REVIEW ARTICLE

CNS Drugs 2008; 22 (5): 367-388
1172-7047/08/0005-0367/$48.00/0

Aripiprazole in the Treatment of Depressive and Anxiety Disorders

A Review of Current Evidence

Chi-Un Pae,[1,2] *Alessandro Serretti*,[3] *Ashwin A. Patkar*[2] and *Praksh S. Masand*[2]

1 Department of Psychiatry, Kangnam St Mary's Hospital, The Catholic University of Korea College of Medicine, Seoul, South Korea
2 Department of Psychiatry and Behavioral Sciences, Duke University Medical Center, Durham, North Carolina, USA
3 Institute of Psychiatry, University of Bologna, Bologna, Italy

Contents

Abstract

Despite the availability of different classes of drugs for the treatment of depressive and anxiety disorders, there are a number of clinically significant unmet needs, such as a high prevalence of treatment resistance, partial response, subsyndromal symptomatology, recurrence and relapse. With the approval of atypical antipsychotics, which are associated with a lower adverse effect burden than typical antipsychotics, consideration of their off-label use for the treatment of affective disorders and various other psychiatric disorders has become a viable option. However, consideration should be given to the US FDA black box warning indicating that atypical antipsychotics may increase mortality risk, particularly in the elderly population with dementia-related psychosis.

There has been much conjecture about the utility of these atypical drugs to facilitate traditional antidepressant therapy, either in combination (from the initiation of therapy) or as adjunctive therapy (in the case of partial/incomplete response). Nevertheless, at present, available evidence from randomized, placebo-controlled trials is sparse, and a formal risk/benefit assessment of the use of these agents in a nonpsychotic patient population is not yet possible.

As a representative agent from the atypical antipsychotic class with a novel mechanism of action and a relatively low adverse effect burden, aripiprazole represents an interesting potential treatment for depressive and anxiety disorders. In this review, we focus on the rationale for the use of aripiprazole in these disorders.

Preclinical data suggests that aripiprazole has a number of possible mechanisms of action that may be important in the treatment of depressive and anxiety disorders. Such mechanisms include aripiprazole action at serotonin (5-HT) receptors as a 5-HT_{1A} partial receptor agonist, a 5-HT_{2C} partial receptor agonist and a 5-HT_{2A} receptor antagonist. Aripiprazole also acts as a dopamine D_2 partial receptor agonist, and has a possible action at adrenergic receptors. Furthermore, aripiprazole may have possible neuroprotective effects.

Clinical studies demonstrate that aripiprazole may be useful in the treatment of bipolar depression, major depressive disorder, treatment-resistant depression and possibly anxiety disorders. Clinical data also suggest that aripiprazole may have a lower adverse effect burden than the other atypical drugs.

Future research may confirm the potential utility of aripiprazole in the treatment of depressive and anxiety disorders.

Significant unmet medical need remains in the treatment of depressive and anxiety disorders. Only about 25–35% of patients with major depressive disorder (MDD) and <50% with bipolar depression (BD) achieve symptom remission with conventional treatments.[1,2] Furthermore, approximately 50% of MDD patients and 40% of bipolar patients experience a recurrent or chronic course of illness for which long-term treatment is recommended.[3] Similarly, anxiety disorders also have a chronic course, with only approximately 30% of patients being successfully treated with standard therapy, and 30–40% of patients falling into the category of incomplete or partial responders.[4,5] The remaining 30% of the patients tend to be resistant to standard treatment.[4,5]

Empirical augmentation or combination of antidepressant/antianxiety therapies with conventional antipsychotics showed some benefit in the treatment of difficult-to-treat patients experiencing BD, MDD and anxiety disorders.[2-4] However, the well known adverse effects of conventional antipsychotics have limited their use in clinical practice. Hence, they have been rapidly replaced by atypical antipsychotics such as olanzapine, quetiapine and risperidone. Nevertheless, the adverse effect profile typically associated with the use of atypical antipsychotics, such as sedation, extrapyramidal symptoms (EPS), metabolic issues (e.g. increased risk of diabetes mellitus), weight gain, sexual dysfunction (e.g. prolactin increase) and hypercholesterolaemia, are also

critical limitations for application of these agents in clinical practice.[3,6,7]

Aripiprazole is a relatively new antipsychotic drug that is differentiated from currently available atypical antipsychotics in its mechanism of action and adverse effect profile. Aripiprazole is a partial agonist at dopamine D_2 receptors, a partial agonist at serotonin (5-HT)$_{1A}$ receptors and an antagonist at 5-HT$_{2A}$ receptors.[8] Its activity at muscarinic and histaminic receptors is minimal.[8] Also important for aripiprazole (as well as some other new antipsychotics such as ziprasidone) is its neutral effect on bodyweight, triglyceride levels, prolactin levels and sedation.[9,10] Aripiprazole is comparable to other atypicals in terms of the occurrence of EPS, and has no clinically meaningful effects on corrected QT interval (QTc) prolongation.[8-13]

This review focuses on the potential role of aripiprazole in the treatment of depressive and anxiety disorders based on currently available findings from preclinical and preliminary clinical studies.

1. Pharmacological Relevance of Aripiprazole for Depressive and Anxiety Disorders

1.1 Basic Pharmacodynamics

Aripiprazole shows a high affinity for the dopamine D_2 and D_3 and serotonin 5-HT$_{1A}$ and 5-HT$_{2A}$ receptors, a moderate affinity for D_4 and 5-HT$_{2C}$, 5-HT$_{2B}$, 5-HT$_6$ and 5-HT$_7$ receptors, and a weak affinity for α_1-adrenergic and histaminergic H_1 receptors.[14-19] Aripiprazole has no appreciable affinity for muscarinic receptors. Finally, aripiprazole has moderate affinity for the serotonin reuptake site (K_i [inhibition constant] values: aripiprazole 98 nmol/L vs fluoxetine 1.3 nmol/L).[19,20]

Aripiprazole acts as a partial agonist at D_2, D_3 and D_4, and 5-HT$_{1A}$, 5-HT$_{2C}$ and 5-HT$_7$ receptors, as an antagonist at 5-HT$_{2A}$ and 5-HT$_6$ receptors, and as an inverse agonist at 5-HT$_{2B}$ receptors.[14-19,21-23]

A summary of *in vitro* receptor-binding profiles of the atypical antipsychotics is presented in table I.[22,23] The theoretical applicability of the action of aripiprazole at each major receptor subtype for its use in the treatment of depressive and anxiety disorders is explored in detail in section 1.2. However, we should bear in mind that direct translation of data from animal studies into humans is not straightforward.

1.2 Theoretical Rationale for Aripiprazole in the Treatment of Depressive and Anxiety Disorders

The proposed mechanism of action for aripiprazole in the treatment of depressive and anxiety disorders, and also schizophrenia, is not yet completely understood. Reflecting the efficacy and mechanism of action of the SSRIs for treating depressive and anxiety disorders, the most probable mechanism of action of aripiprazole in depressive and anxiety disorders might be based on modulation of the serotonergic system through its agonist/antagonist activities on 5-HT receptors. In addition, other neurotransmitters, such as noradrenaline (norepinephrine) and dopamine, may also be involved in its mechanism of action for depressive and anxiety disorders.

1.2.1 Serotonin (5-HT)-Related Action

5-HT$_{1A}$ Receptor

5-HT$_{1A}$ receptor stimulation is believed to be one of the common mediators of antidepressant and antianxiety drug effects.[24-26] 5-HT$_{1A}$ receptors are distributed throughout the brain with their highest concentrations in the frontal cortex, subthalamic nucleus and entopeduncular nucleus, as well as in the dorso-medial raphe nucleus.[24] The intrinsic activity of 5-HT$_{1A}$ receptor agonists at 5-HT$_{1A}$ receptors may determine their antidepressive/anxiolytic effect and the apparent intrinsic activity of 5-HT$_{1A}$ receptor agonists may depend on the pre- or postsynaptic localization of the receptors.[27] In fact, 5-

Table I. Receptor-binding profiles of the atypical antipsychotic drugs[22,23]a

Receptor	Clozapine	Risperidone	Olanzapine	Quetiapine	Ziprasidone	Aripiprazole
D_1	85	460	31	455	525	265
D_2	125	3	11	329	4.8	0.45
D_3	473	10	49	340	7	0.8
D_4	35	9	27	1 600	32	44
5-HT_{1A}	875	210	>7 100	717	3	4.4
5-HT_{1D}	980	100	800	DNP	2	DNP
5-HT_{2A}	12	0.6	4	148	0.4	3.4
5-HT_{2C}	16	25	23	1 500	1.3	15
α_1	7	2	19	94	10	57
α_2	8	3	230	87	DNP	DNP
H_1	6	155	7	30	47	61
M_1	1.9	>10 000b	1.9	>10 000b	>10 000b	>10 000b

a All values represent K_i, nmol/L.

b IC_{50}.

5-HT*x* = serotonin-*x*; α_x = α_x-adrenoreceptor; **D*x*** = dopamine-*x*; **DNP** = data not presented; **H1** = histamine-1; **IC50** = concentration that inhibits 50%; **Ki** = inhibition constant; **M1** = muscarinic-1.

HT_{1A} receptors are located both presynaptically in the raphe nuclei, where they act as autoreceptors inhibiting the firing rate of 5-HT neurons, and postsynaptically in limbic and cortical regions, where they also attenuate firing activity. Although still controversial, the antidepressant effect of 5-HT_{1A} receptor agonists may be predominantly mediated by postsynaptic 5-HT_{1A} receptors, whereas the anxiolytic effect may be mainly associated with presynaptic 5-HT_{1A} receptors.[27]

The short-term effect of the systemic administration of a 5-HT_{1A} receptor agonist is a decrease of serotonergic neurotransmission. In contrast, the long-term effect is more complex and results in serotonergic stimulation,[28] because desensitization does not occur in all brain areas. The serotonergic stimulation is a result of the postsynaptic action of 5-HT_{1A} receptor agonists after presynaptic receptor desensitization, which is also supported by the reduction in density of the 5-HT_2 receptors.[28]

An increase in dopamine levels in the prefrontal cortex[25,29] may also be indirectly related to the antidepressant effect of 5-HT_{1A} receptor agonists. Aripiprazole has been shown to enhance the release of dopamine in the hippocampus and in the medial prefrontal cortex through a mechanism requiring the stimulation of the 5-HT_{1A} receptor.[27,30-32] It has been shown that the simultaneous combination of a 5-HT_{1A} receptor agonist and an SSRI can increase the dopamine level in the prefrontal cortex even more, resulting in greater improvement in depressive symptoms in preclinical studies.[25,29] These findings are also supported by a number of clinical studies that demonstrated the augmentation of the antidepressant effects of SSRIs by the 5-HT_{1A} receptor partial agonist pindolol.[33,34] Some negative results were also reported,[35] but this could be due to the fact that higher dosages of pindolol (15 mg/day vs 7.5 mg/day) may be needed.[36] Interestingly, antidepressants have been found to induce neurogenesis in the hippocampus, an effect that occurs via an action at 5-HT_{1A} receptors.[37]

At a clinical level, pilot studies have demonstrated that some atypical antipsychotic drugs (ziprasidone, olanzapine and quetiapine [which all have 5-HT_{1A} receptor partial receptor agonist properties]) may have some antidepressant effects.[19,38,39] The positive effect of a 5-HT_{1A} partial receptor agonist (buspirone) on anxiety has been reported in both clinical and animal studies;[25,40,41] however, data

from randomized controlled trials (RCTs) of 5-HT_{1A} partial agonists in the treatment of anxiety disorders are still insufficient.

In summary, the partial agonist effect of aripiprazole on the 5-HT_{1A} receptor may be linked to the potential antidepressant and anxiolytic effect through receptor-related activities, which lead to changes in the serotonin and dopamine neurotransmitter systems in the prefrontal cortex and other depression- or anxiety-related specific brain regions (e.g. hippocampus, dorsal raphe nucleus).

5-HT_{2C} Receptor

Abnormalities of 5-HT_{2C} receptor activity have been suggested to be involved in depressive and anxiety disorders.[42] A number of TCAs, and fluoxetine, have been proposed to interact directly with 5-HT_{2C} receptors, although the exact role of 5-HT_{2C} receptors in antidepressant effects has not been fully explained.[42] Long-term treatment with paroxetine has been implicated in the functional desensitization of 5-HT_{2C} receptors.[42,43] Fluoxetine was also found to reverse the overall decrease in 5-HT_{2C} receptor activity in the prefrontal cortex of suicide attempt victims with a history of MDD.[42,44]

The increased inhibitory activity of 5HT_{2C} receptors in the nucleus accumbens may result in a reduction of serotonin-induced dopamine release that is relevant to depressive-like behaviour.[45] This was supported by a clinical study with some antidepressants.[46] It is worth noting that a release of dopamine in the nucleus accumbens mediates motivation and reward, making this neurotransmitter a likely candidate to be involved in anhedonia, which is one of the major symptoms of MDD.[45]

In addition, the 5-HT_{2C} receptor has been proposed to be involved in the development of anxiety-related behaviours.[40,47] In a recent animal study,[47] 5-HT_{2C} receptor agonist activity was found to be associated with increased quiet-waking and decreased rapid-eye-movement sleep, which is characteristic of antidepressant drugs. Other preclinical studies suggested that agonist activity at the 5-HT_{2C} receptor decreased stress-related anhedonia and ameliorated experimentally induced panic symptoms also.[48]

Given that 5-HT_{2C} receptor agonist activity has been proven to be related to reduced compulsive behaviours, improved sleep-wake pattern and reversal of passive avoidance in animal models,[47] the 5-HT_{2C} receptor agonist property of aripiprazole might be associated with its therapeutic potential in depressive and anxiety disorders.

5-HT_{2A} Receptor

The 5-HT_{2A} receptor is widely distributed in the brain with the highest concentration in the cerebral cortex, and it is localized on the cortical and hippocampal pyramidal glutamatergic neurons as well as on GABAergic interneurons.[49] Treatment with SSRIs has been shown to result in the down-regulation of 5-HT_{2A} receptors, which is widely accepted as a critical mechanism for their antidepressant efficacy;[50] however, this mechanism alone may not explain the whole therapeutic benefit observed with all SSRIs.[50]

Animal studies[51,52] have shown that atypical antipsychotic drugs with a 5-HT_{2A} receptor antagonist effect down-regulated 5-HT_{2A} receptors in the frontal cortex. We have previously seen that 5-HT_{1A} receptor agonists are also involved in the down-regulation of 5-HT_{2A}-receptor binding sites, which suggests an intricate interaction between the 5-HT receptors that ultimately provides the basis for the observed efficacy of 5-HT_{1A} receptor agonists in the treatment of depressive symptomatology.[28]

Mounting evidence indicates that the combined blockade of 5-HT_{2A} receptors and 5-HT transporters may boost antidepressant and anxiolytic efficacy compared with blocking either site alone.[53,54] In addition, this combination of effects was also found to increase the synaptic availability of noradrenaline as well as serotonin, suggesting an additional benefit

in the treatment of depression and anxiety disorders.[55]

Finally, 5-HT_{2A} receptor blockade may stimulate the mesocortical dopamine pathway, which is clinically important for the improvement of depression and negative symptoms in schizophrenia patients.[31] In line with these findings, the 5-HT_{1A} receptor partial agonist effect of aripiprazole is linked to the down-regulation of 5-HT_{2A} receptors, which supports the theoretical basis for its utility as an antidepressant and/or antiobsessional agent.[19]

Other 5-HT Receptors

The activation of 5-HT_{2B} receptors, which is possibly a consequence of the sudden increase in serotonin levels, results in the concomitant activation of the sensory trigeminovascular afferent neurons that is associated with the onset of headaches.[56-58] Hence, the 5-HT_{2B} receptor antagonism of aripirazole might play a partial role in the improvement of headaches or the associated somatic symptoms that are commonly observed in patients with depression and anxiety disorders,[59,60] although this is not unequivocal based on currently limited data.[60]

Aripiprazole also acts as an antagonist at the 5-HT_6 receptor and as a weak partial agonist at the 5-HT_7 receptor.[19] The affinity of several antidepressant and antipsychotic drugs for 5-HT_6[61] and 5-HT_7[62] receptors, and the CNS distribution of these receptors, suggest that the therapeutic effect of these drugs in depressive and anxiety disorders may involve actions at these receptors. However, direct evidence of the function of these receptors *in vivo* will be needed to support these perspectives.[62]

1.2.2 Dopamine-Related Action

The involvement of dopamine in the modulation of depressive symptoms is well established, specifically with regard to the processing of signals associated with reward/pleasure, motivation, psychomotor activity and appetite. Practically speaking, agents that facilitate dopaminergic transmission, either as direct agonists (e.g. bromocriptine) or indirectly (e.g. stimulants), have been used to treat the anergic components of depression for at least the past decade.[63-66]

As a dopamine partial receptor agonist, it is speculated that aripiprazole has properties consistent with functional agonism, as functional antagonism. Aripiprazole has distinct dopamine intrinsic activities in various cellular environments, with regionally specific activities that may be influenced by the properties of local dopamine receptors as well as the efficiency of coupling to downstream molecules.[67] The relative absence of hyperprolactinaemia in patients with schizophrenia who receive aripiprazole treatment is supportive of functional agonism. Other manifestations of dopamine functional agonism with aripiprazole include an improvement in negative/depressive symptoms and cognition dysfunction in patients with schizophrenia and/or a lack of sedation normally associated with antipsychotic use.[10,19]

Clearly, properties of functional agonism may explain the purported utility of aripiprazole in the treatment of patients with MDD. However, while the theory of the 'functional selectivity' of aripiprazole at regionally distinct dopaminergic pathways supports its proposed dopamine-related antidepressant-like effect, there is some discrepancy regarding the effect of aripiprazole on the release of dopamine in the prefrontal cortex.[27,30-32,68]

A recent study[69] complimented the hypothesis that the D_2/D_3 receptors in the nucleus accumbens may represent a 'final common pathway' for the effect of antidepressants. This study investigated whether the antidepressant action of SSRIs was reversed by acute administration of sulpiride, a specific D_2/D_3 receptor antagonist in the mesolimbic dopaminergic system. In this study, sulpiride caused a worsening of depressive symptoms when administered acutely to chronic depressive patients treated

with SSRIs, suggesting an inhibitory action at supersensitive postsynaptic D_2/D_3 receptors in mesolimbic terminal regions.[69] In fact, previous animal[70] and human[71,72] studies have showed that antidepressants may increase subcortical D_2/D_3 receptor binding following successful treatment of depressive symptoms.[69] In addition, the antidepressant effects of drugs that act primarily as direct or indirect dopamine receptor agonists are also consistent with the proposed dopaminergic mechanism of antidepressant action.[69]

Many contemporary antidepressants lacking an antagonistic effect at the D_2 receptor have been reported to promote the development of manic symptoms,[39] and excessive dopaminergic neurotransmission might also induce manic symptoms.[39] In contrast, aripiprazole has demonstrated utility in the treatment of acute bipolar mania and in the maintenance of bipolar patients in the clinical trial setting. Aripiprazole, like other atypicals, may also have the advantage of not causing a switch from depressive to manic symptoms because of the property of dopamine blockade.[39]

Indirect facilitation of dopamine transmission via 5-HT receptor-mediated pathways is obviously also a possibility for the mechanism of action of aripiprazole in the treatment of depression and anxiety. Aripiprazole produces identical dose-response effects on the release of dopamine in the prefrontal cortex and hippocampus through the stimulation of the 5-HT_{1A} receptor.[27,30,31,42] It is well known that 5-HT_{2A} heteroreceptor blockade on the presynaptic dopaminergic neurons increases the level of dopamine released in the prefrontal cortex.[31] Aripiprazole can also modulate dopamine release through 5-HT_{2C} partial receptor agonist activity, depending on the prevailing intensity of the serotonergic function.[73]

The exact mechanism by which aripiprazole exerts its central effect on dopamine neurotransmission has not yet been completely explored. Further preclinical studies in this regard may help define whether the effects of aripiprazole on dopamine neurotransmission are involved in its antidepressant and antianxiety properties.

1.2.3 Noradrenaline (Norepinephrine)-Related Action

Aripiprazole also has some affinity for α_1- and α_2-adrenergic receptors, although these effects are weaker than those for the dopamine and 5-HT receptors.[19] Previous studies[74-76] support the involvement of α-adrenergic receptors in the antidepressant effect reported with the use of other atypicals that have been shown to increase release of adrenaline (epinephrine) in the prefrontal cortex. Currently, there are limited preclinical data available to support the putative effect of aripiprazole on the release of noradrenaline.[32]

1.2.4 Other Potential Mechanisms of Action

An impairment in neuroprotective process has also been implicated in the pathophysiology of depressive and anxiety disorders.[77,78] Interestingly, activation of 5-HT_{1A} receptors was shown to be neuroprotective against various brain insults such as NMDA.[79] Several preliminary RCTs have demonstrated a potential role of NMDA receptor antagonists for the treatment of major depression, with these agents showing an early improvement,[80,81] although an 8-week RCT of memantine (a selective NMDA receptor antagonist) failed to support previous positive findings.[82]

A recent *in vivo* study[79] demonstrated the neuroprotective effects of atypical antipsychotics such as aripiprazole and ziprasidone against excitotoxicity. However, assumption of a neuroprotective effect of aripirazole as a mechanism of action in alleviating depressive and anxiety disorders should be considered highly hypothetical, considering the fact that currently available evidence only comes from early experimental studies.

In summary, a schematic presentation of speculative mechanisms of action of aripiprazole for the

treatment of depressive and anxiety disorders is shown in figure 1.

2. Clinical Data on Aripiprazole for the Treatment of Depressive and Anxiety Disorders

2.1 Bipolar Depression

Among recently approved atypical antipsychotic drugs, only quetiapine has been approved as monotherapy or add-on therapy for the treatment of BD.[83] Aripiprazole use in bipolar disorder is less studied compared with other atypicals such as olanzapine, risperidone, ziprasidone and quetiapine.[83,84] However, aripiprazole has been approved for the acute and maintenance treatment of patients with bipolar mania and mixed episode patients on the basis of shorter (3- or 12-week) and longer (24-week) term RCTs.[85-88]

Aripiprazole has convincingly demonstrated a significant benefit in the treatment of depressive or negative symptoms in several previously published RCTs for the treatment of bipolar disorder (manic and mixed episodes, not depressive episodes),[85] schizophrenia[10] and schizoaffective disorders,[10] as

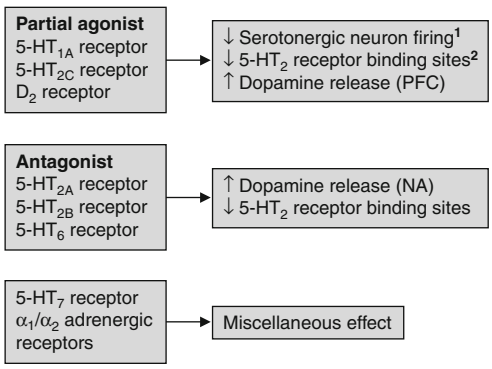

Fig. 1. Schematic presentation of speculative mechanisms of action of aripiprazole in depressive and anxiety disorders. **1** By stimulation of presynaptic serotonin 5-HT_{1A} receptors; **2** By occupation of postsynaptic 5-HT_{1A} receptors. **5-HT** = serotonin; **D** = dopamine; **NA** = nucleus accumbens; **PFC** = prefrontal cortex; ↓ indicates decrease; ↑ indicates increase.

measured by the Hamilton Depression Rating Scale (HAM-D)[89] or on the negative symptom subscale of the Positive and Negative Syndrome Scale (PANSS).[90] However, drawing parallels between a reduction in the depressive and negative symptoms in mania or schizophrenia and potential success in the treatment of depressive disorders is not possible, given that each disorder has a different clinical course, characteristics and drug response, and potentially unique neurobiological basis.

Recently, a naturalistic study on adjunctive therapy of aripiprazole investigated its effect on treatment-resistant BD (see table II).[91] The primary outcome measure was a change in the mean Clinical Global Impression-Severity (CGI-S)[92] score from baseline to endpoint. Secondary efficacy measures included the response (CGI-S improvement of at least two points) and remission (final CGI-S score of two or less) rates, as well as the change from baseline to endpoint in the mean Global Assessment of Functioning (GAF)[92] and depressed mood and suicidal ideation scores on the Clinical Monitoring Form (CMF).[93] Aripiprazole was administered at a mean starting dosage of 6.1 mg/day (5–10 mg/day), with a mean final dosage of 15.3 mg/day (2.5–40 mg/day), for approximately 84 days. Aripiprazole showed significant improvement in the CGI-S scores (mean change = −0.6, −13.6%; p = 0.009). Aripiprazole also produced improvement in the GAF (mean change = 5.3, 10.1%; p = 0.004), and on the depressed mood (mean change = −0.43, −44.4%; p = 0.007) and suicidal ideation (mean change = −0.04, −10.8%; p = 0.005) ratings on the CMF. In addition, suicidal ideation ratings decreased by 36.1% in the 22 nonresponders (p = 0.03). This study was carried out as a part of Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) and included a heterogeneous cohort of bipolar patients with various clinical manifestations, co-morbidities and medications,

which may provide more relevant clinical information reflecting real clinical practice than RCTs.[91]

A small chart review study[94] concerning 12 patients with treatment-resistant BD has been recently published, in which 4 of 12 (33.3%) patients achieved a response (defined as a 50% reduction in the Montgomery-Åsberg Depression Rating Scale [MADRS] score)[95] after 8 weeks of aripiprazole augmentation. However, 5 of 12 patients (41.7%) developed akathisia for the first time. It should be noted that akathisia developed suddenly and severely in two patients at initiation dosages of aripiprazole 10 mg/day and 7.5 mg/day, respectively, indicating that even lower dosages, in the range of 2.5–5 mg/day, could be needed to minimize the development of EPS in the depressive phase.

The current limited evidence, albeit preliminary, appears to indicate that aripiprazole may have some potential therapeutic role in BD. Clearly, whether aripiprazole will be another option for the treatment of BD in the future will depend on the provision of sufficient evidence-based data from adequately powered, well designed RCTs.

2.2 Unipolar Depression

Most data supporting the effectiveness of atypical antipsychotic drugs in unipolar depression focused on partially responsive and treatment-resistant depression (TRD) and originated from open-label trials (OLTs) and case reports.[96] RCTs of olanzapine,[97-99] risperidone[100] and ziprasidone[101] as monotherapy or augmentation therapy produced mixed results for the short- and long-term treatment of TRD.

Barbee et al.[102] showed the effect of aripiprazole augmentation in patients (n = 30) with TRD who did not respond to previous trials with other atypical antipsychotic drugs (risperidone n = 12, olanzapine n = 6, quetiapine n = 9 and ziprasidone n = 3) in a retrospective chart review study. Fourteen of 30 patients (46.7%) responded to aripiprazole augmentation and were rated as much or very much improved in terms of the CGI-improvement (CGI-I) score at the end of observation (week 6). Responders were administered aripiprazole for an average of 3 weeks before being rated as much improved in CGI ratings. The GAF scores also increased by 10.3% (mean change = +4.8; $p < 0.001$) compared with baseline.

In a subsequent 8-week OLT of 15 MDD patients with TRD,[103] aripiprazole augmentation (2.5−10 mg/day) showed a statistically significant reduction in the mean HAM-D score from baseline to the end of treatment (−14.6, −77.2%), and 93.3% (n = 14/15) of patients were rated as responders (≥50% reduction in HAM-D score from baseline). Surprisingly, 46.7% (n = 7/15) and 66.7% (n = 10/15) of patients were rated as responders at weeks 1 and 2, respectively. Moreover, more patients receiving aripiprazole 10 mg/day tended to respond at weeks 1 and 2 compared with those receiving 2.5 mg/day. The rate of remission was also higher in patients receiving aripiprazole 10 mg/day than in those taking 2.5 mg/day. However, the overall discontinuation rates at endpoint favoured the starting dosage of 2.5 mg/day (n = 3/8; 37.5%) compared with 10 mg/day (n = 4/7; 57.1%). In addition, the early withdrawal rate caused by akathisia with the starting dosage of 10 mg/day (n = 2/7; 28.6%) was approximately twice that of those receiving 2.5 mg/day (n = 1/8; 12.5%). Nonetheless, the methodological limitations of this study do not allow any definitive conclusion to be drawn about the effective dosage of aripiprazole augmentation for treatment of patients with TRD.

Another recent OLT[104] investigated the effect of aripiprazole augmentation (10–30 mg/day) for the treatment of TRD (n = 10) for 6 weeks. The mean aripiprazole dosage was 13.2 mg/day and the mean change in the HAM-D score was −14.9 (−64.8%; $p < 0.001$) at the end of treatment. Seventy percent (n = 7/10) of patients were responders, achieving a

Table II. Summary of effectiveness results of aripiprazole studies for bipolar and unipolar depression, and anxiety disorders

Study (y)	Design (duration, dosage)	Diagnosis	Number (ITT[a])	Combined treatment	Primary endpoint	Response/remission (or secondary endpoint)
Ketter et al.[91] (2006) [STEP-BD]	op Adjunctive Tx (mean duration = 84 days, 2.5–40 mg/day)	TR in BD[b] (11 type I, 15 type II, 4 NOS)	30 (30)	MS/AD/AX	Changes in CGI-S (−13.6%; p = 0.009)	8/30 (27%) [CGI-S improvement ≥2]; 4/30 (13%) [CGI-S score of 1 or 2]
Barbee et al.[102] (2004)	Chart review Adjunctive Tx (mean duration = 6 wk, starting dosage = 10–15 mg/day)	TR in UD[b]	30 (30)	AD/MS/PS/AX	DNP	CGI-I (score of 1 or 2; 14/30, 46.7%) Changes in GAF (+4.8, +10.3%; p < 0.001)
Simon and Nemeroff[103] (2005)	op Adjunctive Tx (8 wk, 2.5–10 mg/day)	TR in UD[b]	15 (15)	AD	HAM-D remission (score <7; 13/15, 86.7%)	HAM-D response (≥50% reduction; 14/15, 93.3%) CGI-I (score of 1 or 2; 14/15, 93.3%)
Patkar et al.[104] (2006)	op Adjunctive Tx (6 wk, 10–30 mg/day)	TR in UD	10 (10)	AD	Changes in HAM-D (−14.9, −64.8%; p < 0.001)	HAM-D response (7/10, 70.0%) HAM-D remission (3/10, 30.0%)
Pae et al.[105] (2007)	op Adjunctive Tx (6 wk, 5–30 mg/day)	TR in UD	13 (11)	AD/AX	Changes in HAM-D (−14.1, −53.8%; p = 0.003)	HAM-D response (7/11, 63.6%) HAM-D remission (3/11, 27.3%)
Papakostas et al.[107] (2005)	op Adjunctive Tx (8 wk, 10–30 mg/day)	TR in UD	12 (12)	AD (SSRIs)	DNP	HAM-D response (7/12, 58.3%) HAM-D remission (5/12, 41.7%)
Worthington et al.[106] (2005)	op Adjunctive Tx (12 wk, 7.5–30 mg/day)	TR in UD[b]	17 (17)	AD (SSRIs)	Changes in CGI-S (−29.6%; p < 0.001)	CGI-I (score of 1 or 2; 10/17, 58.8%)
Connor et al.[111] (2005)	op Monotherapy (8 wk, 10–30 mg/day)	Obsessive-compulsive disorder	8 (7)	DNP	Changes in YBOCS (−6.3, −26.4%; p = 0.06)	YBOCS response (≥30% reduction; 3/7, 42.9%)

Continued next page

Table II. Contd

Study (y)	Design (duration, dosage)	Diagnosis	Number (ITT[a])	Combined treatment	Primary endpoint	Response/remission (or secondary endpoint)
Adson et al.[112] (2005)	op Adjunctive Tx (9 wk, 5–20 mg/day)	TR in UD/DD/ anxiety disorders	10 (10)	AD (SSRIs)	Changes in HAM-A (−20.6, −80.2%; p < 0.001)	Changes in MADRS (−22.4, −77.5%; p < 0.001) Changes in HADS (−13.5, −59.2%; p-value not presented) Changes in SDS (−11.7, −63.6%; p-value not presented)
Nickel et al.[113]c (2006)	RCT (8 wk, fixed 15 mg/day and PL)	BPD with UD/ anxiety disorders/ SD	52 (52)	DNP	Changes in HAM-D (drug, −6.4, −31.5%; PL, −2.1, −10.0%; p = 0.002) Changes in HAM-A (drug, −7.0, −30.0%; PL, −3.3, −14.5%; p = 0.007)	DNP
Kemp et al.[94] (2007)	Chart review Adjunctive Tx (8 wk, mean dosage = 10.7 mg/day)	TR in BD/anxiety disorders	12 (12)	AD/MS/PS/AX	MADRS response (≥50% reduction, 4/12, 33.3%)	Among four responders, three patients achieved a CGI-I score of 2 and a MADRS score ≤9
Berman et al.[108] (2007)	RCT (6 wk, 5–20 mg/day)	TR in UD	362 (DNP)	AD	Changes in MADRS (drug, −8.8, −33.8%; PL, −5.8%, −22.3%; p < 0.001)	MADRS response (≥50% reduction, drug 33.7% vs PL 23.8%; p < 0.05) MADRS remission (MADRS total score ≤10 and ≥50% reduction, drug 26.0% vs PL 15.7%; p < 0.05)
Kim et al.[109] (2007)	RCT (5–20 mg/day)	TR in UD with and without chronic features	362 (DNP)	AD	Changes in MADRS (drug w/c, −8.9, vs PL p = 0.016; drug wt/c, −8.8, vs PL p = 0.012; PL, −5.9)	

a ITT-LOCF population.

b Co-morbid conditions included, such as anxiety disorders and personality disorders.

c Results of Symptom Checklist and State-Trait Anger Expression Inventory.

AD = antidepressants; **AX** = anxiolytics; **BD** = bipolar depression; **BPD** = borderline personality disorder; **CGI-I** = Clinical Global Impression-Improvement; **CGI-S** = Clinical Global Impression-Severity; **DD** = dysthymic disorder; **DNP** = data not presented; **GAF** = Global Assessment of Functioning; **HADS** = Hospital Anxiety Scale; **HAM-A** = Hamilton Anxiety Rating Scale; **HAM-D** = Hamilton Depression Rating Scale-17 item; **ITT** = intention-to-treat; **LOCF** = last observation carried forward; **MADRS** = Montgomery-Åsberg Depression Rating Scale; **MS** = mood stabilizers; **NOS** = not otherwise specified; **op** = open-label trial; **PL** = placebo; **PS** = psychostimulants; **RCT** = randomized, controlled trial; **SD** = somatoform disorder; **SDS** = Sheehan Disability Scale; **STEP-BD** = Systematic Treatment Enhancement Program for Bipolar Disorder; **TR** = treatment resistance; **Tx** = treatment; **UD** = unipolar depression; **w/c** = with chronic features; **wt/c** = without chronic features; **YBOCS** = Yale-Brown Obsessive Compulsive Scale.

≥50% reduction in the HAM-D score, and 30% of patients reached remission (HAM-D score ≤7) at the endpoint. In addition, one patient responded at week 1, and seven patients responded at week 2. This early improvement is in line with a previously mentioned study in which the authors reported that most patients began to respond by week 2,[103] as the dosage was titrated from 10 to 15 mg/day in the study of Patkar et al.[104] This indicates that aripiprazole dosages may need to be titrated up to dosages used in the treatment of schizophrenia or bipolar disorder, in order to demonstrate its efficacy in the treatment of TRD.[104]

Our group has also conducted an open-label study that supports the efficacy of aripiprazole in the treatment of patients with TRD.[105] Aripiprazole augmentation (5–30 mg/day) was carried out in 13 patients (intention-to-treat population = 11) with TRD for 6 weeks. The HAM-D and CGI-S scores decreased significantly from baseline to the end of treatment, by 53.8% and 56.0%, respectively ($p = 0.003$; $p = 0.003$). Compared with baseline, 7 of 11 patients (63.6%) showed a ≥ 50% reduction in the HAM-D score at the end of treatment. Three (27.3%) patients met the remission criteria at the end of treatment. The mean daily and exit dosage of aripiprazole throughout the study was 10.8 ± 2.4 mg and 10.0 ± 3.8 mg/day, respectively.[105]

Other OLTs[106,107] also reported the effect of aripiprazole augmentation in the treatment of patients who have TRD, with similar magnitude of responder rates of 58.3% (≥50% reduction in HAM-D score)[107] and 58.8% (CGI ratings of much or very much improved).[106]

Recently, the efficacy and tolerability/safety of aripiprazole as an adjunctive treatment for patients with MDD that was partially responsive to SSRIs or serotonin-noradrenaline reuptake inhibitors (SNRIs) was demonstrated.[108] This study randomized 362 patients with MDD who showed an incomplete response to at least one historical course of therapy and a prospective antidepressant trial. The study was comprised of a screening phase, a prospective treatment phase and a randomization phase. During prospective treatment, each antidepressant (escitalopram, fluoxetine, paroxetine controlled-release [CR], sertraline or venlafaxine extended-release [XR]) was administered with single-blind, adjunctive placebo for 8 weeks. Patients with an incomplete response were then randomized to either continued adjunctive placebo or adjunctive aripiprazole 2–20 mg/day for 6 weeks. The primary efficacy endpoint was the mean change in MADRS total score from end of prospective treatment to end of randomized treatment (week 14, last observation carried forward). 178 patients were randomized to adjunctive placebo and 184 to adjunctive aripiprazole.

Mean changes in MADRS total scores were significantly greater with adjunctive aripiprazole versus adjunctive placebo (−8.8 vs −5.8; $p < 0.001$). Adjunctive therapy of aripiprazole also produced greater remission (26.0% vs 15.7%, defined as MADRS total score ≤10 and ≥50% reduction in MADRS total score from end of prospective treatment) and response (33.7% vs 23.8%, ≥50% decrease in MADRS total score from end of prospective treatment) rates, as shown in figure 2. Notably, the differences in remission and response rates between adjunctive aripiprazole and placebo were significantly evident by week 3 ($p < 0.001$) and week 1

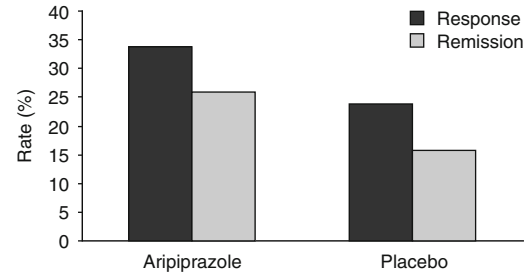

Fig. 2. Remission and response rates in a multicentre, randomized, double-blind, placebo-controlled study of the efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder.[108]

($p < 0.05$), respectively, and remained significant throughout the study ($p < 0.05$, $p < 0.01$ or $p < 0.001$). The mean changes in CGI-S score from baseline were also significantly greater with adjunctive aripiprazole versus adjunctive placebo by week 1 ($p < 0.01$) and remained significant throughout the study ($p < 0.0001$). In the study, the mean aripiprazole dosage across all antidepressants during the last week of treatment was 11.8 mg/day. The mean dosages of aripiprazole for patients receiving fluoxetine and paroxetine CR were 14.1 mg/day and 10.3 mg/day, compared with 29.9 mg/day, 20.1 mg/day and 25.5 mg/day for those receiving escitalopram, sertraline and venlafaxine XR, respectively, indicating a need for aripiprazole dosage adjustment in combination with antidepressants having a cytochrome 450 (CYP) 2D6 inhibitory effect.

Adverse events occurring in ≥10% of patients in either the adjunctive placebo or adjunctive aripiprazole groups were akathisia (4.5% vs 23.1%), headache (10.8% vs 6.0%) and restlessness (3.4% vs 14.3%). Incidence rates of adverse events leading to discontinuation were low in patients treated with adjunctive placebo (1.7%) and with adjunctive aripiprazole (2.2%); only one adjunctive aripiprazole-treated patient (0.5%) discontinued as a result of akathisia. However, overall EPS-related adverse events were reported in 27.5% of adjunctive aripiprazole-treated and 9.7% of placebo-treated patients, although there were partly significant differences in mean changes in the scores on the Simpson-Angus Scale ($p = 0.137$), Abnormal Involuntary Movement Scale ($p = 0.560$) and Barnes Akathisia Rating Scale (aripiprazole 0.24 vs placebo 0.02; $p < 0.001$) at end of treatment. Weight gain ≥7% was seen in 1.2% and 7.1% of adjunctive placebo- and adjunctive aripiprazole-treated patients, respectively.

The efficacy and safety of adjunctive aripiprazole versus placebo for MDD patients with and without chronic features were evaluated in the *post hoc* analysis from the dataset of the original study.[109] Patients with durations of current episode of ≥24 months were classified as the chronic group. In 362 randomized patients, the median duration of the current episode was 21.5 months, with a mean duration of 40.9 months (range 1.7–474.0 months). 171 (47.0%) patients were chronic and 191 (53.0%) were nonchronic. In both chronic and nonchronic patients, the mean change in MADRS total score from the end of prospective treatment to the end of the randomization phase was significantly greater in those receiving adjunctive aripiprazole than placebo (−3.0; 95% CI −5.50, −0.58 and −2.9; 95% CI −5.1, −0.64, respectively), in which the between-group difference (vs placebo) was observed from week 2 through to endpoint, respectively (figure 3).

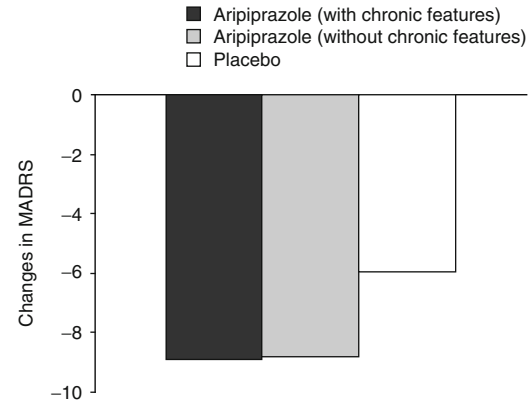

Fig. 3. Changes in total scores on the Montgomery-Åsberg Depression Rating Scale (MADRS) in a multicentre, randomized, double-blind, placebo-controlled study of aripiprazole as adjunctive therapy in major depressive disorder with (vs placebo; $p = 0.016$) and without (vs placebo; $p = 0.012$) chronic features.[109]

Taken together, these data indicate that adjunctive aripiprazole may have a therapeutic role and is well tolerated in patients with MDD, regardless of chronic features, who demonstrate an incomplete response with standard antidepressant treatment. A currently ongoing study will also provide information on the long-term safety issue of adjunctive aripiprazole in this difficult-to-treat population. However, more adequately powered RCTs are

needed to confirm the exact role of aripiprazole for TRD treatment. Currently, several RCTs of aripiprazole for the treatment of unipolar depression as a short- and long-term augmentation therapy are underway or completed in the US.[110] The full availability of these data in the near future will hopefully provide clinicians with a more practical understanding on the role of aripiprazole for the treatment of unipolar depression, as well as treatment parameters to guide its use in this population.

2.3 Anxiety Disorders

There have been no RCTs of aripiprazole for the treatment of anxiety disorders, so the following evidence needs to be cautiously interpreted. Aripiprazole was found to be effective in treating anxiety and personality disorders through several prospective OLTs and retrospective chart review studies.[106,111-113]

Patients experiencing depressive (n = 6) and anxiety disorders including panic disorder (n = 2), generalized anxiety disorder (n = 4), social anxiety disorder (n = 2), post-traumatic stress disorder (n = 2) and obsessive-compulsive disorder [OCD] (n = 1) who had an incomplete response to a variety of SSRIs received aripiprazole augmentation (7.5–30 mg/day) over a 12-week period.[106] At the end of treatment, the CGI-S score decreased significantly by 29.6% (mean change = −1.6; $p < 0.001$), and 58.8% of patients received CGI-I ratings of much or very much improved, in terms of their depression and anxiety symptoms.[106]

Eight patients with OCD entered an 8-week OLT of aripiprazole monotherapy (10–30 mg/day).[111] The efficacy assessments included the Yale-Brown Obsessive Compulsive Scale (YBOCS[114,115]) and the CGI-I score. The YBOCS score decreased by 26.4% (mean change = −6.3; $p = 0.06$), with more noticeable improvement being observed in the compulsive symptoms (mean change = −3.5; $p < 0.05$) compared with the obsessive symptoms (mean change = −2.9; $p = 0.09$). Three subjects (42.9%) met the response criteria based on a 30% or greater reduction in the total YBOCS score from baseline. This preliminary study showed promising effects of aripiprazole as a monotherapy for the treatment of OCD, supporting the need to conduct and report larger RCTs.

A 9-week, OLT of aripiprazole augmentation (5–20 mg/day) was conducted for the treatment of ten patients with treatment-resistant mixed depressive and anxiety disorders.[112] The effectiveness assessments included MADRS, Hamilton Anxiety Rating Scale (HAM-A),[116] Hospital Anxiety and Depression Scale (HADS)[117] and the Sheehan Disability Scale (SDS).[118] The mean MADRS, HAM-A, SDS and HADS scores significantly decreased from baseline by 77.5%, 80.2%, 63.6% and 59.2% at endpoint, respectively. By week 2, eight of ten patients showed a 50% or greater reduction in the HAM-A and MADRS scores, indicating earlier improvement in the depressive and anxiety symptoms with aripiprazole augmentation. Moreover, the authors reported that the remission of symptoms associated with depression and anxiety symptoms was observed by weeks 3 or 4.[112]

In another trial, patients with borderline personality disorder with co-morbid anxiety disorders (n = 26) receiving aripiprazole 15 mg/day were randomly compared with placebo (n = 26) for 8 weeks.[113] Aripiprazole treatment resulted in a significantly higher rate of improvement compared with placebo on all of the Symptom Checklist-90-Revised (SCL-90-R[119]) scales, with observed differences ranging from 6.8% to 22.3%, particularly in the obsessive-compulsive, insecurity in social contacts, depression, anxiety, aggressiveness/hostility, phobic anxiety, paranoid thinking and psychoticism scales. In addition, aripiprazole (mean change = −7; −30.0%) was superior to placebo (mean change = −3.3; −14.5%) on improvement in the HAM-A score ($p = 0.007$), as well as on im-

provement in the HAM-D score (observed difference = 21.5%; p = 0.002).[113] Table II summarizes these findings.

As data emerge from ongoing trials with aripiprazole, relevant dosage strategies may facilitate appropriate use and expectations in patients with anxiety disorders. Currently available data suggest that aripiprazole augmentation in patients with anxiety disorders/OCD may have similar effectiveness to that observed with other atypical antipsychotic drugs.[120]

2.4 Safety and Tolerability

The risk/benefit assessment is obviously critical in the decision to use atypical antipsychotic drugs for the treatment of depressive and anxiety disorders. The adverse effect burden of second-generation antidepressants is lower than that of atypical antipsychotic drugs. In general, aripiprazole is known to be well tolerated. Commonly reported adverse events, including nausea, headache, agitation and akathisia, were observed in a number of RCTs and randomized comparative trials in the treatment of schizophrenia, schizoaffective disorder and bipolar disorders.[8-13,85-88] In contrast to other atypical antipsychotic drugs, aripiprazole has been considered a relatively neutral agent with regard to treatment-emergent weight gain, hyperprolactinaemia, metabolic parameters and sedation.[8-13,85-88] However, because of its limited use, data on adverse effects that take time to develop (such as metabolic adverse effects) are limited for aripiprazole compared with for agents such as olanzapine, and therefore the risk of these adverse effects occurring with aripiprazole is currently hard to assess.

Consideration of patient compliance is also an extremely important component of the risk/benefit equation, as the patient's decision to interrupt treatment is thought to involve negative subjective experience associated with treatment-emergent adverse events. With the use of aripiprazole, factors such as weight gain, sexual performance (hyperprolactinaemia), overall health concerns (metabolic issues) and cognitive/social functioning (sedation) are not generally a primary concern.[121] Therefore, a risk/benefit assessment appears to favour the use of aripiprazole compared with many of the drugs that have been utilized in the past, in terms of safety and patient compliance.

The safety and tolerability data regarding aripiprazole, derived from clinical trials for the treatment of depressive and anxiety disorders are summarized in table III.

Aripiprazole augmentation for the treatment of patients with depressive and anxiety disorders was associated with early attrition due to adverse events such as akathisia. In such studies,[102,103] a lower starting dosage of aripiprazole improved tolerability in regard to EPS-related adverse events. This is particularly important in patients with mood disorders (e.g. bipolar mania), who have been suggested to have higher rates of EPS compared with patients with schizophrenia when treated with typical antipsychotic drugs.[122]

Aripiprazole is not a substrate of cytochrome CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19 or CYP2E1 enzymes,[123] indicating a low risk for interaction with inhibitors or inducers of these enzymes. However, aripiprazole is extensively metabolized by both CYP3A4 and CYP2D6.[123] Hence, some of the frequently prescribed psychotropic drugs that have a potential to inhibit individual CYP enzymes, in particular carbamazepine (a CYP3A4 inducer), some of the SSRIs (fluoxetine, sertraline and paroxetine [CYP2D6 inhibitors]) and several newer antidepressants (nefazodone [CYP2D6 inhibitor]), could affect the blood concentrations and clearance rate of aripiprazole.[124] Combination of these medications with aripiprazole may require a dosage modification of aripiprazole to prevent unwanted adverse events. The product label provides guidance that the dosage

Table III. Summary of safety and tolerability results of aripiprazole studies for bipolar and unipolar depression, and anxiety disorders

Study (y)	Number (ITT)	Safety and tolerability			
		overall attrition rates (%)	attrition rates due to AEs (%)	commonly reported AEs	others
Ketter et al.[91] (2006)	30 (30)	14/30 (46.7)	6/30 (20.0) [3 due to agitation; 2 due to cognitive problems; 1 due to hypomania]	Sedation/nausea/constipation	5/30 patients (all female) switched into mania MCW = +3.7 kg
Barbee et al.[102] (2004)	30 (30)	9/30 (30.0)	6/30 (20.0) [NS]	Insomnia/restlessness/agitation	NR
Simon and Nemeroff[103] (2005)	15 (15)	7/15 (46.7) [3/8 in 2.5 mg/day[a]; 4/7 in 10 mg/day[a]]	4/15 (26.7) [1/8 in 2.5 mg/day; 2/7 in 10 mg/day; 1 was NS; all 3 due to akathisia]	Akathisia/sedation/insomnia	MCW = +0.9 kg
Patkar et al.[104] (2006)	10 (10)	2/10 (20.0)	1/10 (10.0) [due to akathisia]	Akathisia/nausea/restlessness	MCW = −1.4 kg
Pae et al.[105] (2007)	13 (11)	6/13 (46.2)	2/13 (15.4) [1 due to headache; 1 due to sedation]	Headache/nausea/sedation	MCW = +1.7 kg
Papakostas et al.[107] (2005)	12 (12)	3/12 (25.0)	2/12 (16.7) [1 due to restlessness; 1 due to fatigue]	Fatigue/sedation/nausea	MCW = +1.4 kg
Worthington et al.[106] (2005)	17 (17)	5/17 (29.4)	3/17 (17.6) [1 due to restlessness; 1 due to fatigue; 1 due to weight gain >2.3 kg]	Restlessness/sedation/fatigue	Weight was not systematically recorded 5/17 NR any AEs
Connor et al.[111] (2005)	8 (7)	2/8 (25.0)	2/8 (25.0) [1 due to akathisia; 1 due to nausea]	Drowsiness/dry mouth/nausea	MCW = +1.8 kg
Adson et al.[112] (2005)	10 (10)	2/10 (20.0)	0/10 (0.0)	Restlessness/stiffness/insomnia	MCW = +3.2 kg Two patients gained weight >7%
Nickel et al.[113] (2006)	52 (52)	5/52 (9.6)	NR	Headache/insomnia/nausea	No significant weight changes (NS)
Kemp et al.[94]a (2007)	12 (12)	3/12 (25.0)[a]	3/12 (25.0)[a]	Akathisia/restlessness	Only one of four responders developed akathisia
Berman et al.[108] (2007)	362 (NR)	Drug: 22/182 (12.1) PL: 16/176 (9.1)	Drug: 6/182 (3.3) PL: 4/176 (2.3)	Drug: akathisia PL: headache	MCW: Drug +2.0 kg; PL 0.3 kg ($p < 0.001$)

a Systematic collection of AEs was not conducted and only reported the rates of akathisia.

AEs = adverse events; **ITT** = intention-to-treat; **MCW** = mean change in weight from baseline to the end of treatment; **NR** = not reported; **NS** = not specified; **PL** = placebo.

of aripiprazole, when given in combination with CYP3A4 inducers, should be doubled,[123] whereas, combination with CYP2D6 inhibitors requires a halving of the normally prescribed dosage.

The serotonin syndrome, a characteristic symptom triad of altered mental status, neuromuscular abnormalities and autonomic dysfunction, might appear when two or more serotonergic agents are combined. To our knowledge, there have been no reports of the serotonin syndrome occurring with the combination of aripiprazole with SSRIs or SNRIs. However, there has been a case report of possible neuroleptic malignant syndrome caused by the combination of aripiprazole 30 mg/day and fluoxetine 20 mg/day,[125] in which the authors were not sure of the complete exclusion of the serotonin syndrome. Despite the rare incidence of serotonin syndrome, several cases have been reported with the combination of atypical antipsychotics and antidepressants (olanzapine plus mirtazapine;[126] risperidone plus paroxetine[127]). Hence, careful consideration and an evaluation of the patient's individual vulnerability or risk factors for the serotonin syndrome would be reasonable when combining aripiprazole with serotonergic agents.

A black box warning from regulatory authorities in the US also indicates an increased mortality risk in elderly patients with dementia-related psychosis treated with all atypical antipsychotic drugs (class labelling that included aripiprazole). In addition, retinal degeneration, biliary lithiasis, fetal toxicity and teratogenicity have been proposed as potential risks from basic research studies of aripiprazole.[128]

3. Dosage Issues

The available evidence indicates that the target dosages of aripiprazole in BD, MDD and anxiety disorders appear to be in the lower range compared with those found to be efficacious in the treatment of schizophrenia, schizoaffective disorder and bipolar mania. As reported in the above-mentioned OLTs (see table II), which examined the effects of aripiprazole augmentation in patients who were partially responsive to ongoing therapy, a starting dosage of 2.5–5.0 mg/day enhanced tolerability compared with a starting dosage of 10 mg/day. Gradual titration to a terminal dosage of aripiprazole 10–20 mg/day was well tolerated.[103] Comparative placebo-controlled, fixed-dose studies will hopefully generate more definitive information on dosage strategies in the treatment of these patient populations.

4. Conclusions

In this review we have suggested a mechanistic basis for the potential utility, and presented preliminary clinical evidence, that aripiprazole may be useful to complement the present options for the treatment of depressive and anxiety disorders.

However, safety issues should always be taken into consideration. Nonschizophrenic patients treated with antipsychotic drugs are vulnerable to the development of severe long-term adverse effects such as tardive dyskinesia.[129] This is proposed to have limited the use of atypical antipsychotic drugs in depressive and anxiety disorders. Aripiprazole has been demonstrated to be relatively safe and well tolerated,[130] although a number of possible adverse events have been reported. For example, aripiprazole may cause neuroleptic malignant syndrome[131] and dose-dependent QTc prolongation at higher dosages than are approved.[123] The most critical adverse effect would be tardive dyskinesia, which has been very rarely reported with the use of aripiprazole.[132] Given the mechanism of action of aripiprazole, it is not surprising that a potential benefit for the treatment of pre-existing tardive dyskinesia has been also reported.[133]

Pharmacokinetic factors should also be considered, as the dosage of aripiprazole must be either doubled or halved when combined with inducers or

inhibitors of CYP 3A4 and CYP 2D6, respectively.[134]

Finally, it is premature to draw any conclusions regarding the efficacy of aripiprazole in these 'off-label' indications, given the paucity and quality of the currently available data. The continued use of aripiprazole as an adjunctive or combination therapy for the treatment of depression and anxiety will depend on whether the drug demonstrates any incremental value in terms of efficacy for the treatment of these disorders, in future adequately-powered, well designed, placebo-controlled trials.

Acknowledgements

The authors received no financial support to prepare this review and have no conflicts of interest directly relevant to its contents.

Dr Pae has received research grants from the Korean divisions of GlaxoSmithKline, AstraZeneca, Janssen Pharmaceuticals, Eli Lilly and Company, Otsuka, Wyeth Pharmaceuticals, the Korean Research Foundation and the Korean Institute of Science and Technology Evaluation and Planning; and has received honoraria and is on the speaker's bureaus of the Korean divisions of GlaxoSmithKline, Lundbeck, AstraZeneca, Janssen Pharmaceuticals, Eli Lilly and Company, McNeil Consumer and Specialty Inc. and Otsuka.

Dr Patkar is a consultant for Bristol-Myers Squibb, GlaxoSmithKline and Reckitt Benckiser; is on the speaker's bureau of Bristol-Myers Squibb, GlaxoSmithKline and Reckitt Benckiser; and has received research support from National Institutes of Health, AstraZeneca, Bristol-Myers Squibb, Forest, GlaxoSmithKline, Janssen, McNeil Consumer and Specialty Inc., Organon, Jazz Pharmaceuticals and Pfizer Inc.

Dr Masand is a consultant for Bristol-Myers Squibb Company, Cephalon Inc., Eli Lilly and Company, Forest Laboratories Inc., GlaxoSmithKline, i3CME, Janssen Pharmaceutica, Jazz Pharmaceuticals, Organon, Pfizer Inc., Targacept Inc. and Wyeth Pharmaceuticals; is on the speaker's bureau of AstraZeneca, Bristol-Myers Squibb Company, Forest laboratories Inc., GlaxoSmithKline, Janssen Pharmaceutica, Pfizer Inc., and Wyeth Pharmaceuticals; and has received research support from AstraZeneca, Bristol-Myers Squibb Company, Cephalon Inc., Eli Lilly and Company, Forest laboratories Inc., GlaxoSmithKline, Ortho McNeil Pharmaceutical, Inc., Janssen Pharmaceuticals and Wyeth Pharmaceuticals.

References

1. Crown WH, Finkelstein S, Berndt ER, et al. The impact of treatment-resistant depression on health care utilization and costs. J Clin Psychiatry 2002; 63 (11): 963-71
2. Dilsaver SC, Swann AC, Shoaib AM, et al. Depressive mania associated with nonresponse to antimanic agents. Am J Psychiatry 1993; 150 (10): 1548-51
3. Grunze H. Reevaluating therapies for bipolar depression. J Clin Psychiatry 2005; 66 Suppl. 5: 17-25
4. Bystritsky A. Treatment-resistant anxiety disorders. Mol Psychiatry 2006; 11 (9): 805-14
5. Brown C, Schulberg HC, Madonia MJ, et al. Treatment outcomes for primary care patients with major depression and lifetime anxiety disorders. Am J Psychiatry 1996; 153 (10): 1293-300
6. Practice guideline for the treatment of patients with major depressive disorder (revision). American Psychiatric Association. Am J Psychiatry 2000; 157 (4 Suppl.): 1-45
7. Baldwin DS, Anderson IM, Nutt DJ, et al. Evidence-based guidelines for the pharmacological treatment of anxiety disorders: recommendations from the British Association for Psychopharmacology. J Psychopharmacol 2005; 19 (6): 567-96
8. Casey DE, Carson WH, Saha AR, et al. Switching patients to aripiprazole from other antipsychotic agents: a multicenter randomized study. Psychopharmacology (Berl) 2003; 166 (4): 391-9
9. McQuade RD, Stock E, Marcus R, et al. A comparison of weight change during treatment with olanzapine or aripiprazole: results from a randomized, double-blind study. J Clin Psychiatry 2004; 65 Suppl. 18: 47-56
10. Potkin SG, Saha AR, Kujawa MJ, et al. Aripiprazole, an antipsychotic with a novel mechanism of action, and risperidone vs placebo in patients with schizophrenia and schizoaffective disorder. Arch Gen Psychiatry 2003; 60 (7): 681-90
11. Mallikaarjun S, Salazar DE, Bramer SL. Pharmacokinetics, tolerability, and safety of aripiprazole following multiple oral dosing in normal healthy volunteers. J Clin Pharmacol 2004; 44 (2): 179-87
12. Kane JM, Carson WH, Saha AR, et al. Efficacy and safety of aripiprazole and haloperidol versus placebo in patients with schizophrenia and schizoaffective disorder. J Clin Psychiatry 2002; 63 (9): 763-71
13. Marder SR, McQuade RD, Stock E, et al. Aripiprazole in the treatment of schizophrenia: safety and tolerability in short-term, placebo-controlled trials. Schizophr Res 2003; 61 (2-3): 123-36
14. Bristol-Myers Squibb. Abilify®: prescribing information [online]. Available from URL: http://www.bms.com [Accessed 2007 May 1]
15. Green B. Focus on aripiprazole. Curr Med Res Opin 2004; 20 (2): 207-13
16. Swainston-Harrison T, Perry CM. Aripiprazole: a review of its use in schizophrenia and schizoaffective disorder. Drugs 2004; 64 (15): 1715-36
17. Lieberman JA. Dopamine partial agonists: a new class of antipsychotic. CNS Drugs 2004; 18 (4): 251-67

18. Jordan S, Koprivica V, Chen R, et al. The antipsychotic aripiprazole is a potent, partial agonist at the human 5-HT1A receptor. Eur J Pharmacol 2002; 441 (3): 137-40
19. Shapiro DA, Renock S, Arrington E, et al. Aripiprazole, a novel atypical antipsychotic drug with a unique and robust pharmacology. Neuropsychopharmacology 2003; 28 (8): 1400-11
20. Stark AD, Jordan S, Allers KA, et al. Interaction of the novel antipsychotic aripiprazole with 5-HT1A and 5-HT 2A receptors: functional receptor-binding and in vivo electrophysiological studies. Psychopharmacology (Berl) 2007; 190 (3): 373-82
21. Kikuchi T, Tottori K, Uwahodo Y, et al. 7- (4-[4- (2,3-Dichlorophenyl)-1-piperazinyl]butyloxy)-3,4-dihydro-2 (1H)-quinolinone (OPC-14597), a new putative antipsychotic drug with both presynaptic dopamine autoreceptor agonistic activity and postsynaptic D2 receptor antagonistic activity. J Pharmacol Exp Ther 1995; 274 (1): 329-36
22. Farah A. Atypicality of atypical antipsychotics. Prim Care Companion J Clin Psychiatry 2005; 7 (6): 268-74
23. DeLeon A, Patel NC, Crismon ML. Aripiprazole: a comprehensive review of its pharmacology, clinical efficacy, and tolerability. Clin Ther 2004; 26 (5): 649-66
24. Matsubara K, Shimizu K, Suno M, et al. Tandospirone, a 5-HT1A agonist, ameliorates movement disorder via non-dopaminergic systems in rats with unilateral 6-hydroxydopamine-generated lesions. Brain Res 2006; 1112 (1): 126-33
25. Yoshino T, Nisijima K, Katoh S, et al. Tandospirone potentiates the fluoxetine-induced increases in extracellular dopamine via 5-HT (1A) receptors in the rat medial frontal cortex. Neurochem Int 2002; 40 (4): 355-60
26. Assie MB, Ravailhe V, Faucillon V, et al. Contrasting contribution of 5-hydroxytryptamine 1A receptor activation to neurochemical profile of novel antipsychotics: frontocortical dopamine and hippocampal serotonin release in rat brain. J Pharmacol Exp Ther 2005; 315 (1): 265-72
27. De Vry J, Schreiber R, Melon C, et al. 5-HT1A receptors are differentially involved in the anxiolytic- and antidepressant-like effects of 8-OH-DPAT and fluoxetine in the rat. Eur Neuropsychopharmacol 2004; 14 (6): 487-95
28. Blier P, Ward NM. Is there a role for 5-HT1A agonists in the treatment of depression? Biological Psychiatry 2003; 53 (3): 193-203
29. Gobert A, Rivet JM, Cistarelli JM, et al. Buspirone enhances duloxetine- and fluoxetine-induced increases in dialysate levels of dopamine and noradrenaline, but not serotonin, in the frontal cortex of freely moving rats. J Neurochem 1997; 68 (3): 1326-9
30. Li Z, Ichikawa J, Dai J, et al. Aripiprazole, a novel antipsychotic drug, preferentially increases dopamine release in the prefrontal cortex and hippocampus in rat brain. Eur J Pharmacol 2004; 493 (1-3): 75-83
31. Ichikawa J, Ishii H, Bonaccorso S, et al. 5-HT (2A) and D (2) receptor blockade increases cortical DA release via 5-HT (1A) receptor activation: a possible mechanism of atypical antipsychotic-induced cortical dopamine release. J Neurochem 2001; 76 (5): 1521-31
32. Zocchi A, Fabbri D, Heidbreder CA. Aripiprazole increases dopamine but not noradrenaline and serotonin levels in the mouse prefrontal cortex. Neurosci Lett 2005; 387 (3): 157-61
33. Landen M, Bjorling G, Agren H, et al. A randomized, double-blind, placebo-controlled trial of buspirone in combination with an SSRI in patients with treatment-refractory depression. J Clin Psychiatry 1998; 59 (12): 664-8
34. Jenkins SW, Robinson DS, Fabre Jr LF, et al. Gepirone in the treatment of major depression. J Clin Psychopharmacol 1990; 10 (3): 77-85S
35. Berman RM, Anand A, Cappiello A, et al. The use of pindolol with fluoxetine in the treatment of major depression: final results from a double-blind, placebo-controlled trial. Biol Psychiatry 1999; 45 (9): 1170-7
36. Artigas F, Adell A, Celada P. Pindolol augmentation of antidepressant response. Curr Drug Targets 2006; 7 (2): 139-47
37. Santarelli L, Saxe M, Gross C, et al. Requirement of hippocampal neurogenesis for the behavioral effects of antidepressants. Science 2003; 301 (5634): 805-9
38. Kinon BJ, Lipkovich I, Edwards SB, et al. A 24-week randomized study of olanzapine versus ziprasidone in the treatment of schizophrenia or schizoaffective disorder in patients with prominent depressive symptoms. J Clin Psychopharmacol 2006; 26 (2): 157-62
39. Yatham LN, Goldstein JM, Vieta E, et al. Atypical antipsychotics in bipolar depression: potential mechanisms of action. J Clin Psychiatry 2005; 66 Suppl. 5: 40-8
40. Overstreet DH, Knapp DJ, Angel RA, et al. Reduction in repeated ethanol-withdrawal-induced anxiety-like behavior by site-selective injections of 5-HT1A and 5-HT2C ligands. Psychopharmacology (Berl) 2006; 187 (1): 1-12
41. Chessick CA, Allen MH, Thase M, et al. Azapirones for generalized anxiety disorder. Cochrane Database Syst Rev 2006; (3): CD006115
42. Giorgetti M, Tecott LH. Contributions of 5-HT (2C) receptors to multiple actions of central serotonin systems. Eur J Pharmacol 2004; 488 (1-3): 1-9
43. Ni YG, Miledi R. Blockage of 5HT2C serotonin receptors by fluoxetine (Prozac). Proc Natl Acad Sci U S A 1997; 94 (5): 2036-40
44. Gurevich I, Tamir H, Arango V, et al. Altered editing of serotonin 2C receptor pre-mRNA in the prefrontal cortex of depressed suicide victims. Neuron 2002; 34 (3): 349-56
45. Dremencov E, Newman ME, Kinor N, et al. Hyperfunctionality of serotonin-2C receptor-mediated inhibition of accumbal dopamine release in an animal model of depression is reversed by antidepressant treatment. Neuropharmacology 2005; 48 (1): 34-42
46. Sanchez C, Hyttel J. Comparison of the effects of antidepressants and their metabolites on reuptake of biogenic amines and on receptor binding. Cell Mol Neurobiol 1999; 19 (4): 467-89
47. Martin JR, Bos M, Jenck F, et al. 5-HT2C receptor agonists: pharmacological characteristics and therapeutic potential. J Pharmacol Exp Ther 1998; 286 (2): 913-24
48. Moreau JL, Bos M, Jenck F, et al. 5HT2C receptor agonists exhibit antidepressant-like properties in the anhedonia model of depression in rats. Eur Neuropsychopharmacol 1996; 6 (3): 169-75

49. Meltzer HY, Li Z, Kaneda Y, et al. Serotonin receptors: their key role in drugs to treat schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 2003; 27 (7): 1159-72
50. Massou JM, Trichard C, Attar-Levy D, et al. Frontal 5-HT2A receptors studied in depressive patients during chronic treatment by selective serotonin reuptake inhibitors. Psychopharmacology (Berl) 1997; 133 (1): 99-101
51. Tarazi FI, Zhang K, Baldessarini RJ. Long-term effects of olanzapine, risperidone, and quetiapine on serotonin 1A, 2A and 2C receptors in rat forebrain regions. Psychopharmacology (Berl) 2002; 161 (3): 263-70
52. Moran-Gates T, Massari C, Graulich A, et al. Long-term effects of JL 13, a potential atypical antipsychotic, on rat dopamine and serotonin receptor subtypes. J Neurosci Res 2006; 84 (3): 675-82
53. Marek GJ, Martin-Ruiz R, Abo A, et al. The selective 5-HT2A receptor antagonist M100907 enhances antidepressant-like behavioral effects of the SSRI fluoxetine. Neuropsychopharmacol 2005; 30 (12): 2205-15
54. Ramasubbu R, Ravindran A, Lapierre Y. Serotonin and dopamine antagonism in obsessive-compulsive disorder: effect of atypical antipsychotic drugs. Pharmacopsychiatry 2000; 33 (6): 236-8
55. Szabo ST, Blier P. Effects of serotonin (5-hydroxytryptamine, 5-HT) reuptake inhibition plus 5-HT (2A) receptor antagonism on the firing activity of norepinephrine neurons. J Pharmacol Exp Ther 2002; 302 (3): 983-91
56. Johnson KW, Phebus LA, Cohen ML. Serotonin in migraine: theories, animal models and emerging therapies. Prog Drug Res 1998; 51: 219-44
57. Schmuck K, Ullmer C, Kalkman HO, et al. Activation of meningeal 5-HT2B receptors: an early step in the generation of migraine headache? Eur J Neurosci 1996; 8 (5): 959-67
58. Fozard JR, Kalkman HO. 5-Hydroxytryptamine (5-HT) and the initiation of migraine: new perspectives. Naunyn Schmiedebergs Arch Pharmacol 1994; 350 (3): 225-9
59. Demyttenaere K, De Fruyt J, Stahl SM. The many faces of fatigue in major depressive disorder. Int J Neuropsychopharmacol 2005; 8 (1): 93-105
60. Hamel E. The biology of serotonin receptors: focus on migraine pathophysiology and treatment. Can J Neurol Sci 1999; 26 Suppl. 3: S2-6
61. Mitchell ES, Neumaier JF. 5-HT6 receptors: a novel target for cognitive enhancement. Pharmacol Ther 2005; 108 (3): 320-33
62. Guscott M, Bristow LJ, Hadingham K, et al. Genetic knockout and pharmacological blockade studies of the 5-HT7 receptor suggest therapeutic potential in depression. Neuropharmacology 2005; 48 (4): 492-502
63. Willner P. The mesolimbic dopamine system as a target for rapid antidepressant action. Int Clin Psychopharmacol 1997; 12 Suppl. 3: S7-14
64. Fava M, Thase ME, DeBattista C. A multicenter, placebo-controlled study of modafinil augmentation in partial responders to selective serotonin reuptake inhibitors with persistent fatigue and sleepiness. J Clin Psychiatry 2005; 66 (1): 85-93
65. Wada T, Kanno M, Aoshima T, et al. Dose-dependent augmentation effect of bromocriptine in a case with refractory depression. Prog Neuropsychopharmacol Biol Psychiatry 2001; 25 (2): 457-62
66. Lattanzi L, Dell'Osso L, Cassano P, et al. Pramipexole in treatment-resistant depression: a 16-week naturalistic study. Bipolar Disord 2002; 4 (5): 307-14
67. Lawler CP, Prioleau C, Lewis MM, et al. Interactions of the novel antipsychotic aripiprazole (OPC-14597) with dopamine and serotonin receptor subtypes. Neuropsychopharmacol 1999; 20 (6): 612-27
68. Jordan S, Koprivica V, Dunn R, et al. In vivo effects of aripiprazole on cortical and striatal dopaminergic and serotonergic function. Eur J Pharmacol 2004; 483 (1): 45-53
69. Willner P, Hale AS, Argyropoulos S. Dopaminergic mechanism of antidepressant action in depressed patients. J Affect Disord 2005; 86 (1): 37-45
70. Papp M, Klimek V, Willner P. Parallel changes in dopamine D2 receptor binding in limbic forebrain associated with chronic mild stress-induced anhedonia and its reversal by imipramine. Psychopharmacology (Berl) 1994; 115 (4): 441-6
71. Moresco RM, Colombo C, Fazio F, et al. Effects of fluvoxamine treatment on the in vivo binding of [F-18]FESP in drug naive depressed patients: a PET study. Neuroimage 2000; 12 (4): 452-65
72. Bowden C, Theodorou AE, Cheetham SC, et al. Dopamine D1 and D2 receptor binding sites in brain samples from depressed suicides and controls. Brain Res 1997; 752 (1-2): 227-33
73. Zhang JY, Kowal DM, Nawoschik SP, et al. Distinct functional profiles of aripiprazole and olanzapine at RNA edited human 5-HT2C receptor isoforms. Biochem Pharmacol 2006; 71 (4): 521-9
74. Amargos-Bosch M, Artigas F, Adell A. Effects of acute olanzapine after sustained fluoxetine on extracellular monoamine levels in the rat medial prefrontal cortex. Eur J Pharmacol 2005; 516 (3): 235-8
75. Dawe GS, Huff KD, Vandergriff JL, et al. Olanzapine activates the rat locus coeruleus: in vivo electrophysiology and c-Fos immunoreactivity. Biol Psychiatry 2001; 50 (7): 510-20
76. Pira L, Mongeau R, Pani L. The atypical antipsychotic quetiapine increases both noradrenaline and dopamine release in the rat prefrontal cortex. Eur J Pharmacol 2004; 504 (1-2): 61-4
77. Myint AM, Kim YK, Verkerk R, et al. Kynurenine pathway in major depression: evidence of impaired neuroprotection. J Affect Disord 2007; 98 (1-2): 143-51
78. McEwen BS, Olie JP. Neurobiology of mood, anxiety, and emotions as revealed by studies of a unique antidepressant: tianeptine. Mol Psychiatry 2005; 10 (6): 525-37
79. Cosi C, Waget A, Rollet K, et al. Clozapine, ziprasidone and aripiprazole but not haloperidol protect against kainic acid-induced lesion of the striatum in mice, in vivo: role of 5-HT1A receptor activation. Brain Res 2005; 1043 (1-2): 32-41
80. Zarate Jr CA, Singh JB, Carlson PJ, et al. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. Arch Gen Psychiatry 2006; 63 (8): 856-64
81. Berman RM, Cappiello A, Anand A, et al. Antidepressant effects of ketamine in depressed patients. Biol Psychiatry 2000; 47 (4): 351-4

82. Zarate Jr CA, Singh JB, Quiroz JA, et al. A double-blind, placebo-controlled study of memantine in the treatment of major depression. Am J Psychiatry 2006; 163 (1): 153-5
83. Shelton RC. Olanzapine/fluoxetine combination for bipolar depression. Expert Rev Neurother 2006; 6 (1): 33-9
84. Post RM, Calabrese JR. Bipolar depression: the role of atypical antipsychotics. Expert Rev Neurother 2004; 4 (6 Suppl. 2): S27-33
85. Sachs G, Sanchez R, Marcus R, et al. Aripiprazole in the treatment of acute manic or mixed episodes in patients with bipolar I disorder: a 3-week placebo-controlled study. J Psychopharmacol 2006; 20 (4): 536-46
86. Keck Jr PE, Calabrese JR, McQuade RD, et al. A randomized, double-blind, placebo-controlled 26-week trial of aripiprazole in recently manic patients with bipolar I disorder. J Clin Psychiatry 2006; 67 (4): 626-37
87. Keck Jr PE, Marcus R, Tourkodimitris S, et al. A placebo-controlled, double-blind study of the efficacy and safety of aripiprazole in patients with acute bipolar mania. Am J Psychiatry 2003; 160 (9): 1651-8
88. Vieta E, Bourin M, Sanchez R, et al. Effectiveness of aripiprazole v. haloperidol in acute bipolar mania: double-blind, randomised, comparative 12-week trial. Br J Psychiatry 2005; 187: 235-42
89. Hamilton M. Development of a rating scale for primary depressive illness. Br J Soc Clin Psychol 1967; 6 (4): 278-96
90. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 1987; 13 (2): 261-76
91. Ketter TA, Wang PW, Chandler RA, et al. Adjunctive aripiprazole in treatment-resistant bipolar depression. Ann Clin Psychiatry 2006; 18 (3): 169-72
92. Guy W. ECDEU assessment manual for psychopharmacology, revised. Rockville (MD): National Institute of Mental Health, 1976. DHEW pub. no. (ADM) 76-338
93. Sachs GS, Thase ME, Otto MW, et al. Rationale, design, and methods of the systematic treatment enhancement program for bipolar disorder (STEP-BD). Biol Psychiatry 2003; 53 (11): 1028-42
94. Kemp DE, Gilmer WS, Fleck J, et al. Aripiprazole augmentation in treatment-resistant bipolar depression: early response and development of akathisia. Prog Neuropsychopharmacol Biol Psychiatry 2007; 31 (2): 574-7
95. Montgomery SA, Åsberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry 1979; 134: 382-9
96. Barbee JG, Conrad EJ, Jamhour NJ. The effectiveness of olanzapine, risperidone, quetiapine, and ziprasidone as augmentation agents in treatment-resistant major depressive disorder. J Clin Psychiatry 2004; 65 (7): 975-81
97. Rothschild AJ, Williamson DJ, Tohen MF, et al. A double-blind, randomized study of olanzapine and olanzapine/fluoxetine combination for major depression with psychotic features. J Clin Psychopharmacol 2004; 24 (4): 365-73
98. Shelton RC, Williamson DJ, Corya SA, et al. Olanzapine/fluoxetine combination for treatment-resistant depression: a controlled study of SSRI and nortriptyline resistance. J Clin Psychiatry 2005; 66 (10): 1289-97
99. Shelton RC, Tollefson GD, Tohen M, et al. A novel augmentation strategy for treating resistant major depression. Am J Psychiatry 2001; 158 (1): 131-4
100. Rapaport MH, Gharabawi GM, Canuso CM, et al. Effects of risperidone augmentation in patients with treatment-resistant depression: results of open-label treatment followed by double-blind continuation. Neuropsychopharmacology 2006; 31 (11): 2505-13
101. Dunner D, Amsterdam JD, Shelton RC, et al. Adjunctive ziprasidone for resistant depression: 8-week pilot study [abstract]. Eur Neuropsychopharmacol 2005; 15 Suppl. 3: 444
102. Barbee JG, Conrad EJ, Jamhour NJ. Aripiprazole augmentation in treatment-resistant depression. Ann Clin Psychiatry 2004; 16 (4): 189-94
103. Simon JS, Nemeroff CB. Aripiprazole augmentation of antidepressants for the treatment of partially responding and nonresponding patients with major depressive disorder. J Clin Psychiatry 2005; 66 (10): 1216-20
104. Patkar AA, Peindl K, Mago R, et al. An open-label, rater-blinded, augmentation study of aripiprazole in treatment-resistant depression. Prim Care Companion J Clin Psychiatry 2006; 8 (2): 82-7
105. Pae CU, Patkar AA, Jun TY, et al. Aripiprazole augmentation for treatment of patients with inadequate antidepressants response. Depress Anxiety 2007; 24 (7): 522-6
106. Worthington III JJ, Kinrys G, Wygant LE, et al. Aripiprazole as an augmentor of selective serotonin reuptake inhibitors in depression and anxiety disorder patients. Int Clin Psychopharmacol 2005; 20 (1): 9-11
107. Papakostas GI, Petersen TJ, Kinrys G, et al. Aripiprazole augmentation of selective serotonin reuptake inhibitors for treatment-resistant major depressive disorder. J Clin Psychiatry 2005; 66 (10): 1326-30
108. Berman RM, Marcus R, Swanink R, et al. Efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder: a multicenter, randomized, double-blind, placebo-controlled study (study CN138-139) [poster no. 310]. 160th Annual Meeting of the American Psychiatric Association; 2007 May 19-24; San Diego (CA)
109. Kim D, Berman RM, Marcus R, et al. Aripiprazole as adjunctive therapy in major depressive disorder with and without chronic features (CN138-139) [poster no. 283]. 160th Annual Meeting of the American Psychiatric Association; 2007 May 19-24; San Diego (CA)
110. Clinicaltrials.gov (a service of the US National Institutes of Health [online]. Available from URL: http://www.clinicaltrials.gov [Accessed 2007 May 1]
111. Connor KM, Payne VM, Gadde KM, et al. The use of aripiprazole in obsessive-compulsive disorder: preliminary observations in 8 patients. J Clin Psychiatry 2005; 66 (1): 49-51
112. Adson DE, Kushner MG, Fahnhorst TA. Treatment of residual anxiety symptoms with adjunctive aripiprazole in depressed patients taking selective serotonin reuptake inhibitors. J Affect Disord 2005; 86 (1): 99-104
113. Nickel MK, Muehlbacher M, Nickel C, et al. Aripiprazole in the treatment of patients with borderline personality disorder: a double-blind, placebo-controlled study. Am J Psychiatry 2006; 163 (5): 833-8

114. Goodman WK, Price LH, Rasmussen SA, et al. The Yale-Brown obsessive compulsive scale. I. Development, use, and reliability. Arch Gen Psychiatry 1989; 46 (11): 1006-11

115. Goodman WK, Price LH, Rasmussen SA, et al. The Yale-Brown obsessive compulsive scale: II. Validity. Arch Gen Psychiatry 1989; 46 (11): 1012-6

116. Hamilton M. The assessment of anxiety states by rating. Br J Med Psychol 1959; 32 (1): 50-5

117. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983; 67 (6): 361-70

118. Sheehan D. The anxiety disease. New York: Charles Scribner's Sons, 1983

119. Franke G. SCL-90-R: Symptom-checkliste von LR Derogatis. Goettingen: Beltz, 2002

120. Gao K, Muzina D, Gajwani P, et al. Efficacy of typical and atypical antipsychotics for primary and comorbid anxiety symptoms or disorders: a review. J Clin Psychiatry 2006; 67 (9): 1327-40

121. El-Sayeh HG, Morganti C. Aripiprazole for schizophrenia. Cochrane Database Syst Rev 2006; (2): CD004578

122. Nasrallah HA, Churchill CM, Hamdan-Allan GA. Higher frequency of neuroleptic-induced dystonia in mania than in schizophrenia. Am J Psychiatry 1988; 145 (11): 1455-6

123. BMS. Aripiprazole: prescribing information [online]. Available from URL: http://www.bms.com. [Accessed 2007 Mar 22]

124. Spina E, de Leon J. Metabolic drug interactions with newer antipsychotics: a comparative review. Basic Clin Pharmacol Toxicol 2007; 100 (1): 4-22

125. Duggal HS, Kithas J. Possible neuroleptic malignant syndrome with aripiprazole and fluoxetine. Am J Psychiatry 2005; 162 (2): 397-8

126. Duggal HS, Fetchko J. Serotonin syndrome and atypical antipsychotics. Am J Psychiatry 2002; 159 (4): 672-3

127. Hamilton S, Malone K. Serotonin syndrome during treatment with paroxetine and risperidone. J Clin Psychopharmacol 2000; 20 (1): 103-5

128. Aripiprazole: new drug. Just another neuroleptic. Prescrire Int 2005; 14 (79): 163-7

129. Keck Jr PE, McElroy SL, Strakowski SM, et al. Antipsychotics in the treatment of mood disorders and risk of tardive dyskinesia. J Clin Psychiatry 2000; 61 Suppl. 4: 33-8

130. Kasper S, Lerman MN, McQuade RD, et al. Efficacy and safety of aripiprazole vs haloperidol for long-term maintenance treatment following acute relapse of schizophrenia. Int J Neuropsychopharmacol 2003; 6 (4): 325-37

131. Srephichit S, Sanchez R, Bourgeois JA. Neuroleptic malignant syndrome and aripiprazole in an antipsychotic-naive patient. J Clin Psychopharmacol 2006; 26 (1): 94-5

132. Maytal G, Ostacher M, Stern TA. Aripiprazole-related tardive dyskinesia. CNS Spectr 2006; 11 (6): 435-9

133. Grant MJ, Baldessarini RJ. Possible improvement of neuroleptic-associated tardive dyskinesia during treatment with aripiprazole. Ann Pharmacother 2005; 39 (11): 1953

134. Molden E, Lunde H, Lunder N, et al. Pharmacokinetic variability of aripiprazole and the active metabolite dehydroaripiprazole in psychiatric patients. Ther Drug Monit 2006; 28 (6): 744-9

Correspondence: Dr *Chi-Un Pae*, Department of Psychiatry, Kangnam St Mary's Hospital, The Catholic University of Korea College of Medicine, Seoul 137-701, South Korea.
E-mail: pae@catholic.ac.kr