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Aripiprazole as adjunct to a mood stabilizer and citalopram in bipolar depression: a randomized placebo-controlled pilot study

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Objective The use of atypical antipsychotics (AAPs) for the treatment of unipolar and bipolar depression has been more and more frequently evaluated, and aripiprazole showed positive effects in the treatment of unipolar depression. However, no placebo-controlled studies of adjunctive aripiprazole for the treatment of bipolar depression have been performed yet.
Methods In this prospective, double-blind, placebo-controlled, randomized trial, 23 inpatients with bipolar depression according to DSM-IV criteria were included. Before randomization, patients had to be on a constant mood stabilizer treatment with lithium or valproate for at least 1 week. After inclusion, all patients were openly treated with additional citalopram and with additional aripiprazole or placebo for 6 weeks. The primary outcome parameter was the reduction in depressive symptoms according to the Hamilton Depression Rating Scale (HDRS) within 6 weeks.
Results After 6 weeks of treatment, the HDRS score decreased in both groups. There was no significant difference between both the groups at any point of time with respect to the HDRS.
Conclusions Derived from this small pilot study, adjunctive aripiprazole does not seem to be a promising strategy for the acute treatment of bipolar depression. However, this lack of additional benefit seems to stem from the already good effectiveness of the control group, namely the treatment with citalopram. Copyright © 2010 John Wiley & Sons, Ltd.

KEY WORDS — aripiprazole; bipolar depression; bipolar disorder; combination therapy; antidepressant; mood stabilizer

OBJECTIVE

Bipolar disorder is a very serious disease with a lifetime prevalence of 0.8–1.5% regarding bipolar I disorder and up to 5% regarding the whole bipolar spectrum (Angst and Sellaro, 2000). In comparison to general population, risk of death due to suicide is estimated to be approximately 20 times higher (Sharma and Markar, 1994) and, despite therapeutic efforts, the risk of a chronic course is relatively high. About 75% of the patients have a recurrent episode within 5 years (Tohen *et al*., 2000). The burden of disease is high and mainly a consequence of depressive episodes and symptoms. The depression/mania frequency ratio during the course of the disease is about 3:1 (Kupka *et al*., 2007), and depressive episodes last longer, are harder to treat, and patients suffer more than during their manic episodes (Angst and Sellaro, 2000). The understanding and treatment of a depressive episode is the present challenge regarding bipolar disorder. Compared to the treatment of manic episodes, there are only a few studies depicting the treatment of depression in bipolar disorder up to now.

The treatment with an antidepressant alone is impaired by the risk of triggering a switch into a manic episode. This risk as discussed in the literature is 25–30% for tricyclic antidepressants and 10–15% for selective serotonin reuptake inhibitors (SSRIs) (Hausmann *et al*., 2007; Moller and Grunze, 2000; Sachs *et al*., 2000). According to more recent data from the National Institute of Mental Health (NIMH) systematic treatment enhancement program for bipolar disorder (STEP-BD) the general switch rate is up to 44%, according to retrospective, self-reported switch events (Truman *et al*., 2007). There seems to be no increased risk for a treatment-emergent switch to mania if the antidepressant is accompanied by a mood stabilizer (Carlson *et al*., 2007; Leverich *et al*., 2006; Sachs *et al*., 2007).

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There is an increasing body of data which shows that the combination of an SSRI and an atypical antipsychotic (AAP) may enhance antidepressive efficacy, at least in unipolar depression, irrespective of the existence of psychotic symptoms. This has been shown for olanzapine and risperidone (Ostroff and Nelson, 1999; Shelton *et al*., 2001) and recently for aripiprazole (Philip *et al*., 2008; Schule *et al*., 2007). In November 2007, the FDA has approved aripiprazole as an add-on for patients whose major depressive disorder is not relieved by antidepressants alone.

However, there are only a few placebo-controlled studies examining AAPs in the treatment of bipolar depression. Only olanzapine (in combination with fluoxetine) and quetiapine (monotherapy) are FDA approved for bipolar depression due to positive randomized placebo-controlled trials (RCTs) (Calabrese *et al*., 2005; Tohen *et al*., 2003).

However, compared to these and other AAPs, long-term treatment with aripiprazole is associated with less weight gain (Gentile, 2006). Weight gain is an important issue in the long-term treatment of bipolar disorder especially regarding treatment compliance (Johnson *et al*., 2007). The prevalence of obesity and metabolic syndromes in bipolar patients is significantly higher than in the normal population (Bauer *et al*., 2008).

Aripiprazole, a novel second-generation antipsychotic, has been approved for the treatment of acute manic and mixed episodes and for long-term maintenance therapy in bipolar I disorder (Fleischhacker, 2005). In a double-blind, placebo-controlled study aripiprazole was effective in preventing a manic episode in bipolar I disorder over a 100-week treatment period (Keck, Jr *et al*., 2007). There are also placebo-controlled, randomized studies of aripiprazole in acute manic or mixed episodes in patients with bipolar I disorder, which showed a superior efficacy of the substance compared to placebo (Sachs *et al*., 2006). There are indices that bipolar disorder is associated with an alteration of the dopaminergic system and that bipolar depression may be associated with a deficient dopamine function (Yatham *et al*., 2005). As a partial D2 receptor agonist, aripiprazole can therefore be assumed to be effective in the treatment of bipolar depression.

Considering the positive effects of pramipexole, a full dopamine D2/D3 receptor agonist, in the treatment of bipolar depression, this proposition can be supported (Goldberg *et al*., 2004). Moreover, aripiprazole is an antagonist at serotonin 5-HT2A receptors and is also a partial agonist at 5-HT1A receptors as well as an inhibitor of the 5-HT transporter (Keck and McElroy, 2003). These properties of aripiprazole have been hypothesized to mediate its putative antidepressant effects (Keck and McElroy, 2003) especially when combining aripiprazole with a SSRI, which may lead to an additive antidepressant effect. Moreover, aripiprazole has a low interaction potential with other drugs (Conley and Kelly, 2007), which again makes it interesting for the use in bipolar disorder where combination therapies are often necessary. According to a study by Post *et al*. (2003) only 20% of the bipolar patients can be stabilized on monotherapy, whereas 25% need even four drugs or more.

In some studies, including RCTs, aripiprazole showed significant antidepressant properties: the adjunctive use of aripiprazole in patients with major depression, who had responded unsatisfyingly to an antidepressant therapy, was efficient and well-tolerated (Berman *et al*., 2007). For the use of aripiprazole in acute bipolar depression, two open trials showed beneficial effects of aripiprazole mono- and adjunctive treatment: depressive symptoms significantly improved during a 6- and 8-week period, respectively (Dunn *et al*., 2008; McElroy *et al*., 2007). By contrast, two double-blind placebo-controlled trials showed no significant effect of aripiprazole monotherapy in the treatment of bipolar depression (Thase *et al*., 2008). To our knowledge, no placebo-controlled studies of adjunctive aripiprazole to an antidepressant, especially to an SSRI, for the treatment of bipolar depression, have been performed yet. The aim of this study was thus to investigate the acute effect and the tolerability of aripiprazole as adjunct to an SSRI (citalopram) and a mood stabilizer (lithium or valproate) in patients with bipolar depression.

METHODS

The study was approved by the ethics committee of Berlin. Written informed consent was obtained from all participants after the study procedures had been fully explained, before study participation. Twenty-three inpatients with bipolar-1 or -2 disorder with a current non-treatment-resistant depressive episode according to DSM-IV criteria were included in this prospective, double-blind, placebo-controlled, randomized trial. Severity of depression was rated with the Hamilton Depression Rating Scale (HDRS, 21-item version) (Hamilton, 1960), and a score of ≥ 20 was required for inclusion in the study.

Patients with at most one antidepressant treatment course before randomization and a duration of their respective episode of ≤ 6 months were classified as non-treatment resistant. Patients with a history of rapid

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cycling and substance abuse were excluded. Before randomization, patients had to be on a stable mood stabilizer treatment with lithium or valproate (with sufficiently high plasma levels: for lithium 0.5–1.0 mmol/l, for valproate 50–100 mg/dl) for at least 1 week. Thus, only patients without response to the above-described treatment for at least 1 week were randomized. See Table 1 for the baseline demographic characteristics.

After inclusion, every patient received citalopram, starting with 20 mg/day. This dose was increased to 40 mg/day after 3 days.

Patients were then randomly assigned in a 1:1 ratio to either aripiprazole (15 mg/day) or placebo. After 2 weeks this dose could be changed to 10 mg/day or 30 mg/day. Reduction of the doses due to intolerable side effects was allowed at any time up to a minimum of aripiprazole/placebo of 10 mg/day and citalopram of 20 mg/day. Lithium and valproate had to be kept on stable doses sufficiently high to maintain therapeutic serum levels. All other psychotropic medication was discontinued before randomization. After 6 weeks, patients had the opportunity to receive aripiprazole in an open label design. Regarding concomitant medication, lorazepam with up to 2 mg/d, and zolpidem (10 mg/d) or zopiclone (7.5 mg/d) were permitted during the whole study period to treat anxiety or agitation, and insomnia, respectively.

The primary outcome was the reduction of the HDRS within 6 weeks. Response was defined as a $\geq 50\%$ reduction in the HDRS total score as compared to baseline. Remission was defined as a HDRS total score of ≤ 9. Secondary outcomes were the duration until response or remission, the reduction of the Montgomery-Åsperg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979), the amount of side-effects such as akathisia (measured with the Barnes Akathisia Rating Scale (BAS) (Barnes, 1989)), and switches to manic episodes. Additional assessments of effectiveness included the Clinical Global Impression Scale modified for Bipolar Illness (CGI-BP) (Spearing *et al.*, 1997), the Young Mania Rating Scale (YMRS) (Young *et al*., 1978), and the Beck Depression Inventory (BDI) (Beck *et al*., 1961). All ratings were carried out by an experienced psychiatrist on a weekly basis. Moreover, quality of life was measured with the SF12-questionaire (Ware, Jr *et al*., 1996), a self-rating-scale estimating the patients' global physical condition, at baseline and at the end of the study after 6 weeks of treatment.

ECG, a routine blood sample, and the serum concentrations of prolactine, lihium, and valproate were assessed at baseline, at week 3 and after 6 weeks of treatment.

Table 1. Demographic characteristics at baseline. Data depicted as means (SD)

	Aripiprazole group	Placebo group
Age	53.6 (14.38)	48.2 (6.74)
Sex	$f=5$, m = 6	$f=6$, m = 6
Bipolar-1 disorder	$n=9$	$n=8$
Bipolar-2 disorder	$n=3$	$n=3$
Weight	76.5 (11.2)	70.9 (10.0)
Lithium serum concentration	0. 71 mmol/l (0.12)	0.70 mmol/l (0.14)
Valproate serum concentration	55.4 mg/dl (21.48)	75.15 mg/dl (28.46)

DATA ANALYSIS

By means of χ^2-tests the distribution of gender in the two groups was controlled, and amount of dropouts between the two groups were compared. Independent samples' *t*-tests were performed to compare age, weight, lithium, and valproate serum concentrations at baseline. Differences between HDRS and MADRS scores, as well as BDI ratings were assessed via *t*-tests at all visits. *t*-tests for paired samples were computed to control for possible weight gain and increase of prolactine during study scope.

CGI, Global Assessment of Functioning (GAF), YMRS ratings, SF-12-Questionaire and BAS were compared by *t*-tests at baseline and after 6 weeks. We applied a repeated-measures two-way analysis of variance (ANOVA) to compare the decreases of HDRS and MADRS ratings during the study between the two groups. All means are reported $\pm$ standard deviation (SD). Significant effects yielded by the ANOVA degrees of freedom were Greenhouse-Geisser corrected when appropriate. The α-level was set at 0.05.

RESULTS

Of the 23 randomized patients, 12 subjects were assigned to receive aripiprazole. The mean dosage of aripiprazole was 16.8 mg/day ($\pm$ 2.4) after adapting the individual dosages within the study's scope. Eleven subjects received placebo. Eighteen patients (78. 3%) completed 6 weeks of treatment, 5 patients dropped out due to side effects including akathisia ($n=2$ patients in the aripiprazole group), QTc-prolongation ($n=1$ patient in the placebo group), pneumonia ($n=1$ in the aripiprazole group) and nausea ($n=1$ in the aripiprazole group). Concomitant psychotropic medication (lorazepam or zopiclone) to treat sleep disturbance

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or agitation was used in five patients in the aripiprazole group, and in one patient in the placebo group.

χ^2-tests revealed no significant differences between the distribution of females and males in the two groups (aripipazole group: 6m/6f; placebo group: 6m/5f; $\chi^2 = 0.17$; $p =$ n.s.). There were also no differences in the ratio of dropouts (DO) vs. completers (COM) between the two groups (aripiprazole group: 3DO/9COM; placebo group: 2DO/9COM; $\chi^2 = 0.2$; $p =$ n.s.).

t-tests revealed no differences between age ($t[17] = 1$; $p =$ n.s.), weight ($t[17] = 1.1$; $p =$ n.s.), lithium ($t[8] = 0.1$; $p =$ n.s.), or valproate serum concentrations ($t = [9] - 1.1$; $p =$ n.s., Table 1) at baseline. *t*-tests did not yield any significant group differences with respect to depressivity scores (HDRS; all $ts[17] < -0.6$, $p =$ n.s.; MADRS: all $ts[17] < -0.9$, $p =$ n.s.; BDI: all $ts[17] < -1.8$, $p =$ n.s. at baseline, as well as after any visit. Likewise, *t*-tests show comparable YMRS scores in both groups at any point in time (all $ts[17] < 1.5$, $p =$ n.s; see also Table 2 for YMRS scores at baseline and week 6).

At T6 ($n = 18$) there were altogether 12 remitters (67%, aripiprazole $n = 6$, placebo $n = 6$), 5 responders (28%, aripiprazole $n = 2$, placebo $n = 3$), and 1 non-responder (5%, in the placebo group) in the study. As shown in Table 2, there were no significant differences in the mean HDRS and MADRS scores at baseline. Both scores decreased in both groups after 6 weeks of treatment. At the end of the study, the mean HDRS score was 7.29 points (SD 3.81) in the aripiprazole group and 7.67 points (SD 8.15) in the placebo group.

Repeated measures two-way ANOVAs revealed significant effects for HDRS: $F[2,6] = 57.0$; $p < 0.001$ and MADRS: $F[3,3] = 35.4$; $p < 0.001$ for the factor ''time''; (Table 2 and Figure 1), indicating a significant decrease of the scores over time. No significant differences of the decrease of depression scores between both groups could be observed with respect to interaction effects ''time × group'' (HDRS: $F[2,6] = 1$; $p =$ n.s; MADRS: $F[2,6] = 1$; $p =$ n.s.; see Table 2 and Figure 1).

Table 2. Mean (SD) outcome scores at baseline and after 6 weeks of treatment

	Aripiprazole group		Placebo group	
	Baseline	Week 6	Baseline	Week 6
HDRS-21	26.00 (4.87)	7.29 (3.81)	23.10 (5.44)	7.67 (8.15)
MADRS	29.56 (7.23)	6.71 (6.7)	25.30 (8.27)	7.56 (7.0)
YMRS	2.78 (2.33)	3.71 (6.84)	1.20 (1.98)	0.33 (0.7)
BDI	23.67 (13.2)	3.33 (3.98)	23.70 (11.7)	10.5 (8.98)
GAF	43.11 (9.5)	70.57 (19.6)	42.80 (8.57)	66.13 (15.8)

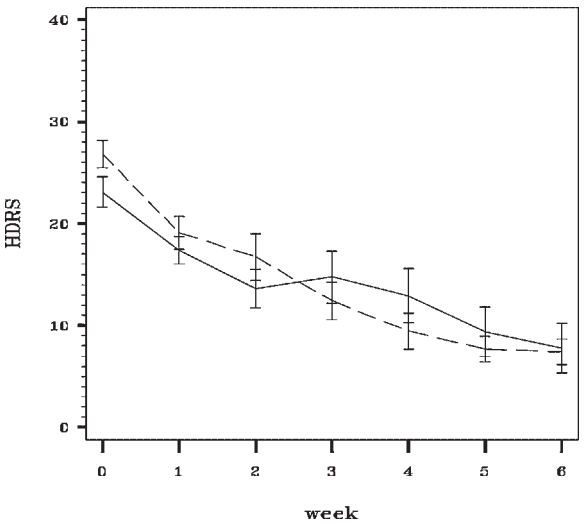

Figure 1. Depression scores (means ± 1 SD) of the aripiprazole (dashed line) and placebo (solid line) groups across time

Thus, there was no significant effect of additional aripiprazole in comparison to placebo after 6 weeks. Moreover, two subjects treated with aripiprazole experienced akathisia as a relevant side effect which led to discontinuation. A *t*-test detected a trendwise higher BAS score in the aripiprazole group (1.3 ± 1.4 vs. 0.1 ± 0.4; $t[6,6] = 2.2$; $p = 0.07$) at week 6.

Paired-samples' *t*-tests indicated neither significant weight gain (baseline: 75.5 ± 11.7 kg vs. week 6: 74.7 ± 12 kg, $t[11] = 1.4$, $p =$ n.s.) nor elevation of prolactine serum levels (baseline: 98.5 ± 136.8 nmol/l vs. week 6: 62.5 ± 143.7 nmol/l, $t[11] = 0.6$, $p =$ n.s.) in the whole study population from baseline to end of study.

The repeated-measures two-way ANOVA yielded that the patients' global physical condition, as rated by the SF12, improved significantly across patient groups from baseline throughout the end of the study (main effect ''time'': $F[1] = 15$; $p < 0.004$). However, the interaction (group × time) did not prove to be significant ($F[9] = 0.6$; $p =$ n.s.).

DISCUSSION

Derived from this small pilot study, adjunctive aripiprazole does not seem to be a promising strategy for the acute treatment of bipolar depression. After 6 weeks of treatment, there were no statistically significant additional effects in the aripiprazole group in comparison to the placebo group regarding the primary and secondary outcome parameters. However, this lack of additional benefit seems to stem from the

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already good effectiveness of treatment in the control group, i.e., the additional citalopram to their respective mood stabilizer. The remission rates in both groups were surprisingly high, which might be related to our study population. We only included bipolar inpatients with a non-treatment-resistant depressive episode. However, many bipolar patients have a longer duration of illness (>6 months) than that of our study population, a history of polypharmacy and substance abuse. Our study population was rather exclusive and possibly a minority population within the bipolar spectrum. No severe side effects occurred in both groups. Only in the aripiprazole group, two patients suffered from akathisia and had an increased Barnes Akathisia scale. It has to be noted that the use of concomitant medication because of agitation and sleep disturbance was higher in the aripiprazole group.

These results are similar to the findings of recently published studies by Thase *et al*. (2008): taken together 833 patients with a bipolar depressive episode participated in their 2 placebo-controlled, randomized trials, and 373 patients were randomized to aripiprazole (monotherapy treatment). In the aripiprazole group, statistically significant differences were observed during the first 5 weeks, but there was no statistically significant effect of aripiprazole monotherapy versus placebo after 8 weeks of treatment (end point). Moreover, the discontinuation rate was significantly higher due to side effects, especially due to akathisia, in the aripiprazole group. There are also studies showing positive effects of aripiprazole in the treatment of unipolar depression, especially in the combination with an SSRI: in the studies of Berman *et al*. (2007) and Marcus *et al*. (2008), adjunctive aripiprazole to an SSRI led to significant improvements of depressive symptoms in patients who incompletely responded to an SSRI alone before. For bipolar depression, there is not much evidence showing antidepressive properties for aripiprazole: only two open trials showed significant positive effects of adjunctive aripiprazole or monotherapeutic treatment (Dunn *et al*., 2008; McElroy *et al*., 2007). Another study conducted a chart review to examine the effect of aripiprazole as an augmentation strategy to different psychotrophic medications (including antidepressants, antipsychotics, and mood stabilizers) in treatment-resistant bipolar depression. In this small study, only four out of 12 patients showed a response (defined as 50% reduction in the MADRS) and five out of 12 patients developed akathisia. This suggests that the usefulness of aripiprazole in the treatment of bipolar depression, in contrast to unipolar depression, may be limited by insufficient antidepressant efficacy, at least partially due to good effectiveness of the comparator, and high incidence of akathisia (Kemp *et al*., 2007).

The only placebo-controlled trials of aripiprazole for the treatment of bipolar depression were the two studies conducted by Thase *et al*. (2008), but the design of these studies deviated from European treatment principles for bipolar depression. Thase *et al*. examined an aripiprazole monotherapy and not a combination with an antidepressant and/or a mood stabilizer. However, there is evidence that antipsychotic monotherapy can be effective in bipolar depression, e.g., with quetiapine which has been approved to be used monotherapeutically for the treatment of bipolar disorder.

Adjunct aripiprazole to an SSRI has been shown to lead to significant improvements in the treatment of unipolar depression. It has even been FDA approved for this indication.

There is an ongoing debate whether, despite having identical phenotypes, unipolar- and bipolar depression may be two distinct disorders regarding pathophysiology, which entails the question of whether these two depressive syndromes have to be treated differently, even regarding only the acute antidepressive treatment, without taking into account long-term course considerations like switch-risk or cycle acceleration. To answer this question, RCTs are needed that evaluate the antidepressant effect of treatments in a similar design in unipolar- vs. bipolar depression. Sachs *et al*. (2007) examined the effectiveness of adjunctive antidepressant treatment (with paroxetine or bupropion) for bipolar depression, and they came to the surprising result, that there was no positive effect of adjunctive antidepressants to standard mood stabilizers in comparison to adjunctive placebo. Assuming that the antidepressant effect of the mood stabilizer is negligible, which is questionable, this result may identify the treatment with antidepressants as the first treatment that works differently in unipolar- vs. bipolar depression.

Consistent with the results obtained by Thase *et al*. (2008), our findings confirm a lack of efficacy of aripiprazol in bipolar depression. Considering the positive results of the RCTs of Berman *et al*. and Marcus *et al*. (2007; 2008) regarding the efficacy of aripiprazole in unipolar depression, one might assume a different efficacy of the substance depending on the type of depression (unipolar vs. bipolar). The relative high incidence of akathisia with aripiprazole mirrors preliminary results that bipolar patients, especially in depression, were more vulnerable to acute antipsychotic-induced movement disorders than those with schizophrenia (Gao *et al*., 2008).

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Taken together, these findings suggest that aripiprazole, both as an adjunct to an SSRI plus mood stabilizer and as a monotherapy, does not seem to have additional positive effects for the treatment of acute bipolar depression after a longer duration of treatment (in our study within 6 weeks).

However, there are also limitations considering the comparison of our study with the positive findings of Berman *et al*. and Marcus *et al*. Their design differed from ours in the sense that they added aripiprazole to partial responders to the SSRI, and we combined aripiprazole with the SSRI from the beginning. Furthermore, Berman, Marcus and colleagues had used lower doses of arpiprazole. Both factors might have favored a positive antidepressant effect of aripiprazole when added to an SSRI. Secondly, treatment guidelines suggest the use of mood stabilizers as a monotherapy as a first line strategy for bipolar depression. Positive effects of such a treatment could be expected after a longer duration of treatment. In our study, participants had to be on a mood stabilzer for only at least 1 week. Moreover, the use of a serotonin-reuptake-inhibitor *per se* causes antidepressive effects. At last, the small sample size is a limitation in itself. Putative positive effects of aripiprazole could have been missed with our study design. For confirmation of our findings, further studies with a higher number of participants are needed.

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