, anergia, anhedonia or sexual dysfunction that are associated with MDD,[37] enhanced dopamine signalling may influence improvement in such symptomatology in patients with resistant MDD.[37] The antidepressant effect may also be mediated by serotonin 5-HT_{1A} receptor partial agonism and/or antagonism at 5-HT_{2A} receptors.[38-40] Aripiprazole has low affinity for the serotonin reuptake site (inhibition constant [Ki] values: aripiprazole, 98 nM vs fluoxetine, 1.3 nM),[41,42] suggesting that inhibition of serotonin reuptake is unlikely to be a major mechanism of its antidepressant effect. The 5-HT_{2A} receptor-mediated activity may influence downstream subcortical/cortical dopamine signalling and perhaps exert a positive influence on slow-wave sleep, which may underlie common sleep deficits in depressed patients.

Aripiprazole has low to moderate affinity for D_4, 5-HT_{2C} and 5-HT_7, α_1-adrenergic and histamine H_1 receptors, but no appreciable affinity for muscarinic receptors.[43] This pharmacological profile may explain the relatively favourable safety and tolerability of aripiprazole, including the low incidence of parkinsonian symptoms, hyperprolactinaemia, adrenergic and anticholinergic side effects and bodyweight gain.[38,40,44]

3. Evidence for Efficacy of Aripiprazole as Adjunctive Therapy for Major Depressive Disorder (MDD)

3.1 Preclinical Evidence

As discussed in section 2.2, the mechanism for the antidepressant effect of aripiprazole is postulated to be a complex interaction between multiple transmitter systems, which may involve D_2/D_3/5-HT_{1A} receptor agonism and 5-HT_{2A} receptor antagonism, each of which has been consistently proposed as a target for rational drug discovery and implicated in the treatment of MDD.[39]

The mouse forced swimming test[45] and the tail suspension test[46] have been used to provide evidence of antidepressant activity for most approved antidepressants. Various agents such as modafinil,[47] ropinirole[41] and bromocriptine[42] that enhance dopamine transmission show antidepressant activity (i.e. decrease immobility time) in these animal models.[48] Furthermore, selegiline exerts an antidepressant effect mainly through its impact on D_1 receptor activation.[49] In addition, the antidepressant activity of various SSRIs also involves different dopamine receptor subtypes, suggesting that effects on both serotonergic and dopaminergic systems may be required for optimal antidepressant effect.[42]

In line with these findings, the coadministration of aripiprazole with subactive doses of antidepressants induced an antidepressant-like effect in the forced swimming and tail suspension tests in mice, whereas administration of aripiprazole alone failed to demonstrate any influence on immobility time; this suggests that the actions of aripiprazole alone, without antidepressant augmentation, are insufficient to mediate an antidepressant effect.[50,51] In a recent study,[50] pharmacologically inactive doses of aripiprazole (0.03 and 0.06 mg/kg) potentiated the effect of subthreshold doses of the SSRIs paroxetine and citalopram (4 and 8 mg/kg) and of the SNRIs venlafaxine and minalcipran (4 and 8 mg/kg) in the mouse forced swimming test. However, this augmentation activity was not found when aripiprazole was combined with drugs that do not inhibit serotonin reuptake (desipramine 2 and 4 mg/kg and bupropion 4 and 8 mg/kg). Furthermore, the combination of aripiprazole with antidepressants did not produce a psychostimulant effect, indicating that the anti-immobility effect of aripiprazole may be related to antidepressant-like activity rather than to a stimulant-like effect.[50] These data suggest that aripiprazole, when used in conjunction with SSRIs or SNRIs, exerts an antidepressant effect only when the serotonergic system is activated, implicating a complex regulation (perhaps a synergistic interaction) of the serotonergic system via effects on dopamine,

5-HT_{1A} and 5-HT_{2A} receptors in the treatment of MDD.[50]

Aripiprazole has also been shown to release dopamine and noradrenaline in the prefrontal cortex in an animal model through 5-HT_{1A} receptor partial agonism, at levels comparable to full 5-HT_{1A} receptor agonist effects.[37,52] The antidepressant effects of adjunctive aripiprazole may also be related to a reversal of SSRI-induced inhibition of noradrenergic neurons via 5-HT_{2A} receptor antagonism.[39] In addition, studies in animals[53] and humans[54,55] have shown that antidepressants may increase subcortical D_2/D_3 receptor binding following successful treatment of depressive symptoms,[56] and the partial agonism of aripiprazole at D_3 receptors may promote this effect.[57]

3.2 Clinical Evidence

3.2.1 Open-Label Trials

Evidence from short-term, small-scale, open-label studies has consistently supported the effectiveness of adjunctive aripiprazole for treating patients with MDD.[58-67] The majority of these open-label trials showed that response and remission rates (defined *a priori*) with aripiprazole augmentation of antidepressants or cognitive behavioural therapy reach at least 50%, respectively, and that at least a 30% improvement in depressive symptoms was observed compared with that measured at baseline.

3.2.2 Short-Term, Randomized, Placebo-Controlled Trials

Three identically designed, large-scale studies of aripiprazole as adjunctive therapy in MDD have been conducted,[68-70] two of which (Berman et al.[68] and Marcus et al.[69]) were registration trials. Briefly, patients with one to three historical failures to respond to an adequate trial of an antidepressant entered a screening phase, in which prohibited psychotropic medications such as benzodiazepines and sedative agents were discontinued. Patients with a total score ≥18 on the 17-item Hamilton Rating Scale for Depression (HAMD-17) at the end of the screening phase then entered an 8-week prospective treatment phase, with various antidepressants determined at the discretion of the investigator. The goal of this phase was to identify incomplete responders (i.e. to exclude patients who had demonstrated a complete response to antidepressant treatment). Response was defined as a ≥50% reduction in the HAMD-17 total score from baseline to the end of the prospective treatment phase, a HAMD-17 total score of <14 or a Clinical Global Impression-Improvement (CGI-I) score of <3. Incomplete responders were then randomized for treatment with either aripiprazole or placebo augmentation (of the antidepressant drug and dosage that they were receiving at the end of the prospective treatment phase) in a double-blind fashion for 6 weeks. The primary efficacy endpoint was the mean change from baseline (defined as the end of the prospective treatment phase) in the Montgomery-Åsberg Depression Rating Scale (MADRS) total score. Response and remission were defined as an absolute reduction of ≥50% for the MADRS total score, and at least a 50% reduction in the MADRS score plus an absolute MADRS score of ≤10, respectively. The key secondary endpoint was the change in the mean Sheehan Disability Scale (SDS) score. Other outcome measures included the CGI-I, CGI-Severity of Illness (CGI-S), Inventory of Depressive Symptomatology-Self-Report Scale (IDS-SR) and Quick Inventory of Depressive Symptoms-Self-Report Scale (QIDS-SR). Safety was evaluated by monitoring adverse events (AEs) and laboratory measures. Extrapyramidal symptoms rating scale evaluations included changes in the Simpson-Angus Scale, Abnormal Involuntary Movement Scale (AIMS) and Barnes Akathisia Clinical Assessment. The Sexual Functioning Inventory (SFI) scale was also evaluated.

In these RCTs, 1092 prospectively identified incomplete responders were randomized, of whom 1088 received double-blind treatment with adjunctive aripiprazole or placebo. 940 (86.4%) patients completed the 6-week randomized phase. Patient disposition across these three studies and the study designs are summarized in figures 1 and 2.

In these three RCTs, significantly greater mean changes in the MADRS total score were observed with adjunctive aripiprazole compared to placebo (−8.8 vs −5.8; −8.5 vs −5.7; −10.1 vs

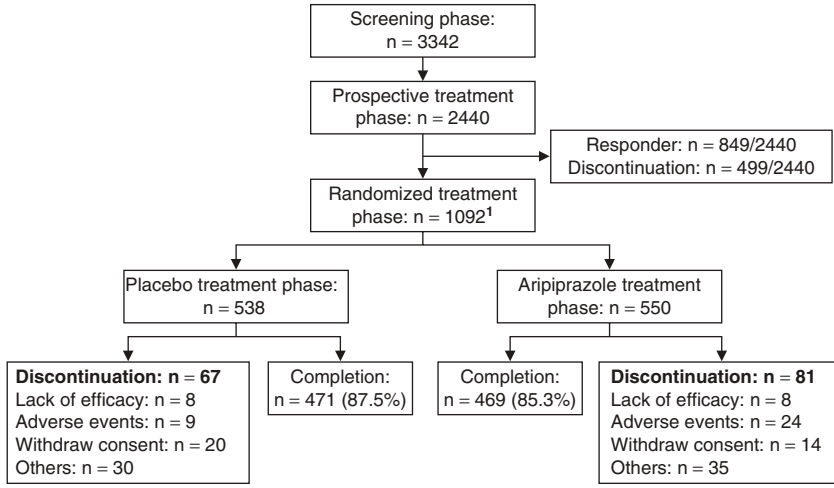

Fig. 1. The patient disposition in three randomized, double-blind, placebo-controlled clinical trials of aripiprazole as adjunctive therapy in the treatment of patients with major depressive disorder.[68-70] **1** Four randomly assigned patients were never treated with double-blind medication.

–6.4, respectively).[68-70] Remission rates were significantly higher with adjunctive aripiprazole than with adjunctive placebo in all three studies (26.0% vs 15.7%; 25.4% vs 15.2%; 36.8% vs 18.9%, respectively).[68-70] In addition, in all three studies, remission was achieved in significantly more patients taking adjunctive aripiprazole versus placebo as early as week 1[68] and week 2.[69,70] A recently published pooled analysis of the two registration studies also confirmed these efficacy findings.[71] The main efficacy findings from the three RCTs are summarized in table I,

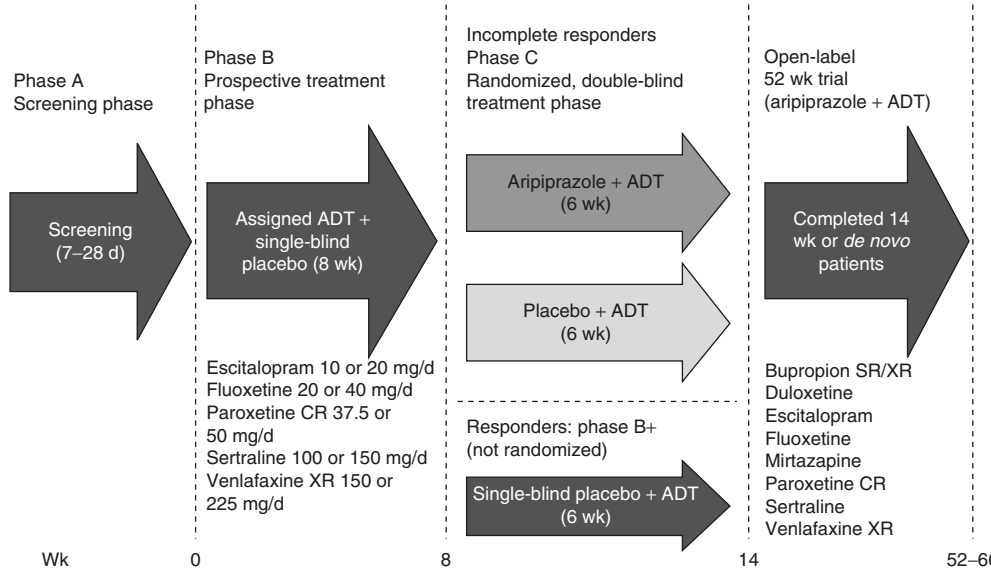

Fig. 2. Study design of the short- and long-term clinical trials of aripiprazole as adjunctive therapy for patients with major depressive disorder. **ADT** = antidepressant therapy; **CR** = controlled release; **SR** = sustained release; **XR** = extended release.

Table I. Summary of efficacy findings of three randomized, double-blind, placebo (PL)-controlled clinical trials of aripiprazole (ARP) as adjunctive therapy for the treatment of patients with major depressive disorder[a]

Study, year	Treatment (no. of patients)	Mean change in MADRS total score (mean)		Response (%)		NNT (95% CI; p-value)	Remission (%)		NNT (95% CI; p-value)
		PL	ARP	PL	ARP		PL	ARP	
Berman et al.,[68] 2007	ARP (181), PL (172)	−5.8	−8.8	23.8	33.7	11 (5, 1000; p = 0.072)	15.7	26.0	10 (5, 53; p = 0.025)
Marcus et al.,[69] 2008	ARP (185), PL (184)	−5.7	−8.5	17.4	32.4	7 (4, 16; p = 0.0010)	15.2	25.4	10 (5, 50; p = 0.021)
Berman et al.,[70] 2009	ARP (174), PL (169)	−6.4	−10.1	26.6	46.6	5 (3, 10; p < 0.0001)	18.9	36.8	6 (4, 12; p < 0.0001)
Pooled data[b]	ARP (540), PL (525)	−6.0	−9.1	22.7	37.4	7 (5, 11; p < 0.0001)	16.6	29.3	8 (6, 13; p < 0.0001)

a Efficacy analyses presented are based on last observation carried forward.

b Pooled data for all three randomized controlled trials[68-70] (see sections 3.2.2. and 3.2.3).

MADRS = Montgomery-Åsberg Depression Rating Scale; **NNT** = number needed to treat (rounded up to the nearest number).

along with a pooled analysis that we have performed that includes the calculation of the number needed to treat (NNT) for response and remission with 95% confidence intervals.

Among additional efficacy measures, the mean change in SDS total score, which was the key secondary endpoint, varied, with a statistically significant separation between adjunctive aripiprazole and placebo in only one of the three studies.[69] Consistent positive findings were observed for the subdomains of the social and home/family life items in all three studies, but not on the work/school subscale. It is likely that the lack of separation on the work/school items was a major contributing factor for the negative outcome on the SDS total score. For this particular demographic, it is worth noting that there was an incomplete collection of data for the work/school items based on the fact that a percentage of patients were not eligible to respond to this question, and this might have driven the negative outcome.

Changes in the CGI-S and CGI-I total scores showed significantly greater improvements in those administered adjunctive aripiprazole compared with adjunctive placebo in all three RCTs. The changes in the IDS-SR and QIDS-SR were consistently in favour of adjunctive aripiprazole over adjunctive placebo (i.e. numerically higher changes and statistically greater improvements at multiple timepoints); however, these were not statistically significant at the endpoints of all three RCTs.

These findings indicate that adjunctive aripiprazole is effective for treating core symptoms of depression and that it also has an impact, albeit less prominent, on additional depression-related functional impairments.

Clinical Implications of Efficacy Findings

As shown in table I, the third RCT[70] not only re-confirmed the efficacy of adjunctive aripiprazole for treating patients with MDD but also showed much better efficacy findings in terms of the primary endpoint (MADRS), as well as response and remission rates, compared with the outcomes from the two registration trials.[68,69] Notably, the NNT was reduced to five (based on responder rates; 95% CI 3, 10) or six (based on remitter rates; 95% CI 4, 12). This result is in

contrast to the findings of a recent meta-analysis comparing duloxetine and venlafaxine XR for treating MDD, in which the respective remission and response rates were 17.8% and 24.4% for venlafaxine XR, and 14.2% and 18.6% for duloxetine, resulting in weak NNTs.[72] Moreover, the remission rates for venlafaxine XR, fluoxetine and placebo were 37% (NNT = 6), 22% (NNT = 25) and 18%, respectively, in a large RCT for patients with MDD.[73] In a recent meta-analysis of the new antidepressant desvenlafaxine that included 1342 patients, the response NNT was eight (53% response rate for desvenlafaxine vs 41% for placebo) and the remission NNT was 11 (32% remission with desvenlafaxine vs 23% remission with placebo).[74] Furthermore, in another recent meta-analysis with pooled data from the entire class of second-generation antidepressants compared with placebo, the NNT for preventing both relapse and recurrence was five.[75] Finally, from our pooled analysis, we calculated that the response and remission NNTs of aripiprazole were seven (95% CI 5, 11) and eight (95% CI 6, 13), respectively, which were statistically significant (table I).

3.2.3 Open-Label Extension Study

Patients who completed the randomized phase of the first two studies were eligible for enrolment in a 52-week, open-label study, for which the primary goal was assessment of patient safety. This study is not yet published in full and is available as data on file from Otsuka Pharmaceuticals.[76] Patients who met the criteria for a response at the end of the prospective treatment phase (week 8 visit) and who did not meet the criteria for remission (defined as a MADRS total score ≤10) at the end of 14 weeks of treatment with a single-blind placebo plus antidepressant were also eligible for enrolment into the study. *De novo* patients who were recruited from sites not participating in the two short-term studies[68,69] and who reported inadequate response to antidepressants (<50% decrease in Massachusetts General Hospital Antidepressant Treatment Response) were eligible to participate in the long-term open-label extension (see figure 2).[68,69,77]

The incidence of AEs, patient weight and laboratory measurements were assessed during the 52-week study. In addition to the primary goal of long-term safety assessment, efficacy was also assessed, by the CGI-S scale with week 14 as the baseline point. The long-term safety sample included 1076 enrolled patients, and 1002 entered the treatment phase. Overall, 32% of all patients completed the 52-week treatment phase. Based on the CGI-S scores, all groups showed sustained improvement

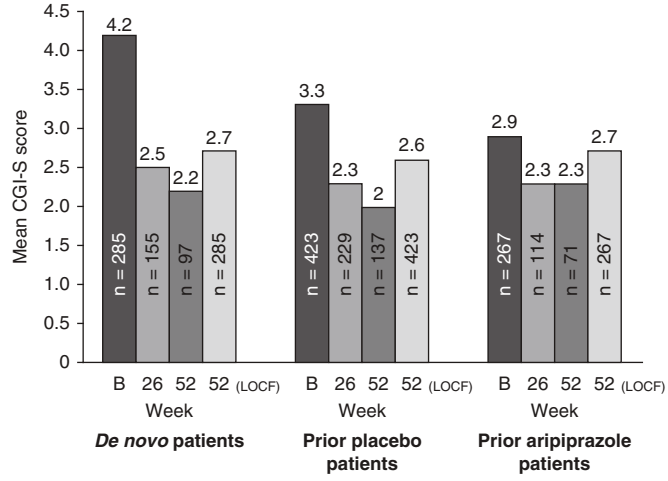

Fig. 3. Mean change from baseline (B) in Clinical Global Impression-Severity (CGI-S) score in a 52-week, open-label study of aripiprazole as adjunctive therapy in patients with major depressive disorder (efficacy sample n = 975).[76] **LOCF** = last observation carried forward.

Table II. Summary of safety findings of three randomized, double-blind, placebo (PL)-controlled clinical trials of aripiprazole (ARP) as adjunctive therapy in the treatment of patients with major depressive disorder[a]

Adverse effect	Berman et al.,[68] 2007		Marcus et al.,[69] 2008		Berman et al.,[70] 2009		Pooled data	
	PL n = 176	ARP n = 182	PL n = 190	ARP n = 185	PL n = 172	ARP n = 176	PL n = 538	ARP n = 543
Akathisia	8 (4.5)	42 (23.1)	8 (4.2)	49 (25.9)	6 (3.5)	32 (18.2)	22 (4.1)	123 (22.7)
Headache	19 (10.8)	11 (6.0)	20 (10.5)	17 (9.0)	14 (8.1)	15 (8.5)	53 (9.9)	43 (7.9)
Somnolence	–	–	7 (3.7)	13 (6.9)	1 (0.6)	10 (5.7)	8 (1.5)	23 (4.2)
Dizziness	–	–	–	–	5 (2.9)	9 (5.1)	5 (0.9)	9 (1.7)
Restlessness	6 (3.4)	26 (14.3)	1 (0.5)	18 (9.5)	6 (3.5)	22 (12.5)	13 (2.4)	66 (12.2)
Insomnia	4 (2.3)	14 (7.7)	3 (1.6)	14 (7.4)	9 (5.2)	15 (8.5)	16 (3.0)	43 (7.9)
Constipation	–	–	5 (2.6)	10 (5.3)	6 (3.5)	10 (5.7)	11 (2.0)	20 (3.7)
Diarrhoea	10 (5.7)	6 (3.3)	–	–	13 (7.6)	10 (5.7)	23 (4.3)	16 (2.9)
Nausea	9 (5.1)	5 (2.7)	8 (4.2)	10 (5.3)	10 (5.8)	7 (4.0)	27 (5.0)	22 (4.1)
URI	7 (4.0)	15 (8.2)	–	–	13 (7.6)	13 (7.4)	20 (3.7)	28 (5.2)
Fatigue	6 (3.4)	11 (6.0)	7 (3.7)	19 (10.1)	8 (4.7)	16 (9.1)	21 (3.9)	46 (8.5)
Blurred vision	3 (1.7)	12 (6.6)	–	–	3 (1.7)	13 (7.4)	6 (1.1)	25 (4.6)
Tremor	–	–	5 (2.6)	12 (6.3)	–	–	5 (0.9)	12 (2.2)
Dry mouth	11 (6.3)	6 (3.3)	–	–	–	–	11 (2.0)	6 (1.1)
Serious adverse effects	3 (exostosis; cellulitis and abscess; contusion and physical assault)	2 (pneumonia; cellulitis)		1 (cellulitis)	1 (arterial occlusive disease)	1 (suicidal ideation)	4	4

a Treatment-emergent adverse effects occurring at an incidence of ≥5% in either treatment group during the randomized phase (safety sample).

URI = upper respiratory infection; – indicates that the adverse effect may have occurred during each study but only adverse effects with an incidence of more than 5% in each study are presented in this table.

in clinical symptoms (figure 3). Hence, aripiprazole augmentation demonstrated acceptable effectiveness and tolerability over the 52-week period, although the study did not include a control arm.

4. Safety and Tolerability of Aripiprazole in Patients with MDD

Overall, adjunctive aripiprazole was safe and well tolerated in the three RCTs.[68-70] When we pooled data from the three short-term studies,[68-70] the completion rates were 85.3% for adjunctive aripiprazole and 87.5% for adjunctive placebo. The overall discontinuation rates owing to AEs in the pooled data set were low: 4.4% for adjunctive aripiprazole and 1.7% for adjunctive placebo (table II). These discontinuation rates are comparable to the findings from aripiprazole treatment for other indications (7% for schizophrenia; 11% for bipolar mania monotherapy; and 12% for bipolar mania adjunct therapy).[78]

Akathisia was the most common AE reported with adjunctive aripiprazole in the three RCTs and, according to our pooled analysis, occurred in 22.7% of patients; however, the vast majority of akathisia reports were considered mild to moderate, a finding supported by the fact that only five patients (yielding 0.9% when divided by the safety sample of n = 543) discontinued treatment due to this AE.[68-70] When the incidence of extrapyramidal syndrome-related AEs seen in the trials of patients with MDD is compared with that among five, 4- to 6-week, short-term aripiprazole RCTs[79-81] for patients with schizophrenia or schizoaffective disorder (aripiprazole 6.0% vs placebo 5.8%), it appears to be approximately 4 times higher. A recent meta-analysis[82] also supported a relatively high number needed to

treat to harm (NNTH) for akathisia in aripiprazole-treated patients: nine for bipolar mania and five for bipolar depression. These findings indicate the need for a cautionary approach with the use of aripiprazole for patients with mood disorders, including MDD (NNTH = 5 from the three RCTs[68-70]).[78] The induction of akathisia is a possible mechanism of the increased risk for suicidality with SSRI treatment;[39,83] however, this association was not supported in any aripiprazole RCTs.

There were no reports of tardive dyskinesia in the three, 6-week RCTs for patients with MDD. The safety findings are summarized in table II. Treatment-emergent tardive dyskinesia was reported in only 0.2% of patients receiving aripiprazole in a 4- to 6-week RCT of adult patients with schizophrenia;[80] this rate was similar to that in subjects receiving placebo (0.2%). There were no reports of tardive dyskinesia in a 26-week adult schizophrenia RCT,[84] whereas there were four events of tardive dyskinesia in the 52-week, open-label extension study in patients with MDD.[77] There was one reported event in a *de novo* patient (history of incomplete response to antidepressants, followed by aripiprazole open-label), one event in the cohort that received a prior placebo and two events in the cohort that received prior aripiprazole. All events were reported as mild (AIMS total scores <4). Two tardive dyskinesia events in the prior aripiprazole group led to discontinuation, and all four cases of tardive dyskinesia resolved with either a dose reduction (n = 2) or discontinuation (n = 2).

Although the findings for weight change and number of patients experiencing clinically significant weight gain at the endpoint (≥7% of baseline weight) were inconsistent between adjunctive aripiprazole and adjunctive placebo treatment in the three RCTs, the mean differences in both measures ranged from 0.4 to 1.7 kg and 3.3–6%, respectively, in favour of adjunctive placebo.[68-70]

In two of the RCTs,[69,70] a statistically significant improvement in sexual interest and satisfaction items on the SFI scale was apparent with adjunctive aripiprazole. However, the other study[68] failed to find a statistical difference between aripiprazole and placebo in this regard, although each of the six items favoured aripiprazole augmentation compared with placebo augmentation.

No clinically meaningful differences were observed between adjunctive aripiprazole and adjunctive placebo with respect to vital signs, ECG findings or laboratory abnormalities in any of the three RCTs. A small number of serious AEs were reported (see table II) but none was considered to be related to study medication.

In the 52-week, open-label study, the incidence of new-onset AEs was lower for prior aripiprazole patients than for rollover placebo and *de novo* patients. Across the whole population, the mean weight change from baseline (88.7 ± 0.8 kg, n = 756) after 52 weeks of treatment was 2.9 ± 0.2 kg (by last observation carried forward). There was no clinically important change in median percentage change from baseline for fasting cholesterol, high-density lipoprotein, low-density lipoprotein, triglyceride or glucose levels. There were no reports of neuroleptic malignant syndrome, completed suicides or deaths.

5. Drug Interactions with Aripiprazole

Aripiprazole is metabolized by CYP3A4 and CYP2D6, forming mainly its active metabolite dehydroaripiprazole.[85,86] The activity of aripiprazole is presumably attributable primarily to the parent drug and to a lesser extent to dehydroaripiprazole, which has an affinity for D_2 receptors similar to that of the parent drug and represents 40% of the parent drug exposure in plasma.[34,36] Aripiprazole is not a CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP2E1 enzyme substrate.[85-87] Hence, CYP3A4 inducers cause increased aripiprazole clearance and lower aripiprazole blood concentrations. Inhibitors of CYP3A4 or CYP2D6 interfere with aripiprazole elimination, leading to increased plasma concentrations.[43]

Aripiprazole is unlikely to cause clinically important pharmacokinetic interactions with drugs metabolized by CYP enzymes. *In vivo* studies have demonstrated that dosages of aripiprazole 10–30 mg/day have no significant effect on the metabolism of CYP2D6, CYP2C9, CYP2C19 and CYP3A4 substrates.[34,36] In addition, aripiprazole

and dehydroaripiprazole show no potential for altering CYP1A2-mediated metabolism *in vitro*.[85,86]

A recent pharmacokinetic study found that aripiprazole (10–20 mg/day) had no substantial effects on the pharmacokinetics of standard antidepressants (e.g. escitalopram 10–20 mg/day; fluoxetine 20–40 mg/day; paroxetine controlled release 37.5–50 mg/day; sertraline 100–150 mg/day; venlafaxine XR 150–225 mg/day) in either healthy subjects or patients with MDD,[88] and this was further evidenced by other studies.[89,90] In fact, all three RCTs of aripiprazole in MDD used the same antidepressant dose ranges as investigated in the previous pharmacokinetic study[88] and reported no AEs related to interactions with the antidepressants. However, fluoxetine and paroxetine may inhibit the metabolism of aripiprazole, as it is a substrate for CYP2D6, and an aripiprazole dose adjustment with the use of these two antidepressants may be prudent, as described on the product label. Combined use of benzodiazepines and aripiprazole produces no known harmful effects.[90] Lamotrigine was also tested with aripiprazole, and no changes in lamotrigine dose-normalized plasma trough concentrations were observed.[91]

Overall, adjunctive aripiprazole in combination with currently marketed antidepressants, regardless of class, may require a slight dosage adjustment within the approved dose range, but the preponderance of the evidence from these studies suggests that a stable dose of antidepressant can be maintained after aripiprazole is added.

6. Specific Issues in Using Aripiprazole as an Adjunctive Therapy in MDD

6.1 Does Aripiprazole Augmentation Lead to a Fast Onset of Effect?

It has been suggested that early improvement in depressive symptoms with antidepressant treatment may predict a more favourable treatment outcome. Studies on the association between the onset time of antidepressant response and the probability of response have yielded some intriguing findings, although there is still some debate about this issue.[92-94] For example, in a naturalistic study of a large sample of inpatients with major depression, the probabilities to achieve response and remission were significantly greater, by approximately 1.5-fold and 2-fold, respectively, in patients who showed early improvement compared with those who did not.[95] Moreover, the time to response in patients who did not show early improvement was approximately twice that in those with an early response.[95]

During the RCTs in patients with MDD, adjunctive aripiprazole treatment produced significantly greater remission or response rates than adjunctive placebo treatment as early as week 1[68,70] or 2,[69] and this continued through to the study endpoint. As shown in figure 4, the overall remission rate in patients receiving adjunctive aripiprazole increased significantly from week 1 throughout the study period. However, we must consider that the speed of onset is difficult to assess definitively in a clinical trial setting because of the confounding factor of early placebo response.

Finally, the response and remission NNT values based on the pooled adjunctive aripiprazole data (with reference to adjunctive placebo) for the treatment of patients with MDD are shown in table III.

6.2 What is an Appropriate Daily Dose?

Although the three short-term RCTs[68-70] were not designed to identify the most appropriate aripiprazole dose for treating patients with MDD, there are some implications about the daily dose of aripiprazole for such patients in the dose findings of these trials. The mean daily dose of aripiprazole at endpoint across the three short-term studies was approximately 11.0 mg. On average, patients achieved a target dosage at week 3 (coincident with the majority of patients switching to 10 mg/day) and were maintained on this dosage for the remainder of the study. The dosing pattern did not differ meaningfully across the individual antidepressants for pooled data from the RCTs (escitalopram 11.2 mg/day; fluoxetine 9.9 mg/day; paroxetine 9.8 mg/day; sertraline 12.2 mg/day; venlafaxine XR 10.8 mg/day).[77] The dose range of aripiprazole in the trials was also associated with a statistically significant and clinically meaningful improvement in efficacy (e.g. 66–95%

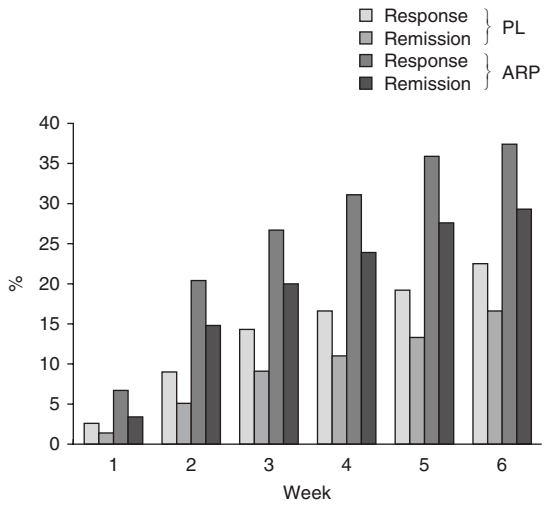

Fig. 4. Percentages of patients with major depressive disorder treated with adjunctive aripiprazole (ARP) or placebo (PL) with a response and in remission at each visit in three randomized controlled trials (pooled data). Response and remission were defined as an absolute reduction of ≥50% in Montgomery-Åsberg Depression Rating Scale (MADRS) total score, and at least a 50% reduction in MADRS score and an absolute score of MADRS ≤10, respectively.[76] Efficacy sample with last observation carried forward.

increase in likelihood of remission with aripiprazole compared with placebo) and with adequate tolerability (e.g. <4.4% discontinuation rate due to AEs in the pooled data and completion rates similar to placebo).[77]

The product label recommends a starting dosage of 2–5 mg/day, with a target range of 5–15 mg/day. According to the authors' clinical experience, starting at a low dose with slow titration to the target dosage, based on the clinician's experience and the patient's response, is prudent for achieving an adequate response and avoiding unnecessary AEs.

6.3 When is it Prudent to Introduce Augmentation with Aripiprazole?

In all three adjunctive aripiprazole RCTs,[68-70] patients were eligible to participate in the studies if they had not responded to one to three adequate treatments with a marketed antidepressant during the current depressive episode. In the three studies,[68-70] 68.5% (748/1092) of all patients had completed one adequate trial prior to entry into the study, and 25.1% had completed two adequate trials. In the STAR*D trial,[4] the remission rates after two or three failed trials averaged <15%. Furthermore, only one-third of the patients remitted with the first prescribed antidepressant.[4] Overall, a therapeutic opportunity appears to exist, as acute remission rates in MDD are greatest with the first two sequential treatments.[96] A late clinical response is also associated with poorer physical, occupational and psychosocial functional outcomes, which contributes to compliance-related under-treatment and an increased risk for relapse or recurrence. Efforts to increase opportunities for early remission are likely to promote patient confidence and insight and, in turn, enhance the probability of recovery and long-term overall good health outcomes.[9,97]

While all three adjunctive aripiprazole RCTs[68-70] were designed to assess the therapeutic benefit of aripiprazole augmentation after demonstrating an incomplete response in at least two adequate antidepressant trials (a minimum of one historical failure and one prospective failure), the aforementioned findings suggest that adjunctive aripiprazole may be warranted after one failed trial with an antidepressant, regardless of antidepressant class, in order to provide the best available therapeutic milieu for patient recovery. However, this issue needs to be confirmed in future well designed and adequately powered studies.

6.4 Does Aripiprazole Successfully Augment Some Antidepressants Better than Others?

A differential augmentation effect of aripiprazole by antidepressant class was not ob-

Table III. Number needed to treat (NNT) for every week in pooled analysis of three placebo-controlled clinical trials of aripiprazole as adjunctive therapy for the treatment of patients with major depressive disorder

Visit (wk)	NNT		95% CI	
	response	remission	response	remission
1	24	50	15, 67	26, 500
2	9	10	6, 14	8, 16
3	8	9	6, 13	7, 15
4	7	8	5, 11	6, 12
5	6	7	5, 9	5, 11
6	7	8	5, 11	6, 13

served in individual trials or in the pooled dataset from the three RCTs, although only SSRIs and SNRIs were tested, as shown in table IV. This lack of differential effect was also seen in previous small open-label trials.[59-62] Therefore, currently available data suggest that adjunctive aripiprazole may have a similar augmentation effect for SSRIs and SNRIs, although this issue clearly warrants further research.

6.5 Are There any Clinical Factors that Predict Response?

Published pooled data from two pivotal trials[71] indicated no specific clinical factors associated with the augmentation effect of aripiprazole for treating MDD, with the exception of a sex interaction effect, which favoured female patients. However, the interaction effect was not qualitative in nature, as greater reductions in the MADRS total score were observed in the aripiprazole group than in the placebo group for both sexes. Although overall greater treatment differences in favour of aripiprazole were observed in female than in male patients, the statistical significance of the treatment-by-sex effect in the combined analysis was primarily due to the results from one of the pivotal trials;[68] the two subsequent trials[69,70] showed similar results between male and female patients for the primary efficacy measure.

There were no treatment interaction effects for adjunctive aripiprazole in relation to the duration of the current episode, severity of depression or age.

6.6 Is There a Role for Adjunctive Aripiprazole in Treating Subgroups of Patients with MDD?

Anxious depression and atypical depression have been at the centre of attention, as atypical depression shows different responses based on the antidepressant class,[98,99] for example, favouring MAOIs over TCAs. Symptom severity, clinical course/outcome and functioning may be worse in patients with atypical/anxious depression than in those without.[100,101]

Hence, a *post hoc* analysis was conducted on the data sets from the two registration trials[68,69] in patients with MDD who also had anxious/atypical features.[102] In this analysis, those treated with adjunctive aripiprazole demonstrated significantly greater improvement in the MADRS total score starting at week 1 or 2 and continuing to the study endpoint than those receiving adjunctive placebo (anxious: −8.72 vs −6.17, $p \leq 0.001$; non-anxious: −8.61 vs −4.97, $p \leq 0.001$; atypical: −9.31 vs −5.15, $p \leq 0.001$; non-atypical: −8.08 vs −6.22, $p < 0.05$). At the endpoint, the response rates were significantly higher for those treated with adjunctive aripiprazole (anxious: 33.0% vs 20.6%, $p < 0.01$; non-anxious: 33.1% vs 20.3%, $p < 0.05$; atypical: 34.5% vs 17.3%, $p < 0.001$) compared with adjunctive placebo, except in the non-atypical subgroup (31.6% vs 23.5%; $p = 0.073$). The remission rates were also significantly higher in those treated with adjunctive aripiprazole (anxious: 25.0% vs 15.7%, $p < 0.05$; non-anxious: 26.6% vs 15.0%, $p < 0.05$; atypical: 23.6% vs 12.5%, $p < 0.01$;

Table IV. The mean changes in Montgomery-Åsberg Depression Rating Scale (MADRS) total score in three randomized, double-blind, placebo (PL)-controlled clinical trials of aripiprazole (ARP) as adjunctive therapy in the treatment of patients with major depressive disorder, according to the antidepressant to which the drug was added[a]

Antidepressant (mg/day)	PL		ARP		Treatment comparison (ARP vs PL)	
	n	mean change[b]	n	mean change[b]	difference	95% CI
Escitalopram (10 or 20)	151	−5.7	175	−9.1	−3.4	−5.2, −1.5
Fluoxetine (20 or 40)	76	−6.7	84	−10.2	−3.6	−6.1, −1.0
Paroxetine (37 or 50)	47	−6.4	43	−9.6	−3.1	−6.3, 0.1
Sertraline (100 or 150)	104	−6.4	89	−10.2	−3.9	−6.1, −1.6
Venlafaxine XR (150 or 225)	147	−6.2	149	−9.0	−2.8	−4.7, −0.9
All SSRIs	378	−6.2	391	−9.6	−3.4	−4.6, −2.3

a Efficacy sample with last observation carried forward.[76]

b Mean was rounded up to the nearest number.

SSRIs = selective serotonin reuptake inhibitors; **XR** = extended release.

non-atypical: 27.4% vs 18.2%, $p < 0.05$) compared with adjunctive placebo.[102]

Furthermore, according to another *post hoc* analysis of the two registration trials, adjunctive aripiprazole was effective in both incomplete responders (≥25% and <50% improvement in MADRS total score) and minimal responders (<25% improvement in MADRS total score).[71] The changes in the MADRS total score were −7.2 with aripiprazole and −5.4 with placebo in incomplete responders, and −9.4 with aripiprazole and −6.0 with placebo in minimal responders.[71] In the *post hoc* analysis,[71] adjunctive aripiprazole also demonstrated a significantly greater reduction in the MADRS total score compared with adjunctive placebo in patients who had experienced one historical antidepressant treatment failure and in those who had experienced two or more historical antidepressant treatment failures.

These data indicate that adjunctive aripiprazole is an effective and reliable treatment for patients with MDD regardless of the presentation of depressive features, past treatment response or previous antidepressant treatment failure.

6.7 How Long Do We Need to Maintain Adjunctive Aripiprazole for Patients with MDD?

As described in section 3.2.3, there is no consensus on the duration of aripiprazole augmentation therapy, but currently available evidence suggests that adjunctive aripiprazole may be administered for at least 1 year, based on the safety data from the open-label extension trial. The limitations with regard to drawing meaningful conclusions based on open-label safety data are clear. This warrants the discretion of clinicians as they weigh potential treatment benefits with potential risks associated with the availability of only limited long-term safety data. Prospectively designed, controlled studies concerning the appropriate timepoint at which to discontinue aripiprazole augmentation for MDD and how to do this (i.e. to avoid potential withdrawal symptoms, relapse, etc.) are needed to address this issue. In addition, clinicians will also be interested in the risk/benefit of long-term aripiprazole use in clinical practice.

7. Summary and Conclusions

An antipsychotic augmentation strategy has been used empirically by clinicians based on patient and clinician preference, currently available evidence and clinical consensus regarding efficacy and safety, as well as local authority prescribing regulations. There are seven currently available and commonly prescribed atypical antipsychotics other than clozapine (aripiprazole, risperidone, olanzapine, amisulpride, quetiapine, ziprasidone and paliperidone) that have potential as augmentation therapy for treating patients with MDD; however, aripiprazole was the first agent (antipsychotic or otherwise) approved by the FDA as an augmentation therapy for treating MDD. The two registration RCTs and one additional RCT for adjunctive aripiprazole to treat MDD are distinguished in both study design and clinical findings. These three RCTs had sufficient sample power (randomized n = 1092) and showed efficacy, which in our pooled analysis translated into clinically acceptable NNTs for response (7) and remission (8). All three RCTs demonstrated the consistent superiority of adjunctive aripiprazole over an adjunctive placebo in patients with an inadequate response to antidepressants. All three RCTs used a modified sequential parallel comparison design aimed at ensuring a careful characterization of the inadequate response to antidepressant monotherapy and enhancing signal detection, in an attempt to reduce the placebo response.[68-70] The adjunctive treatment was also blinded to the patient across the entire 14-week treatment period in all three RCTs, and patients were only aware of the open-label antidepressant assigned. In addition, different scales for baseline entry (HAMD-17) and primary outcomes assessment (MADRS) were used to minimize rater bias. These methodological characteristics resulted in an extraordinarily effective minimization of placebo response and should be used when considering the design of future antidepressant trials.[68-70]

All three adjunctive aripiprazole RCTs employed strict criteria to include one to three historical antidepressant therapy failures along with a prospectively characterized incomplete response to antidepressant treatment prior to

randomization (i.e. up to four prior treatment failures). The treatment response was similar in patients who had demonstrated less than three instances of treatment failure in the current depressive episode. These findings suggest that adjunctive aripiprazole is effective for minimal and incomplete responders to antidepressants as well as for treatment-resistant patients with MDD.

In general, clinicians augment or switch antidepressants or combine them with other agents to enhance the initial antidepressant or to produce a synergistic effect between antidepressants, as recommended in the clinical practice guidelines of the American Psychiatric Association[9] and as evidenced in the STAR*D trial[4] and a large US survey (n = 801) of psychiatry specialists and general practitioners.[103] For patients with MDD who do not respond to the first antidepressant, there are a number of augmentation and combined treatment strategies. However, no clear evidence exists regarding which strategy among the options of augmentation, combination and switching therapy would be the best option for these patients. With the exception of the STAR*D trial[4] there have been only small-scale exploratory trials of augmentation and combination therapy. Furthermore, there is a paucity of controlled data regarding a direct comparison between augmentation and combination therapy. Each strategy has its advantages and disadvantages, as presented in table V. Hence, subsequent well designed studies that compare adjunctive aripiprazole for treating patients who have MDD with other augmentation strategies/agents may increase the understanding of its utility in the context of prior and current treatment practices.

Finally, adjunctive aripiprazole for treating MDD is intriguing with respect to the antidepressant mechanism of action, as aripiprazole may modulate dopamine in the brain based on its pharmacodynamic profile. While it is speculative, we might imagine that triple reuptake inhibition occurs with the addition of aripiprazole to current antidepressant therapies (e.g. adding to SNRIs). Indeed, this has been suggested to be the best possible mechanism of action for the next generation of antidepressants[104] (of course, while minimizing blockade at histaminergic, cholinergic and α-adrenergic receptors, associated with known tolerability issues such as sexual side effects).

Although adjunctive aripiprazole for the acute treatment of MDD is a proven treatment option, there are a number of issues to be resolved: (i) appropriate timing of introduction; (ii) optimal patient population (presently there is no limitation in this regard); (iii) duration of treatment; (iv) treatment response and AE predictors; (v) use in special populations; (vi) long-term treatment; (vii) subgroup

Table V. Advantages and disadvantages of augmentation and combination therapy for the treatment of major depressive disorder

	Augmentation	Combination	Switching
Specific point of intervention	Minimal or partial response	Minimal or partial response	Tolerability issues Non-response
Potential background	Enhance existing antidepressant effect	Synergic effects between combined antidepressants (serotonin plus noradrenaline [norepinephrine] and dopamine, e.g. SSRIs plus DNRI)	Reinstate neurotransmitter system
Advantages	Early response and remission Sustain partial response	Early response and remission Sustain partial response Involves different neurotransmitters	Minimize drug-drug interaction Lower cost Simple regimen
Pitfalls	Additional cost Regulatory issues Potential side effects	Additional cost Regulatory issues Potential side effects Potential to increase drug-drug interaction Weak evidence from controlled trials	Delayed onset of action Jeopardize the partial benefit provided by the first antidepressant

DNRI = dopamine and noradrenaline reuptake inhibitor; **SSRIs** = selective serotonin reuptake inhibitors.

issues; (viii) best-matched antidepressant; (ix) dosing issues; and (x) pharmacoeconomic cost/benefit assessment versus other approved adjunctive therapies or antidepressant combination therapy.

In conclusion, currently available data suggest that aripiprazole is a well tolerated and effective short-term treatment for patients with MDD who are inadequate responders to antidepressants regardless of the class. In addition, adjunctive aripiprazole maintained adequate effectiveness and showed good tolerability for 52 weeks in one long-term, open-label study. Adequately powered and well designed studies are required to provide additional information about the use of adjunctive aripiprazole for treating patients with MDD (e.g. long-term outcomes, differential AEs with combined antidepressants, pharmacoeconomics in comparison with other augmentation agents, specific safety data for special populations, etc.). Finally, currently available findings warrant that clinicians consider the potential risk/benefit on a patient-by-patient basis when making a decision to prescribe adjunctive aripiprazole.

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