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ORIGINAL RESEARCH

Long-term safety and tolerability of open-label aripiprazole augmentation of antidepressant therapy in major depressive disorder

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Background: Effective management of major depressive disorder often includes the long-term use of multiple medications, and the longer-term utility and safety of adjunctive aripiprazole has not been evaluated in a controlled setting.

Patients and methods: Patients (n = 706) completing one of two 14-week double-blind studies of aripiprazole augmentation, as well as de novo patients (n = 296) nonresponsive to current antidepressant therapy, were enrolled in this open-label study. Patients received open-label aripiprazole for up to 52 weeks.

Results: Open-label treatment was completed by 323 patients (32.2%). At endpoint (n = 987), the mean dose of aripiprazole was 10.1 mg/day. Common ($>$15% of patients) spontaneously reported adverse events were akathisia (26.2%), fatigue (18.0%), and weight gain (17.1%). The incidence of serious adverse events was 4.0%. Four spontaneous reports of possible tardive dyskinesia were submitted (0.4%); all resolved within 45 days of drug discontinuation. Mean weight change was 4.4 kg; 36.6% experienced $\geq$7% increase in weight from baseline (observed case analysis, n = 303). No clinically relevant changes in other metabolic parameters were seen. At the end of open-label treatment, 221 patients (69.7%) had a Clinical Global Impression-Severity of Illness score of 1 (not at all ill) or 2 (borderline ill).

Conclusion: Long-term adjunctive aripiprazole therapy was well tolerated with an acceptable long-term safety and tolerability profile in patients with major depressive disorder who had not responded to treatment with one or more antidepressant therapies. Clinically significant weight gain was observed in about one-third of patients. Overall, the adverse event profile was consistent with that reported in the short-term trials and readily managed clinically.

Keywords: adjunctive aripiprazole, antidepressant therapy, major depressive disorder, long-term safety and tolerability

Introduction

More than 60% of patients with major depressive disorder do not achieve remission following treatment with an adequate course of at least one antidepressant.[1,2] For patients who do not obtain adequate benefit from antidepressant therapy, adjunctive therapy with an atypical antipsychotic is one treatment option.[3,4]

Aripiprazole, a partial agonist at the D_2/D_3 receptor and 5-HT$_{1A}$ receptor, and a full antagonist at the 5-HT$_{2A}$ receptor, is approved for use in the US as a treatment adjunctive to antidepressant therapy in adults with major depressive disorder. Results from three large, multicenter, randomized, double-blind, placebo-controlled trials demonstrated that aripiprazole treatment is effective and well tolerated as treatment adjunctive to antidepressant therapy in subjects with an inadequate response to a prospective

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eight-week trial of the same antidepressant therapy and at least one historical antidepressant therapy trial.[5–7] In these short-term major depressive disorder trials, adjunctive aripiprazole demonstrated a safety and tolerability profile similar to that seen in monotherapy studies of patients with schizophrenia[8] or bipolar mania.[9] Furthermore, the rates of discontinuation due to adverse events were low.[5–7] However, in order to prevent recurrence of major depressive episodes, patients with major depressive disorder may require long-term maintenance therapy. The utility, safety, and tolerability of long-term adjunctive aripiprazole therapy have not yet been studied.

The introduction of any new treatment strategy requires extra vigilance with regard to safety, particularly for combination treatment strategies where each class of medication has potential side effects.[10,11] Furthermore, augmentation of standard antidepressant therapies has the potential to induce, or even exacerbate, adverse events. Adverse events commonly seen with atypical antipsychotic monotherapy include weight gain, sedation, extrapyramidal symptoms, metabolic disturbances (eg, diabetes and hyperlipidemia) and hyperprolactinemia, although the risk varies between agents.[12–14] Understanding the longer-term safety and tolerability profile of adjunctive treatment is important in order to optimize clinical management and promote long-term adherence when appropriate.

This paper reports the findings from a 52-week, open-label trial that assessed the long-term safety and tolerability of aripiprazole adjunctive to antidepressant therapy. Assessment of tolerability was the primary objective of this study, and was evaluated by spontaneous reporting of adverse events, assessment of extrapyramidal symptoms using objective rating scales, and assessment of changes in body weight, fasting plasma lipids, and glucose levels. Specific efficacy findings from this long-term, open-label safety extension phase are also presented. Eligible patients included those who had been previously treated with adjunctive aripiprazole or placebo in two of the previous short-term trials,[5,6] as well as de novo subjects with a documented inadequate response to standard antidepressant therapy.

Methods
Study design and patients

This report includes data from a 52-week, open-label study to assess the long-term safety and tolerability of aripiprazole adjunctive to antidepressant therapy. In this reporting, duration of adjunctive aripiprazole dosing includes any exposure a patient may have received in the short-term trials, and any

adverse events that may have emerged upon initiation of adjunctive aripiprazole treatment in those trials.

This study enrolled patients from two sources, ie, patients who had previously been enrolled in two 14-week, double-blind, placebo-controlled trials[5,6] (rollover patients), as well as de novo patients. Rollover patients entering this open-label study from the previously completed 14-week trials had to have had an inadequate response to a prospective antidepressant therapy treatment (venlafaxine, escitalopram, paroxetine, fluoxetine, or sertraline) at week 8 and have completed an additional six-week, randomized, double-blind period with adjunctive aripiprazole (aripiprazole rollover) or placebo (placebo rollover) treatment. Patients who had been antidepressant therapy responders at week 8, and thus were not eligible for randomization, could enter the open-label phase if they did not meet criteria for remission (Montgomery-Åsberg Depression Rating Scale [MADRS][15] ≤10) at week 14.

The patients were men and women, aged 18 years and older, who met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition-Text Revision (DSM-IV-TR) criteria for a major depressive episode.[16] All rollover patients entering this open-label study met the following inclusion criteria at the time of entry into the previously completed double-blind study: they were required to have had a major depressive episode that had lasted at least eight weeks prior to inclusion with an inadequate response, defined as a <50% reduction in depressive symptoms severity, as assessed by the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire [ATRQ][17] to at least one but no more than three antidepressant therapy trials (each of at least six weeks' duration and at an adequate dose). Following screening, patients could then enter an eight-week prospective antidepressant treatment phase if they had a 17-item Hamilton Rating Scale for Depression (HAM-D-17)[18] total score ≥18 and could continue into the double-blind treatment phase if they had a HAM-D-17 total score that represented a <50% reduction in symptoms during prospective treatment, a HAMD-17 total score ≥14, and a Clinical Global Impressions-Improvement (CGI-I)[19] score ≥3. For entry into this long-term study, patients were also required to have the potential to benefit from further pharmacological adjustments (administration of adjunctive aripiprazole) based on the opinion of the investigator.

Inclusion criteria for de novo patients were similar to those for rollover patients, and included a duration of current depressive episode of at least eight weeks, an inadequate response indicated by a <50% improvement on the Massachusetts General Hospital Antidepressant Treatment

Response Questionnaire to at least one but no more than four antidepressant therapy trials (each of at least six weeks' duration and at an adequate dose) and a MADRS total score >10 at baseline and, in the opinion of the investigator, had residual symptoms that may have benefited from pharmacologic modification. De novo patients were also required to be currently taking antidepressant therapy at an adequate dose for a minimum of six weeks by the end of the screening phase. In addition to antidepressant therapies permitted in rollover patients, de novo patients were also permitted to be receiving mirtazapine, bupropion, bupropion sustained-release, bupropion extended-release, or duloxetine.

Both rollover and de novo patients were excluded if they had a current Axis I diagnosis of delirium, dementia, amnestic or other cognitive disorder, schizophrenia or other psychotic disorder, bipolar I or II disorder, eating disorder, or a clinically significant current Axis II diagnosis of borderline, antisocial, paranoid, schizoid, schizotypal, or histrionic personality disorder. Patients who posed a suicide risk were also excluded.

All subjects were required to provide written informed consent to participate and to be willing to discontinue all prohibited psychotropic medication (see below). The study was conducted in accordance with the Declaration of Helsinki, and the ethics committee at each site approved the protocol.

Study treatments

All rollover patients continued to receive their antidepressant therapy at the final prescribed dose in the previous trial in accordance with current product labeling, ie, escitalopram 10–20 mg/day, fluoxetine 20–40 mg/day, paroxetine controlled-release 37.5–50 mg/day (paroxetine 20–40 mg/day could be substituted if paroxetine controlled-release was not available), sertraline 100–150 mg/day, or venlafaxine extended-release 150–225 mg/day. De novo patients were permitted to receive these antidepressant therapies but could also receive bupropion sustained-release 300–400 mg/day, bupropion extended-release 150–450 mg/day, bupropion 300–450 mg/day, duloxetine 40–60 mg/day, or mirtazapine 15–45 mg/day. All patients were required to continue on their initial antidepressant therapy treatment and were not allowed to switch antidepressant medications during the course of open-label treatment. Dose adjustment of antidepressant therapy during the open-label treatment period was permitted for optimal therapeutic effect within the recommended dose range, although dose adjustment of antidepressant therapy should not be made within the same week as aripiprazole

dose adjustment. Concomitant use of psychotropic agents (neuroleptics, anticonvulsants, antidepressants [other than continued antidepressant therapy], mood stabilizers, opioid analgesics, stimulants and barbiturates [except for migraine]) were prohibited during the study. Treatment of extrapyramidal symptoms (benztropine ≤6 mg/day, propranolol ≤120 mg/day) was also permitted during the study except within 12 hours prior to administration of movement rating scales. Clinically appropriate use of benzodiazepines and other hypnotics was permitted during the study (eg, diazepam, lorazepam, zolpidem, and zaleplon).

All patients, regardless of whether they received aripiprazole in the prior double-blind studies, started open-label, adjunctive treatment with aripiprazole 5 mg/day. If the 5 mg dose was well tolerated, the dose was increased to 10 mg/day at the end of week 1. The target dose of aripiprazole was 10 mg/day. Dose adjustments were made based on the clinical judgment of the investigator with respect to tolerability and therapeutic efficacy within the range 2–30 mg/day for patients receiving venlafaxine extended-release, escitalopram, mirtazapine or sertraline; or 2–15 mg/day for patients on fluoxetine, paroxetine, duloxetine, or bupropion (all CYP2D6 inhibitors).

Assessments and statistical analyses

Subjects had study visits at the end of weeks 1, 2, 4, 6, 8, 14, 20, 26, 32, 38, 44, and 52 during open-label treatment or at study termination. Safety was evaluated by monitoring of adverse events and vital signs (at each study visit), body weight (weeks 26 and 52,) and a 12-lead electrocardiogram (weeks 8, 26, and 52). In addition, extrapyramidal symptoms were evaluated using the Simpson-Angus Scale (SAS),[20] and Barnes Akathisia Clinical Assessment (BARS)[21] at weeks 4, 8, 14, 26, 38, and 52, and the Abnormal Involuntary Movement Scale (AIMS)[22] at weeks 4, 8, 14, 20, 26, 32, 38, 44, and 52.

Laboratory tests, including fasting metabolic parameters, were conducted at open-label treatment weeks 8, 26, 38, and 52. Metabolic changes were assessed by mean and median change from baseline to endpoint in fasting levels of total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, triglycerides, and plasma glucose.

Efficacy was assessed at every study visit using the Clinical Global Impression-Severity of Illness (CGI-S) rating scale (1, normal, not at all ill; 2, borderline mentally ill; 3, mildly ill; 4, moderately ill; 5, markedly ill; 6, severely ill; or 7, extremely ill).[19] No other efficacy assessments were conducted.

Safety analyses included all patients who received at least one dose of open-label study medication (safety sample), whereas efficacy analyses included all patients in the safety sample who had at least one CGI-S assessment in the open-label treatment phase (efficacy sample). All analyses were based on the last observation carried forward or observed case datasets.

For patients who had received aripiprazole during weeks 8–14 in the previously completed double-blind studies (aripiprazole rollover patients), baseline for assessment of adverse events, discontinuation due to adverse events, weight, metabolic measures, and extrapyramidal symptoms were defined at week 8 during the short-term trial (ie, prior to the first aripiprazole exposure). Thus, the maximum duration of aripiprazole treatment for rollover patients was 58 weeks (six weeks of double-blind aripiprazole treatment plus 52 weeks of open-label treatment). Demographic and disposition data for aripiprazole rollover patients used assessments from the week 14 visit from the previous study as the baseline measurement. For de novo and placebo rollover patients, baseline was defined using measurements from the start of aripiprazole treatment. Summary statistics for safety data are presented, including mean and standard deviation for continuous variables, and frequency and percent frequency for categorical variables. Rating scale scores are presented as mean change from baseline. No formal statistical testing was planned.

Results
Patient population and treatment
In total, 1076 patients (rollover, n = 706; de novo, n = 370) provided informed consent for study participation, of whom 1002 entered the open-label treatment phase (rollover, n = 706; de novo, n = 296). Patient disposition is shown in Figure 1 and the characteristics of patients included in the safety analyses are shown in Table 1. In total, 323 patients (32.2%) completed 52 weeks of open-label treatment; completion rates were similar between the rollover and de novo groups (Figure 1). Overall, the most common reasons for withdrawal from the open-label treatment phase were adverse events (23.0%), lack of efficacy/relapse (13.5%), and withdrawal of consent (12.5%). Time to discontinuation of aripiprazole due to any reason during open-label treatment is shown in Figure 2.

Treatment and dosing
The distribution of antidepressant therapy at study endpoint (n = 984) was consistent with the distribution at open-label study baseline and was as follows: escitalopram, n = 275 (27.7%); venlafaxine extended-release, n = 249 (25.1%);

sertraline, n = 171 (17.2%); fluoxetine, n = 143 (14.4%); paroxetine controlled-release, n = 61 (6.1%); paroxetine, n = 29 (2. 9%); bupropion extended-release, n = 35 (3.5%); bupropion sustained-release, n = 11 (1.1%); duloxetine, n = 7 (0.7%); and mirtazapine, n = 3 (0.3%).

At endpoint (n = 987), the mean dose of aripiprazole was 10.1 mg/day for the total population. During the last four-weekly dosing interval during the open-label phase (open-label treatment weeks 48–52, n = 320), the distribution of adjunctive aripiprazole dosing was as follows: 2 mg/day, 10.9%; 5 mg/day, 25.6%; 10 mg/day, 28.8%; 15 mg/day, 20.3%; 20 mg/day, 7.2%; and >20 mg/day, 7.2%.

The most commonly used (>5% of patients) concomitant central nervous system medications during open-label treatment were other analgesics and antipyretics (57.0%), anticholinergics (10.6%), opioids (9.2%), hypnotics and sedatives (7.5%), and anxiolytics (7.2%). Overall, 15.2% of patients received concomitant medication for the potential treatment of extrapyramidal symptoms. These included propranolol (5.3%), amantadine (0.1%), benztropine (10.6%), and trihexyphenidyl (0.1%).

Adverse events
During long-term treatment, 931 (93.7%) patients experienced at least one adverse event. Treatment-emergent adverse events that occurred at an incidence ≥10% are shown in Table 2. The most common (>15% of the total population) adverse events with long-term adjunctive aripiprazole treatment were akathisia (26.2%), fatigue (18.0%), and weight increase (17.1%). The majority (75.2%) of treatment-emergent adverse events were mild or moderate in nature.

Overall, 226 (22.7%) patients in the safety sample discontinued study treatment due to adverse events; the rate of discontinuation was 23.7% for aripiprazole rollover patients and 22.4% for the placebo rollover/de novo patients. The most common adverse events leading to discontinuation (>1% of total population) were weight increase (3.3%), akathisia (3.3%), somnolence (2.0%), anxiety (1.7%), fatigue (1.7%), and sedation (1.1%); no other adverse events resulted in discontinuation of more than 1% of patients.

The incidence of serious adverse events was 4.0%; five serious adverse events occurred in two placebo rollover/de novo patients during long-term treatment (suicidal ideation, depression, chest pain, myocardial infarction, and intentional overdose); cellulitis, cholecystitis, and pneumonia were each also experienced by two patients (one placebo rollover/de novo patient and one aripiprazole rollover patient). There were no reports of neuroleptic malignant syndrome, completed suicide, or death due to other causes in this study.
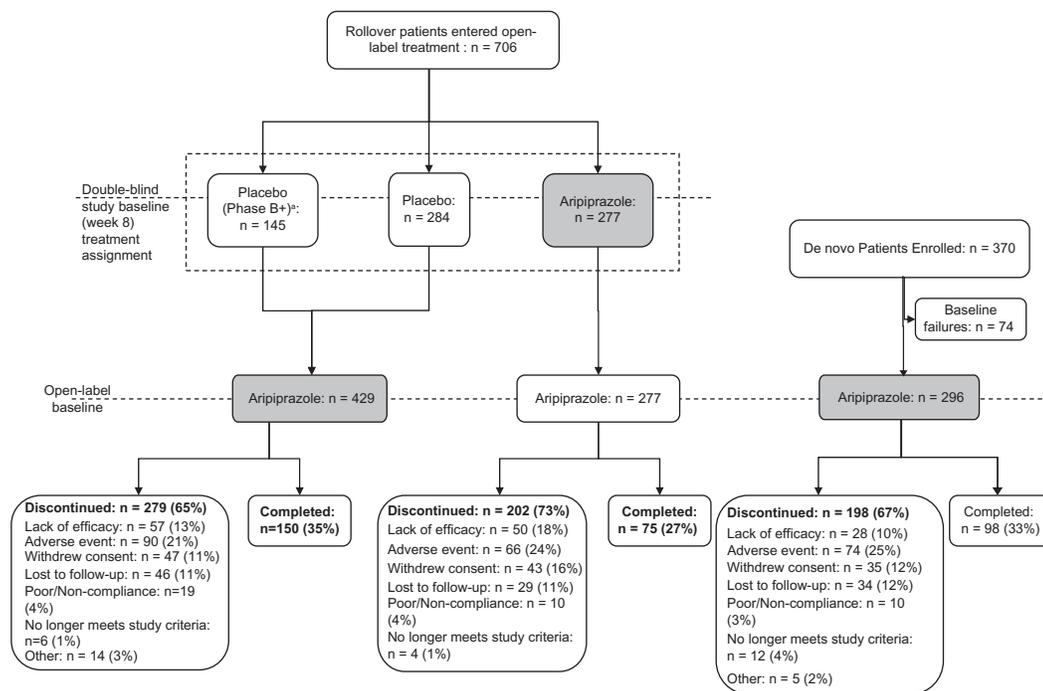
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                          │ Rollover patients entered open-│
                          │   label treatment : n = 706    │
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Figure 1 Enrollment, randomization, and disposition of patients.
Notes: Shaded boxes represent first aripiprazole dosing; [a]Patients in Phase B+ were antidepressant therapy responders at week 8 who received placebo for an additional six weeks.

Double-blind study baseline (week 8) treatment assignment

Placebo (Phase B+)[a]: n = 145
Placebo: n = 284
Aripiprazole: n = 277

De novo Patients Enrolled: n = 370
Baseline failures: n = 74

Open-label baseline: Aripiprazole: n = 429 | Aripiprazole: n = 277 | Aripiprazole: n = 296

Discontinued: n = 279 (65%)
Lack of efficacy: n = 57 (13%)
Adverse event: n = 90 (21%)
Withdrew consent: n = 47 (11%)
Lost to follow-up: n = 46 (11%)
Poor/Non-compliance: n=19 (4%)
No longer meets study criteria: n=6 (1%)
Other: n = 14 (3%)

Completed: n=150 (35%)

Discontinued: n = 202 (73%)
Lack of efficacy: n = 50 (18%)
Adverse event: n = 66 (24%)
Withdrew consent: n = 43 (16%)
Lost to follow-up: n = 29 (11%)
Poor/Non-compliance: n = 10 (4%)
No longer meets study criteria: n = 4 (1%)

Completed: n = 75 (27%)

Discontinued: n = 198 (67%)
Lack of efficacy: n = 28 (10%)
Adverse event: n = 74 (25%)
Withdrew consent: n = 35 (12%)
Lost to follow-up: n = 34 (12%)
Poor/Non-compliance: n = 10 (3%)
No longer meets study criteria: n = 12 (4%)
Other: n = 5 (2%)

Completed: n = 98 (33%)

Extrapyramidal symptoms

The rates of reported extrapyramidal symptom-related adverse events were as follows: dystonic events, 4.0%; parkinsonian events, 10.6%; akathisia events (ie, akathisia, psychomotor hyperactivity), 26.5%; dyskinetic events, 1.8%; and residual events, 2.2%. Akathisia occurred in 26.2% of this open-label population (placebo rollover/de novo patients, 24.0%; aripiprazole rollover patients, 31.8%) and the majority of cases had their onset within the first six weeks of treatment. Akathisia led to discontinuation in 3.3% of study patients. There were small mean changes from baseline in the AIMS, SAS, and BARS scores; mean change from baseline to week 52 (last observation carried forward) was 0.06 for the AIMS total score (mean baseline 0.07), 0.17 points for the SAS (mean baseline 10.32), and 0.11 for the BARS (mean baseline 0.15).

Four spontaneous reports of possible tardive dyskinesia were submitted during the study (0.4%); all the patients
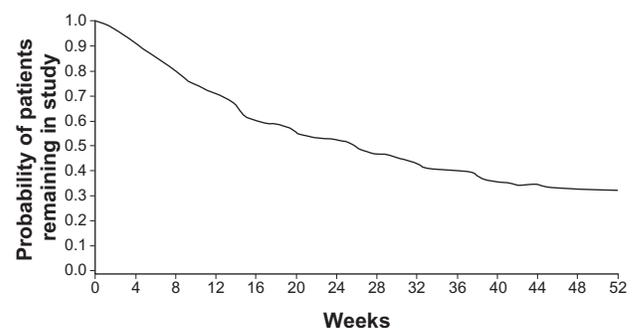
Table 1 Open-label baseline[a] demographic characteristics (safety sample)

Demographic	n = 994
Age (years), mean (SD)	45.8 (11.3)
Gender, n (%) female	658 (66.2)
Race, n (%)	
White	906 (91.1)
Black	62 (6.2)
Asian	9 (0.9)
Other	17 (1.7)
Weight (kg), mean (SD)[b]	88.5 (22.6)
BMI (kg/m²), mean (SD)[c]	31.2 (7.9)
Distribution, n (%)[c]	
BMI ≤ 24 (normal/underweight)	208 (21.0)
BMI 25–29 (overweight)	292 (29.4)
BMI ≥ 30 (obese)	492 (49.6)
Recurrent episode, n (%)[b]	776 (78.1)
MADRS total score, mean (SD)	20.2 (9.0)

Notes: [a]For rollover patients, assessments from the week 14 visit from the previous study served as the baseline measurement; for de novo patients, baseline was defined using the measurements from the start of the open-label study; [b]n = 993; [c]n = 992.
Abbreviations: SD, standard deviation; BMI, body mass index; MADRS, Montgomery-Åsberg Depression Scale.

Figure 2 Time to discontinuation of aripiprazole due to any reason during open-label treatment, safety sample.*
Note: *Aripiprazole rollover patients had been exposed to aripiprazole for six weeks prior to open-label treatment.

Table 2 Treatment-emergent adverse events (≥10% of patients, safety sample)

Adverse event, n (%)	Placebo rollover/de novo patients (n = 720)	Aripiprazole rollover patients (n = 274)	Total (n = 994)
Akathisia	173 (24.0)	87 (31.8)	260 (26.2)
Fatigue	135 (18.8)	44 (16.1)	179 (18.0)
Weight increase	131 (18.2)	39 (14.2)	170 (17.1)
Restlessness	98 (13.6)	44 (16.1)	142 (14.3)
Insomnia	93 (12.9)	29 (10.6)	122 (12.3)
Somnolence	103 (14.3)	33 (12.0)	136 (13.7)
Headache	93 (12.9)	24 (8.8)	117 (11.8)
Upper respiratory tract infection	68 (9.4)	38 (13.9)	106 (10.7)
Nausea	77 (10.7)	18 (6.6)	95 (9.6)
Dizziness	73 (10.1)	18 (6.6)	91 (9.2)

Note: Reporting of adverse events for aripiprazole rollover patients includes any adverse events that may have occurred with aripiprazole treatment during the previous double-blind study period.

involved were receiving aripiprazole adjunctive to escitalopram. Interventions to manage tardive dyskinesia included dose reduction (n = 2) and drug discontinuation (n = 2). In all four cases, highest AIMS total scores were ≤4, and the symptoms completely resolved within 45 days of discontinuing adjunctive aripiprazole treatment.

Body weight

At week 26/32 (n = 491), the mean change in body weight from baseline (observed case) was 3.6 kg (placebo rollover/de novo patients, 3.4 kg; aripiprazole rollover patients, 4.3 kg). For the patients who completed 52/58 weeks of open-label adjunctive treatment (n = 303), the mean change in body weight over time showed that most weight gain occurred in the first 26–32 weeks on treatment. At week 26/32, the mean change in body weight was 4.0 kg, and at week 52/58 was 4.4 kg (placebo rollover/de novo patients, 3.9 kg at week 26, and 4.3 kg at week 52; aripiprazole rollover patients, 4.4 kg at week 32 and 4.9 kg at week 58). Mean change in body weight for aripiprazole rollover patients completing the study at week 6 was 1.8 kg. For aripiprazole rollover patients who had clinically significant weight gain (≥7%) at week 6, the mean change in body weight from baseline (observed case) was 8.7 kg at week 32 and 8.5 kg at week 58 (both n = 7). In aripiprazole rollover patients without clinically significant weight gain at week 6, mean change in body weight from baseline (observed case) was 4.0 kg (n = 106) and 4.5 kg (n = 64) at weeks 32 and 58, respectively.

Clinically significant weight gain (≥7%) occurred in 28.0% of patients (based on a last observation carried forward analysis) and 36.6% of subjects who completed the study (observed case analysis).

Metabolic effects

Figure 3 shows the mean change in fasting metabolic parameters from adjunctive aripiprazole baseline, by treatment period, for patients who continued to receive treatment (observed case analysis). National Cholesterol Education Program (NCEP)-defined cut-offs (see Figure 3) show that, on average, LDL, HDL, and glucose levels remained within normal limits. Baseline levels of cholesterol were higher, but tended to decrease over the 52-week exposure to aripiprazole. Baseline triglyceride levels were also above the normal 150 mg/dL criterion and remained above baseline throughout the course of aripiprazole treatment. Overall, there were no clinically important findings in the mean changes from baseline in fasting cholesterol, HDL, LDL, triglycerides, or glucose. For adjunctive aripiprazole exposure >46 weeks, the median change (range) in fasting metabolic parameters from adjunctive aripiprazole baseline were as follows: fasting cholesterol (n = 264), −4.0 (−154.0 to 90.0) mg/dL; fasting HDL (n = 264), −5.0 (−85.0 to 24.0) mg/dL; fasting LDL (n = 264), 1.0 (−117.0 to 94.0) mg/dL; fasting triglycerides (n = 264), 8.0 (−385.0 to 354.0) mg/dL, and fasting glucose (n = 262), 2.5 (−128.0 to 151.0) mg/dL.

The incidence of treatment-emergent potentially clinically relevant abnormalities in fasting total cholesterol levels (≥240 mg/dL) was 11.9% (n = 33/277) with adjunctive aripiprazole and 13.6% (n = 38/280) with adjunctive placebo during placebo-controlled trials and was 19.4% (n = 135/697) for a pooled population of patients treated with aripiprazole in both the short-term studies and this long-term trial. The incidence of treatment-emergent potentially clinically relevant abnormalities in fasting glucose levels (≥126 mg/dL) was 2.2% (n = 8/358) with adjunctive aripiprazole and 2.8% (n = 10/362) with adjunctive placebo during placebo-controlled trials, and was 4.9% (n = 44/906)
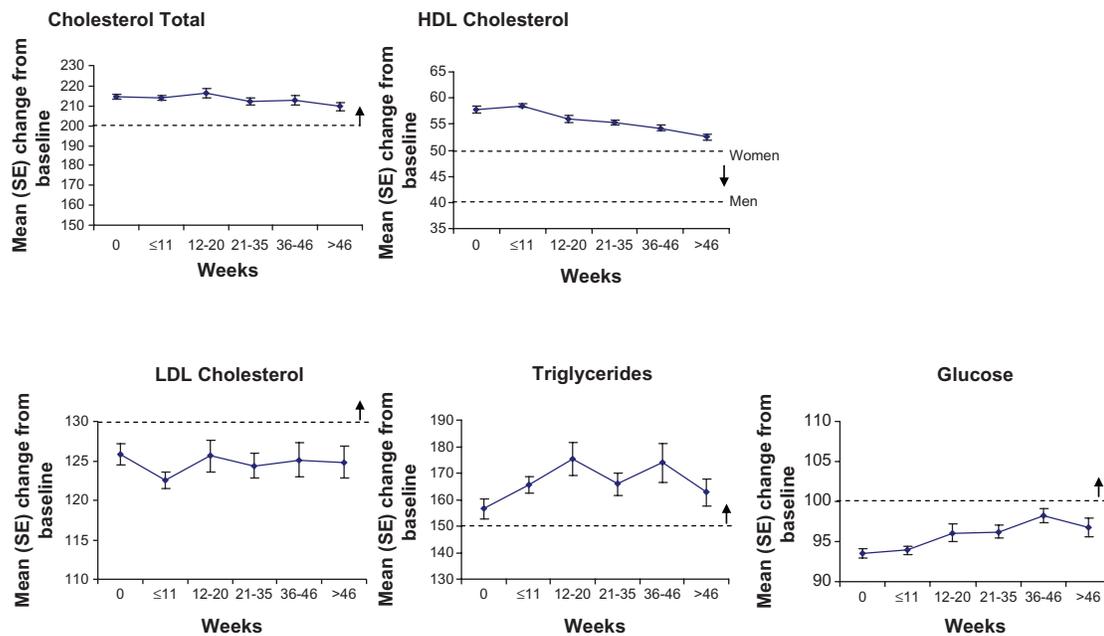
Figure 3 Time-course of fasting metabolic mean changes from baseline (observed case analysis).
Notes: Mean (SE) baseline values: fasting total cholesterol (n = 773), 214.6 (1.5) mg/dL; fasting HDL cholesterol (n = 773), 57.8 (0.6) mg/dL; fasting LDL cholesterol (n = 773), 125.8 (1.3) mg/dL; fasting triglycerides (n = 773), 156.5 (3.9) mg/dL; fasting glucose (n = 769), 93.5 (0.6) mg/dL. Dashed line and arrows represents abnormal lipid values (NCEP-defined criteria) and glucose levels (ADA criteria). Laboratory evaluations were performed at weeks 6, 14, 32, 44, and 58 for aripiprazole rollover patients, and weeks 8, 26, 38, and 52 for placebo rollover/de novo patients. For patients who had received aripiprazole in the previous double-blind study (aripiprazole rollover patients), baseline refers to week 8 scores from double-blind treatment.
Abbreviations: SE, standard error; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NCEP, National Cholesterol Education Program; ADA, American Diabetes Association.

for the pooled total population from short-term and long-term studies.

Vital signs and laboratory findings

The incidence of potentially clinically relevant vital sign and electrocardiographic abnormalities, as well as serum chemistry, hematology, and electrolyte measurements, was low. The exception to this was the incidence of potentially clinically relevant prolactin elevations at at least one blood draw (13.7%). For a number of these patients, there were relevant prolactin elevations at study baseline and aripiprazole treatment was associated with decreased prolactin levels. At week 52 (last observation carried forward), patients showed a mean decrease of 0.5 ng/dL in serum prolactin levels from baseline (12.9 ng/dL).

Efficacy

Mean CGI-S scores over the course of treatment showed sustained improvement in clinical symptoms, regardless of treatment during the double-blind study (Figure 4). At baseline, 33 patients (10.4%) had a CGI-S score of 1 or 2, indicating "normal" or "borderline ill" at adjunctive aripiprazole baseline, whereas at the end of open-label treatment (week 52/58) 221 patients (69.7%) had a CGI-S score of 1 or 2.

Discussion

Major depressive disorder is a chronic and recurrent condition that often requires patients to receive treatment for prolonged periods of time. As such, understanding the long-term tolerability profiles of treatments is essential for optimal clinical management. In this long-term study, the safety and tolerability of aripiprazole augmentation was demonstrated by relatively low discontinuation rates due to adverse events (23%) over a 52–58-week exposure. Furthermore, the adverse event profile was consistent with that reported in the short-term, double-blind, placebo-controlled trials.[23] Most adverse events were mild or moderate in severity and the incidence of serious adverse events was low. The incidence of vital sign/laboratory abnormalities was also low, with the exception of prolactin elevations. The effect of aripiprazole on prolactin elevation is difficult to interpret due to some patients having elevated levels at baseline, and a mean overall decrease in prolactin levels after treatment with adjunctive aripiprazole. Nonetheless, patients should be monitored for signs and symptoms of prolactin elevations due to the potential for sexual dysfunction and decreased bone mineral density.[24] Clinically significant weight gain during extended treatment was evident in a significant minority of patients, and weight gain was one of the most common adverse events with treatment.
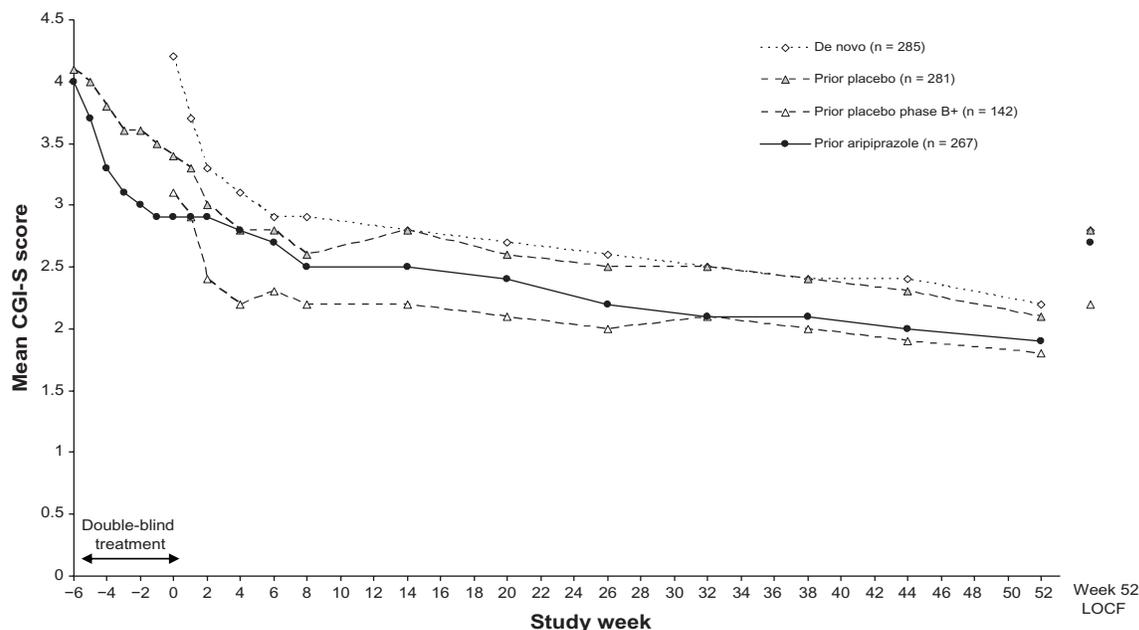
Figure 4 Mean CGI-S scores by treatment week.
Notes: Data by study week is from OC analysis; week 52 LOCF data are also shown. N numbers are week 52 (LOCF); weeks -6 to 0 represents CGI-S scores for aripiprazole rollover and placebo rollover patients during the previous double-blind study period; weeks 0 to 52 represent CGI-S scores during open-label treatment. Patients in the prior placebo Phase B+ group were ADT responders at week 8 who received placebo for an additional six weeks.
Abbreviations: CGI-S, Clinical Global Impression-Severity of Illness Scale; OC, observed case; LOCF, last observation carried forward; ADT, antidepressant therapy.

Although adjunctive aripiprazole was associated with a mean weight gain of 4.4 kg, the relative contribution of aripiprazole to weight gain compared with antidepressants alone is difficult to determine, because long-term administration of antidepressant medications is also associated with medically relevant weight gain.[25–28] For example, in one study, patients treated with fluoxetine for at least one year experienced a mean weight gain of 3.2 kg, and 25.4% had a clinically relevant weight gain (≥7%).[25] Interestingly, the rate of clinically relevant weight gain was similarly high for patients treated with placebo for the same duration.[25]

It is noteworthy that the aripiprazole rollover patients with clinically significant weight gain in the first six weeks of treatment experienced greater weight gain than patients without early weight gain. The majority of weight gain occurred over the first six months of treatment in both groups, suggesting that weight gain plateaus during long-term treatment. Regardless, patients receiving adjunctive aripiprazole over the longer term should be monitored for weight gain and should be proactively managed should it occur, especially given that the relative risk for long-term weight gain is not equal across all selective serotonin reuptake inhibitors.[10] Continued treatment in patients experiencing weight gain should be based on clinical assessment of the patient in the context of benefits and side effects.

Extrapyramidal symptoms and metabolic abnormalities are adverse events of great concern for patients taking antipsychotic medications over the long term. Adjunctive aripiprazole had minimal effects on blood lipid and glucose levels. There were no clinically meaningful increases in mean fasting metabolic parameters over the course of treatment and, on average, patients remained within, or slightly above, NCEP-defined "normal" limits. Similar shifts to "abnormal" levels of total cholesterol or glucose did occur within the first six weeks of treatment for patients treated with adjunctive aripiprazole and antidepressant monotherapy. Some additional shifts were observed over the course of the 52–58-week exposure, yet we cannot determine whether the shifts were directly related to aripiprazole, the antidepressant, or to the population already being overweight and obese at trial entry. Nonetheless, the data underscore the need for regular metabolic monitoring in patients with depression treated with adjunctive atypical antipsychotics. As for extrapyramidal symptoms, in this study, the rate of extrapyramidal symptom-related adverse events was not substantially different from that observed in the short-term, double-blind, placebo-controlled trials.[23] The objective movement disorder rating scales, AIMS, BARS, and SAS, did not reveal substantial evidence of extrapyramidal symptoms.

There were four spontaneous reports of tardive dyskinesia in this study; however, it is important to note that all four cases resolved with dose reduction or drug discontinuation. Given

that tardive dyskinesia is considered to be a chronic, persistent condition, the resolution of symptoms within 45 days of dose reduction or drug discontinuation may suggest that these cases of tardive dyskinesia were readily amenable to conventional intervention or the reports may have represented phenomena other than tardive dyskinesia. Given that tardive dyskinesia is a potentially serious adverse event, clinicians should remain mindful of the emergence of tardive dyskinesia with long-term adjunctive aripiprazole treatment, and take steps to manage patients who present with symptoms.

Of note, all patients started at 5 mg/day and were recommended to increase to 10 mg/day at the end of week 1. Although akathisia was the most common adverse event during long-term treatment, it rarely led to study discontinuation, and generally had its onset early in the course of treatment. Consideration of starting at a lower dose, such as 2 mg, with a slower titration schedule may reduce the incidence of extrapyramidal symptom-related adverse events, including akathisia.

Endpoint CGI-S scores suggest that adjunctive aripiprazole provides clinically meaningful, persistent efficacy with long-term treatment; nearly 70% of subjects who continued long-term treatment had a CGI-S score of 1 (normal) or 2 (borderline ill), indicating that scores are consistent with remission from symptoms. Regardless of previous treatment, all groups had a comparable mean endpoint score, suggesting a stability of effect over time. Also notable is the speed of onset of symptom relief. On average, most improvement in CGI-S scores occurred in the first month of treatment and was sustained over a year of treatment. However, conclusions on long-term efficacy of adjunctive aripiprazole treatment are limited, because this study was not designed to assess the maintenance of effect specifically; a double-blind study using a placebo-controlled discontinuation design will be necessary in order to establish longer-term efficacy.

The findings of this study are strengthened by the large overall patient population with major depressive disorder who received adjunctive aripiprazole treatment over 52–58 weeks of exposure. However, the findings reported here should be evaluated with consideration to several limitations, such as the open-label study design and the lack of a control treatment group, which limits the ability to attribute adverse events solely to adjunctive aripiprazole treatment because some adverse events may have resulted from the long-term use of the antidepressant therapies. It should also be considered that all patients were retitrated to aripiprazole 5 mg/day at entry into open-label treatment; this may have had an impact on the occurrence of adverse events for patients who were previously receiving a stable dose of aripiprazole during the parent studies. The impact of any effect of retitration on adverse events was not evaluated. Finally, patients benefiting from aripiprazole augmentation in this study were receiving a variety of different antidepressants, which were assigned based on investigator judgment. As such, the relative benefit of one antidepressant agent over the other has not been evaluated.

Conclusion
Overall, aripiprazole augmentation was well tolerated, with an acceptable long-term safety and tolerability profile in patients with major depressive disorder who had not responded to treatment with one or more antidepressant therapies. Common adverse events to consider during the long-term use of adjunctive aripiprazole for the treatment of major depressive disorder include weight gain and akathisia, although these events seldom led to treatment discontinuation in this study.

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