Original Research

Effect of Aripiprazole Lauroxil on Metabolic and Endocrine Profiles and Related Safety Considerations Among Patients With Acute Schizophrenia

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ABSTRACT

Objective: Aripiprazole lauroxil, a long-acting injectable antipsychotic, demonstrated safety and efficacy in treating symptoms of schizophrenia in a double-blind, placebo-controlled trial. Because the metabolic profile of antipsychotics is an important safety feature, the effects of aripiprazole lauroxil on body weight, endocrine and metabolic profiles, and safety were examined in a secondary analysis.

Methods: Patients with schizophrenia (*DSM-IV-TR* criteria) were randomly assigned to aripiprazole lauroxil 441 mg, aripiprazole lauroxil 882 mg, or placebo intramuscularly once monthly between December 2011 and March 2014. Changes in body weight, body mass index, fasting blood glucose and serum lipids, glycosylated hemoglobin (HbA_{1c}), and prolactin over 12 weeks were assessed. The incidence of treatment-emergent adverse events (AEs) was evaluated.

Results: Among 622 randomized patients, no clinically relevant changes from baseline to week 12 were observed for any serum lipid, lipoprotein, plasma glucose, or HbA_{1c} value with placebo or either dose of aripiprazole lauroxil. Both doses of aripiprazole lauroxil were associated with reductions in mean prolactin levels, whereas placebo treatment was not. The mean (standard deviation) change from baseline for body weight was 0.74 (3.9) kg, 0.86 (3.7) kg, and 0.01 (3.6) kg for aripiprazole lauroxil 441 mg, aripiprazole lauroxil 882 mg, and placebo groups, respectively. AEs related to metabolic parameters were reported in 2.4%, 1.4%, and 2.4% of patients in the aripiprazole lauroxil 441 mg, aripiprazole lauroxil 882 mg, and placebo groups, respectively.

Conclusions: Aripiprazole lauroxil was well tolerated, with a low-risk metabolic profile relative to published data for other antipsychotics. Changes similar to those observed with placebo were observed in the aripiprazole lauroxil groups for metabolic parameters, with modest weight gain in the active treatment groups over the 12-week course.

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Schizophrenia represents a major medical illness, with a prevalence of 0.5%–1.5% in different regions of the globe, imparting a major burden on patients and their families and on health care systems.[1] Despite the availability of a number of antipsychotics for controlling symptoms of schizophrenia and achieving a clinical response, a large proportion of patients fail to achieve a satisfactory outcome because of side effects or poor adherence to medication.[2,3] Atypical antipsychotics often are preferred to conventional antipsychotics for treating schizophrenia because they provide comparable efficacy with an improved safety and neurologic tolerability profile. However, some atypical antipsychotics are associated with potential adverse metabolic and endocrine effects, including clinically significant weight gain, prolactin abnormalities, lipid abnormalities, insulin resistance, and increased risk for diabetes.[4–9] These adverse events (AEs) are associated with increased burden and impact on medication adherence[10–12] and potentially contribute to observed increases in cardiovascular risk and morbidity and mortality in this population.[13,14]

The severity of metabolic- and endocrine-related side effects varies across individual antipsychotic medications, with aripiprazole generally manifesting low levels of risk relative to other antipsychotics.[7,15–17] In addition, treatment of schizophrenia with aripiprazole offers comparable therapeutic efficacy and symptom control[18–21] and has been associated with reduced risk of cardiovascular morbidity and mortality.[22]

An underutilized alternative to oral antipsychotics is long-acting injectable antipsychotics, which offer efficacy and tolerability profiles that are comparable to those of oral antipsychotics, with more consistent rates of adherence and greater patient satisfaction.[23] In an early clinical study in 40 patients with schizophrenia, single doses of aripiprazole lauroxil 221 mg, 441 mg, and 588 mg were not associated with clinically significant safety concerns.[24] Results from a phase 3, randomized, placebo-controlled trial of patients with acute schizophrenia found that aripiprazole lauroxil 441 mg and 882 mg doses were effective and well tolerated.[25] More detailed descriptions of metabolic and endocrine outcomes were subsequently conducted from this phase 3 study in order to better characterize the effects of aripiprazole lauroxil in this population. This descriptive analysis from the phase 3 trial reports on the effects of aripiprazole lauroxil on prolactin and metabolic parameters including body weight, plasma lipids, and glycemic control.

Clinical Points

- As the metabolic profile of antipsychotics is an important safety feature, the effects of aripiprazole lauroxil on metabolic parameters were examined.
- Characterization of the risk/benefit profile of newer formulations of antipsychotics is helpful when planning treatment strategies for patients with schizophrenia.
- This analysis may be helpful when assessing treatment options for an individual patient given the currently available long-acting injectable antipsychotics.

METHODS

The detailed methodology for this study was presented previously and is summarized briefly.[25] The study was conducted across 8 countries between December 2011 and March 2014 in accordance with the Declaration of Helsinki, 1964, and Good Clinical Practice principles (International Conference on Harmonization, 1997). At each clinical study site, the protocol, amendments, and informed consent were approved by a qualified institutional review board, and all participants completed written informed consent prior to study participation. This study was registered at ClinicalTrials.gov: NCT01469039.

Study Design

This phase 3, randomized, double-blind, placebo-controlled study evaluated 2 doses of aripiprazole lauroxil in patients with schizophrenia (*DSM-IV-TR* criteria) who were experiencing an acute relapse. After admission to an inpatient setting, all current antipsychotics were discontinued, and a test dose of oral aripiprazole 5 mg was administered daily for 2 days prior to randomization to assess tolerability for those who had not previously taken aripiprazole.

Patient Selection

Patients were aged 18 to 70 years with a body mass index (BMI) of 18.5 to 40 kg/m^2. Patients were eligible if they were experiencing a current acute exacerbation or relapse of schizophrenia with an onset < 2 months prior to screening (< 2 weeks for the current exacerbation if hospitalized) and ≥ 2 years had elapsed since the initial onset of symptoms. Patients also were required to have a clinically significant beneficial response to treatment with an antipsychotic medication other than clozapine and to have been an outpatient for > 3 months during the past year. At screening and baseline, a Positive and Negative Syndrome Scale (PANSS)[26] total score of 70 to 120, a score of ≥ 4 for ≥ 2 of the Positive Scale items (item 1: delusions; item 2: conceptual disorganization; item 3: hallucinatory behavior; item 6: suspiciousness/persecution), and a Clinical Global Impression—Severity of Illness (CGI-S)[27] score of ≥ 4 were required.

Patients were excluded who (1) had a poor or inadequate response to aripiprazole; (2) had a history of treatment resistance (failure to respond to 2 adequate trials of different antipsychotics for ≥ 4 weeks at a maximum tolerated dose); (3) had hypersensitivity to aripiprazole, other antipsychotics, or fat emulsion; (4) had any other clinically significant neuropsychiatric disorder, medical illness, or laboratory abnormality that would interfere with the conduct of the study; and (5) were women who were pregnant, lactating, or breastfeeding. In addition, patients using long-acting antipsychotics within 60 days of screening or who were under current involuntary hospitalization or underwent psychiatric hospitalization for > 30 days during the 90 days before screening were excluded.

On day 1, patients were randomized to an intramuscular (IM) dose of aripiprazole lauroxil 441 mg, aripiprazole lauroxil 882 mg, or placebo. In addition to IM study drug, patients randomized to an aripiprazole lauroxil treatment group received oral aripiprazole 15 mg, and patients randomized to placebo received matching oral placebo for 3 weeks after randomization. Patients remained in the inpatient study unit for at least 2 weeks after administration of the first dose of IM study drug. Two subsequent doses of IM study drug were administered on days 29 and 57.

Study Assessments

A blood sample for serum chemistry was obtained at screening and on days 1, 29, 57, and 85 (12 weeks) to measure total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, glycosylated hemoglobin (HbA$_{1c}$), plasma glucose levels, and prolactin. Body weight was measured at screening and on days 1, 15, 29, 57, and 85, and BMI was calculated. All AEs during the treatment period, including those related to metabolic and endocrine parameters, were recorded. An AE was any untoward medical occurrence, which may or may not have had a causal relation to the investigational treatment and may have included any clinical or laboratory change that was considered clinically significant.

Statistical Methods

The safety population included all randomized patients who received at least 1 dose of IM study drug (N = 622). Analyses were descriptive including mean, standard deviation (SD), range, and mean change from baseline to the last postbaseline value obtained during the treatment period. Shifts in total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides, HbA$_{1c}$, and plasma glucose levels from "normal" at baseline to "high" at last postbaseline assessment and "high" at baseline to "normal" at last postbaseline assessment were evaluated (see Supplementary eTable 1 at PSYCHIATRIST.COM). The proportions of patients with a body weight change of at least 7% and at least 10% were determined. An analysis of the effect of baseline BMI category (< 25 kg/m^2, 25 to < 30 kg/m^2, and ≥ 30 kg/m^2) on PANSS total score was undertaken using analysis of covariance and last observation carried forward.

Table 1. Baseline Demographic Characteristics

| | Aripiprazole Lauroxil | | Placebo |
| | 441 mg | 882 mg | |
Characteristic	(N = 207)	(N = 208)	(N = 208)
Male, n (%)	141 (68.1)	143 (68.8)	139 (66.8)
Age, mean (SD), y	39.9 (10.1)	39.7 (11.1)	39.5 (11.9)
BMI, kg/m², mean (SD)	27.7 (5.3)	27.3 (5.7)	27.0 (5.1)
BMI range	18.5–40.3	18.6–40.9	18.5–39.5
Normal (BMI < 25), n (%)	73 (35.3)	81 (38.9)	83 (39.9)
Overweight (BMI 25 to < 30), n (%)	62 (30.0)	67 (32.2)	70 (33.7)
Obese (BMI ≥ 30), n (%)	72 (34.8)	60 (28.8)	55 (26.4)
Weight, mean (SD), kg	80.8 (17.6)	80.3 (19.3)	78.9 (18.7)
Weight range, kg	44.5–140.0	43.0–143.8	46.2–148.7
Race, n (%)			
White	99 (47.8)	98 (47.1)	94 (45.2)
Black or African-American	83 (40.1)	81 (38.9)	84 (40.4)
Asian	24 (11.6)	28 (13.5)	29 (13.9)
Other	1 (0.5)	1 (0.5)	1 (0.5)

Abbreviations: BMI = body mass index, SD = standard deviation.

Table 2. Baseline Values and Changes From Baseline for Metabolic Parameters

| | Aripiprazole Lauroxil | | Placebo |
| | 441 mg | 882 mg | |
Parameter	(N = 207)	(N = 208)	(N = 207)
Total cholesterol, mg/dL			
Baseline	192.3 (43.5)	192.9 (40.5)	189.2 (39.4)
Change[b]	−5.1 (36.0)	−11.6 (31.9)	−6.5 (30.9)
HDL cholesterol, mg/dL			
Baseline	52.9 (16.5)	53.8 (16.0)	55.2 (16.6)
Change[b]	1.3 (11.5)	−1.3 (12.5)	−2.4 (11.6)
LDL cholesterol, mg/dL			
Baseline	110.1 (35.2)	112.5 (34.9)	109.8 (33.6)
Change[b]	−3.9 (27.7)	−9.4 (28.1)	−5.7 (28.0)
Triglycerides, mg/dL			
Baseline	142.9 (102.3)	133.9 (76.3)	121.2 (68.8)
Change[b]	−5.8 (95.0)	−4.4 (83.6)	7.4 (81.3)
Glucose, mg/dL			
Baseline	92.3 (21.7)	88.4 (12.9)	89.9 (15.6)
Change[b]	0 (19.0)	−1.3 (15.8)	2.7 (29.5)
HbA$_{1c}$ (%)			
Baseline	5.4 (0.6)	5.4 (0.5)	5.4 (0.5)
Change[b]	0.03 (0.3)	0.03 (0.3)	0.01 (0.3)
Body weight, kg			
Baseline	80.8 (17.6)	80.3 (19.3)	79.0 (18.7)
Change[b]	0.74 (3.9)	0.86 (3.7)	0.01 (3.6)
Increase of ≥ 7% at any postbaseline visit, %	9.7	8.7	5.8
Decrease of ≥ 7% at any postbaseline visit, %	2.9	3.4	5.8

[a]Values expressed as mean (SD) unless otherwise noted.
[b]Change from baseline to last postbaseline value during the treatment period.
Abbreviations: HbA$_{1c}$ = glycosylated hemoglobin, HDL = high-density lipoprotein, LDL = low-density lipoprotein, SD = standard deviation.

RESULTS

Of 848 patients who were screened, 623 were randomized, and 622 received at least 1 dose of IM study drug. One patient randomized to placebo was discontinued for a protocol violation prior to receiving IM study drug. Baseline demographics, including body weight and BMI, were comparable among treatment groups (Table 1). More than 60% of patients were either overweight (BMI 25 to < 30 kg/m²) or obese (BMI ≥ 30 kg/m²) at baseline.

Changes in Body Weight and BMI

Mean body weight increased modestly in both aripiprazole lauroxil groups relative to placebo, with similar SD values for all groups (Table 2). Mean (SD) change from baseline to the last postbaseline visit for body weight was 0.7 (3.9) kg, 0.9 (3.7) kg, and 0.01 (3.6) kg for aripiprazole lauroxil 441 mg, aripiprazole lauroxil 882 mg, and placebo. Greater proportions of patients in the aripiprazole lauroxil groups gained ≥ 7% body weight. Of the 50 patients with ≥ 7% increase in body weight, 31 experienced ≥ 10% increase (9 each in the aripiprazole lauroxil 441 mg and placebo groups and 13 in the aripiprazole lauroxil 882 mg group). Of the 50 patients with ≥ 7% increase in body weight, 70% were nonwhite and male, and of the 31 patients with ≥ 10% increase, 77% were nonwhite and male.

The greatest percent increase in body weight in an individual patient within each group was +14.8% (aripiprazole lauroxil 441 mg), +28.5% (aripiprazole lauroxil 882 mg), and +24.3% (placebo). The greatest percent decrease in weight in an individual patient in each group was –28.8% (aripiprazole lauroxil 441 mg), –18.3% (aripiprazole lauroxil 882 mg), and –11.1% (placebo).

An analysis was undertaken of the effect of BMI on PANSS total score. Least squares mean change from baseline to day 85 for PANSS total score was analyzed for patients in 3 BMI subgroups (< 25 kg/m², 25 to < 30 kg/m², and ≥ 30 kg/m²). Significant (P < .025) improvement was observed with both aripiprazole lauroxil dose groups vs placebo for all 3 BMI subgroups. The mean decrease in PANSS total score

with placebo was 6 in the overweight group (25 to < 30 kg/m²) and 13 in the obese group (≥ 30 kg/m²). In contrast, mean decreases from baseline in PANSS total score for both aripiprazole lauroxil dose groups ranged from 17 to 24.
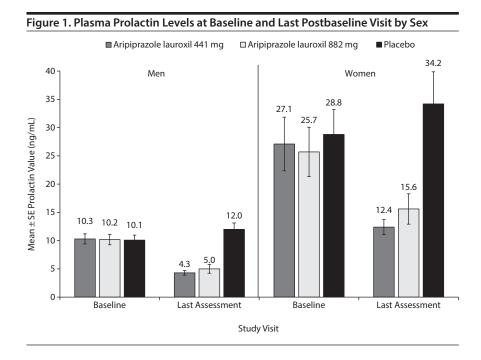
Glycemic Control

Shifts from normal at baseline to high at last postbaseline assessment were similar across groups for glucose and HbA$_{1c}$ (Table 3). For HbA$_{1c}$, only minor changes from baseline values to last postbaseline visit of 0.01%–0.03% were observed (Table 2). For glucose, mean values increased from baseline by up to 3% in the placebo group but remained unchanged in the aripiprazole lauroxil 441 mg group and decreased 1% from baseline in the 882 mg group; shifts from high to normal were 47% and 83% vs 55% for aripiprazole lauroxil 441 mg and 882 mg vs placebo, respectively (Table 3). One patient in the placebo group experienced levels of plasma glucose that were at least ≥ 3 times the upper limit of normal (ULN).

Changes in Lipid Parameters

The mean change from baseline for lipid parameters was similar between treatment groups (Table 2). Total cholesterol, LDL cholesterol, and triglyceride levels decreased by 5%–8% from baseline in the aripiprazole lauroxil groups. Shifts from normal levels of total cholesterol, LDL cholesterol, and triglycerides at baseline to high levels at last postbaseline assessment were < 20% among aripiprazole lauroxil 441

Table 3. Shifts in Metabolic and Endocrine Parameters

| | Shift From Normal at Baseline to High at Last Postbaseline Assessment | | | Shift From High at Baseline to Normal at Last Postbaseline Assessment | | |
| | Aripiprazole Lauroxil | | | Aripiprazole Lauroxil | | |
Parameter	441 mg n/m (%)	882 mg n/m (%)	Placebo n/m (%)	441 mg n/m (%)	882 mg n/m (%)	Placebo n/m (%)
Total cholesterol	19/117 (16.2)	9/110 (8.2)	11/113 (9.7)	25/69 (36.2)	34/79 (43.0)	21/70 (30.0)
HDL cholesterol	0/142 (0)	0/146 (0)	0/152 (0)	0/0 (0)	0/0 (0)	0/0 (0)
LDL cholesterol	14/133 (10.5)	10/133 (7.5)	14/127 (11.0)	23/48 (47.9)	28/55 (50.9)	22/53 (41.5)
Triglycerides	12/114 (10.5)	19/128 (14.8)	18/133 (13.5)	28/68 (41.2)	30/59 (50.8)	22/50 (44.0)
Glucose	12/165 (7.3)	5/169 (3.0)	17/165 (10.3)	7/15 (46.7)	10/12 (83.3)	6/11 (54.5)
HbA$_{1c}$	7/160 (4.4)	3/167 (1.8)	8/159 (5.0)	2/16 (12.5)	2/10 (20.0)	5/11 (45.5)
Prolactin	6/104 (5.8)	3/124 (2.4)	20/108 (18.5)	20/33 (60.6)	11/26 (42.3)	12/31 (38.7)

Abbreviations: HbA$_{1c}$ = glycosylated hemoglobin, HDL = high-density lipoprotein, LDL = low-density lipoprotein, m = total number of patients with nonmissing numeric values at baseline and the corresponding postbaseline visit for each treatment group, n = number of patients in each category.

Figure 1. Plasma Prolactin Levels at Baseline and Last Postbaseline Visit by Sex

mg and 882 mg and placebo groups (Table 3). Shifts from high levels at baseline to normal levels at last postbaseline assessment were similarly comparable among both dose groups and placebo. The majority of patients (80%) who entered the study had normal HDL cholesterol levels, and no patients had shifts in HDL levels from normal to high. More patients shifted from normal to low levels of HDL cholesterol in the placebo group (15.1%) than aripiprazole lauroxil 441 mg (11.3%) and 882 mg (10.3%) groups. No increases to ≥ 3 times ULN were observed for total, HDL, and LDL cholesterol levels. However, 3 (1.6%) patients in the placebo group, 4 (2.2%) in the aripiprazole lauroxil 441 mg group, and 2 (1.1%) in the 882 mg group had shifts or remained with triglyceride levels to ≥ 3 times ULN.

Prolactin

Both aripiprazole lauroxil dose groups were associated with decreases in prolactin levels. When further evaluated by

sex, reductions seen in both men and women were clinically meaningful (Figure 1). Mean prolactin levels decreased in both aripiprazole lauroxil dose groups compared to the placebo group starting on day 29 and continued to decrease through day 85. In contrast, decreases in mean prolactin levels were not seen with placebo.

Potentially clinically significant increases in prolactin levels to ≥ 3 times ULN at any postbaseline visit occurred in 0 patients, 1 (1.1%) male and 1 (2.9%) female patient, and 2 (2.7%) male and 5 (14.3%) female patients in the aripiprazole lauroxil 441 mg, aripiprazole lauroxil 882 mg, and placebo groups, respectively (Table 4). The 2 patients in the aripiprazole lauroxil 882 mg group had single elevations of prolactin to 108.8 ng/mL and 268.9 ng/mL, respectively, and both patients completed the study without adverse consequences.

In the aripiprazole lauroxil groups, the proportion of men that had a shift from normal or low prolactin level at

Table 4. Proportion of Patients With Potentially Clinically Significant Values for Metabolic Parameters at Any Postbaseline Visit

Parameter	Criterion	Aripiprazole Lauroxil 441 mg (N = 207) n/m (%)	882 mg (N = 208) n/m (%)	Placebo (N = 207) n/m (%)
Cholesterol	> 300 mg/dL	3/181 (1.7)	2/188 (1.1)	2/182 (1.1)
Total cholesterol (fasting)	≥ 240 mg/dL	12/145 (8.3)	4/132 (3.0)	7/132 (5.3)
HDL cholesterol	≤ 30 mg/dL	2/153 (1.3)	3/149 (2.0)	6/149 (4.0)
LDL cholesterol	≥ 160 mg/dL	11/148 (7.4)	4/139 (2.9)	6/136 (4.4)
Triglyceride (fasting)	Female ≥ 120 mg/dL Male ≥ 160 mg/dL	14/103 (13.6)	17/104 (16.3)	23/111 (20.7)
Glucose low	< 50 mg/dL	0/182 (0)	0/187 (0)	0/183 (0)
Glucose high	≥ 200 mg/dL	1/182 (0.5)	0/187 (0)	4/183 (2.2)
Prolactin (male)	≥ 3 x ULN	0/75 (0)	1/90 (1.1)	2/73 (2.7)
Prolactin (female)	≥ 3 x ULN	0/29 (0)	1/34 (2.9)	5/35 (14.3)

Abbreviations: HDL = high-density lipoprotein, LDL = low-density lipoprotein, m = number of subjects with normal baseline and at least 1 postbaseline assessment, n = number of subjects who met the prolactin potentially clinically significant criterion, ULN = upper limit of normal.

baseline to ≥ 3 times ULN at any postbaseline visit (2.9% and 3.6% for aripiprazole lauroxil 441 mg and 882 mg) was much lower than in the placebo group (25.5%). Among patients with elevated prolactin levels at baseline, men in the aripiprazole lauroxil groups with baseline levels ≥ 3 times ULN tended to normalize (86.4% and 70.6% for aripiprazole lauroxil 441 mg and 882 mg). A lesser proportion of women in both aripiprazole lauroxil dose groups shifted from a normal baseline to ≥ 3 times ULN (15.8% and 7.3% for aripiprazole lauroxil 441 mg and 882 mg vs 34% for placebo). The proportion of women with elevations ≥ 3 times ULN at baseline who normalized in each aripiprazole lauroxil group (60.0% and 57.9% for aripiprazole lauroxil 441 mg and 882 mg) was greater than in the placebo group (30.0%) (Supplementary eTable 2).

Adverse Events Related to Metabolic Effects

Four patients in the aripiprazole lauroxil 441 mg group (blood glucose increased [2]; serum triglycerides increased [2]), 2 patients in the aripiprazole lauroxil 882 mg group (hypoglycemia; hyperlipidemia), and 2 patients in the placebo group (serum cholesterol increased; blood glucose increased) experienced AEs related to metabolic effects. All patients had elevated levels at baseline, and none discontinued from the study. One patient in the aripiprazole lauroxil 882 mg group had a serious AE of hypoglycemia after the second injection. The patient had a history of recurrent hypoglycemic episodes, and this event was considered not related to study drug. Three (1.4%) patients in the placebo group and 1 (0.5%) each in the aripiprazole lauroxil groups had AEs of increased prolactin. Prolactin levels were elevated at baseline and did not increase further during treatment in the aripiprazole lauroxil groups.

An AE of weight increased was reported by 6 (2.9%) of patients in the aripiprazole lauroxil 441 mg group, 5 (2.4%) in the aripiprazole lauroxil 882 mg group, and 1 (0.5%) in the placebo group. Of these, 5 patients on aripiprazole lauroxil had a ≥ 7% increase in body weight at any study visit, and 1 patient in the aripiprazole lauroxil 441 mg group had a > 10% increase in weight.

DISCUSSION

Results from the primary analysis of this study revealed that aripiprazole lauroxil was effective and tolerated for the treatment of patients with acute schizophrenia.[25] The more detailed descriptive analysis included in the present report demonstrates that aripiprazole lauroxil had few clinically relevant AEs on metabolic parameters among a population of patients with acute schizophrenia.

In contrast to placebo, both doses of aripiprazole lauroxil were associated with decreased mean prolactin below baseline levels toward the normal range. This result of decreased prolactin production toward the normal range is consistent with results from other studies of aripiprazole in patients with schizophrenia.[28,29] Thus, it would be expected that aripiprazole lauroxil would have a low rate of hyperprolactinemic effects with treatment. This significant result represents potential advantages of aripiprazole lauroxil treatment.

Results of this 12-week study also indicated that aripiprazole lauroxil succeeded in limiting the pronounced weight gain and other metabolic risks commonly encountered during antipsychotic treatment. Minimal changes from baseline to last postbaseline assessment were observed for lipid parameters, plasma glucose, and HbA$_{1c}$ with aripiprazole lauroxil, consistent with results from other studies of oral aripiprazole.[9,30–34] While a clinically meaningful change in HbA$_{1c}$ is not feasible in a short-term study, this outcome was included along with other metabolic parameters because of the well-known AEs of antipsychotics. The change in mean plasma glucose, which is a more immediate measure of glycemic control, with aripiprazole lauroxil was similar to that with placebo. Longer-term studies of aripiprazole lauroxil are needed to fully characterize the effects on HbA$_{1c}$. Mean changes to last postbaseline assessment for lipid and glycemic parameters were mostly unchanged from baseline for the majority of patients. While mean body weight and BMI increased in both aripiprazole lauroxil dose groups, the number of patients with at least a 7% increase from baseline

in body weight was < 10% among all groups. No adverse outcomes were reported from these elevations. In fact, total and LDL cholesterol levels decreased by 6.0% and 8.4% in the aripiprazole lauroxil 882 mg group. Clinically relevant adverse outcomes related to any metabolic abnormality were uncommon.

The results from this study can be compared and contrasted with results from studies of other atypical antipsychotics that report significant AEs on metabolic parameters.[7,35] A 12-week study with aripiprazole monohydrate found significant increases in weight and numerically greater fasting glucose vs placebo but no significant effects on lipid profile.[28] During a placebo-controlled, 52-week study of aripiprazole monohydrate, no clinically significant metabolic abnormalities of new onset were observed.[36] In a case-control study, Olfson et al[37] found a significant increase in the risk of hyperlipidemia with all first- and second-generation antipsychotics except for aripiprazole. The risk of diabetes was significantly increased with commonly used doses of olanzapine, quetiapine, and risperidone but not with aripiprazole or ziprasidone in schizophrenic patients.[9] A large claims database study found that olanzapine, quetiapine, and risperidone, but not aripiprazole, were associated with elevated HbA$_{1c}$ levels.[32]

Serum prolactin levels decreased with aripiprazole lauroxil, which is consistent with results from other studies of aripiprazole in patients with schizophrenia.[28,29] Effects of some atypical antipsychotics on body weight are varied. A meta-analysis found that mean increases in body weight over a period of 10 weeks were > 4 kg with clozapine and olanzapine and > 2 kg with risperidone, while the increase with ziprasidone was 0.04 kg.[38] This compares with < 1 kg increases in our study. Results from a 52-week, randomized, double-blind trial found ≥ 7% increases in body weight among 80% of patients on olanzapine, 50% on quetiapine, and 58% on risperidone.[39] In our analysis, 9.2% of patients in either dose group of aripiprazole lauroxil had an increase in body weight of ≥ 7%. Thus, our analysis demonstrated a substantially lower, clinically nonsignificant change in body weight with aripiprazole lauroxil. Using baseline BMI status, we noted that for patients in the categories of normal (< 25 kg/m^2), overweight (25 to < 30 kg/m^2), and obese (≥ 30 kg/m^2), the improvement in PANSS total score from baseline to endpoint (day 85) was statistically significant for both aripiprazole lauroxil doses compared to placebo (data not shown). During treatment with some antipsychotics, positive associations between weight gain and/or increased BMI and therapeutic improvements have also been reported.[40,41]

Limitations of the present analysis include the 12-week duration of the study; the time course of developing metabolic abnormalities may be longer. A planned long term-extension study will provide additional information on these outcomes. The present study also suggests that further analysis into baseline characteristics including age, race, and weight at baseline, as well as AEs, may be warranted in future studies. The proportion of patients with an increase in body weight of at least 7% was greater in the aripiprazole lauroxil 441 mg group than the 882 mg and placebo groups, providing no clear dose-response relation.

In summary, these findings of a low risk for metabolic abnormalities with aripiprazole lauroxil are important when considering overall patient health in the management of schizophrenia. Aripiprazole lauroxil represents an important option for the treatment of schizophrenia, with demonstrated efficacy and tolerability and a low risk of metabolic side effects that often impede maintenance of long-term antipsychotic treatment and may lead to higher cardiovascular risk.

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Supplementary Material

List of Supplementary Material for the article

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Supplementary eTable 1. Values used to define shifts from normal and high from baseline.

Parameter	Normal Value	High Value
Total cholesterol (mg/dL)	<200	≥240
LDL cholesterol (mg/dL)	<100	>160
HDL cholesterol (mg/dL)	≥40	<40
Triglycerides (mg/dL)	<150	≥200
Glycated hemoglobin (g/dL)	4.0–6.0	>6.5
Plasma glucose (mg/dL)	<100	≥126
Prolactin (ng/mL) – males	<4.0	≥15.2
Prolactin (ng/mL) – females	<4.8	≥23.3

Supplementary eTable 2. Shifts in Prolactin

Parameter	Shift From low/Normal at Baseline to High/3xULN at any Post Baseline Assessment			Shift from High/3xULN at Baseline to low/Normal at Last Post Baseline Assessment		
	Aripiprazole Lauroxil			Aripiprazole Lauroxil		
	441 mg n/m (%)	882 mg n/m (%)	Placebo n/m (%)	441 mg n/m (%)	882 mg n/m (%)	Placebo n/m (%)
Prolactin (Male)	3/105 (2.9)	4/111(3.6)	26/102 (25.5)	19/22 (86.4)	12/17 (70.6)	9/20 (45)
Prolactin (Female)	6/38 (15.8)	3/41 (7.3)	14/41 (34.1)	12/20 (60)	11/19 (57.9)	6/20 (30)

n is the number of patients in each category; m is the total number of patients with non-missing numeric values at baseline and any post-baseline visit for each treatment group.