A 52-Week, Double-Blind Evaluation of the Metabolic Effects of Aripiprazole and Lithium in Bipolar I Disorder

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ABSTRACT

Introduction: Metabolic risk factors, termed *metabolic syndrome*, which include obesity, diabetes, dyslipidemia, and hypertension, are more common in patients with bipolar disorder than in the general population. Moreover, medications used to treat bipolar disorder carry some risk of worsening metabolic parameters.

Method: The study was conducted at 46 study centers in the United States, although only 31 study centers enrolled patients in the 40-week extension phase. Patients with acute bipolar I mania, manic or mixed (*DSM-IV-TR* criteria; Young Mania Rating Scale score ≥ 20), who required hospitalization were randomly assigned to double-blind aripiprazole (15–30 mg/d), lithium (900–1500 mg/d), or placebo for 3 weeks. Patients treated with aripiprazole or lithium continued treatment to week 12, after which they could enter a double-blind 40-week extension phase. Patients were enrolled in the 12-week acute treatment phase between April 2004 and July 2006; the first patient entered extension treatment in October 2004, and the last patient completed treatment in May 2007. Changes in metabolic parameters were compared between patients treated with aripiprazole or lithium for up to 52 weeks using last observation carried forward and analysis of covariance. Analysis stratified by baseline body mass index (BMI) was also conducted.

Results: Modest increases in body weight were observed in both groups: +0.97 kg (2.1 lb) for aripiprazole (n = 127) and + 0.74 (1.6 lb) for lithium (n = 136), *P* = .60. A significant difference in body weight increase was observed only among patients with a BMI < 25: + 2.66 kg (5.9 lb) for aripiprazole (n = 35) and + 0.40 kg (0.9 lb) for lithium (n = 37), *P* = .02. Mean changes from baseline to week 52 in fasting levels of total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, plasma glucose, triglycerides, or insulin (last observation carried forward) were small in both aripiprazole and lithium treatment groups; no significant differences were observed. Mean laboratory values were within the normal or borderline range for both treatment groups across all BMI categories.

Conclusion: Comparably modest and similar changes in metabolic parameters were observed in patients with bipolar disorder treated for up to 1 year with either lithium or aripiprazole.

Trial Registration: clinicaltrials.gov Identifier: NCT00095511

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Individuals with bipolar disorder are at higher risk of medical mortality than the general population, primarily due to increased risk of cardiovascular disease.[1] Subsequently, metabolic abnormalities such as weight gain, dyslipidemia, hyperglycemia, and diabetes, known risk factors for cardiovascular disease, are important long-term health concerns in individuals with bipolar disorder. Additionally, a collection of metabolic risk factors, termed *metabolic syndrome*, which includes obesity, diabetes, dyslipidemia, and hypertension, is more common in patients with bipolar disorder than in the general population, further contributing to the increased risk of cardiovascular disease in this patient group.[2–4]

There are a number of reasons why individuals with bipolar disorder may be at increased risk for metabolic disturbances. These reasons include socioeconomic and behavioral mechanisms, such as the impact of the condition on lifestyle and nutrition, and possible direct pathophysiologic links between mental illness and metabolic disturbance. For example, depressive and mixed episodes may be associated with hypothalamic pituitary-adrenal axis disturbance, leading to sustained cortisol elevation and ultimately obesity and insulin resistance.[5] Although causal relationships between psychiatric illnesses such as bipolar disorder and metabolic abnormalities remain unclear, a number of medications carry a potential risk of worsening metabolic parameters and weight gain.[6] For example, weight gain is commonly reported with mood stabilizer treatment with lithium and valproate,[7] and atypical antipsychotics are associated with a differing potential to cause weight gain.[8–10] Although the atypical antipsychotics also carry a class warning for hyperglycemia, published data suggest that the metabolic liability of each atypical antipsychotic is different, with varying effects on lipids and glucose metabolism.[9,11] In general, associations between treatment and diabetes risk are lower for aripiprazole, haloperidol, and ziprasidone and relatively higher for clozapine and olanzapine.[12–15] In addition to low potential for metabolic disturbance with aripiprazole, some data suggest that switching to aripiprazole may lead to improvement in metabolic parameters.[16,17]

As weight gain, obesity, and metabolic disturbances have important long-term health consequences, it is important to fully understand the metabolic effects of treatments used in the long-term management of bipolar disorder. Furthermore, the presence of metabolic abnormalities in individuals with bipolar disorder may be associated with nonremission and an increased likelihood of recurrence and poor functional outcome[18,19] and may also play a role in neurocognitive impairment.[20,21]

The safety and efficacy of aripiprazole for the treatment of patients with manic or mixed episodes of bipolar I disorder have been demonstrated in both placebo- and active-controlled patients.[22–26] In addition, aripiprazole has been shown to maintain symptomatic stability for up to 100 weeks in a placebo-controlled monotherapy study.[27,28] Aripiprazole monotherapy is considered to have a low

Clinical Points

- Individuals with bipolar disorder are at high risk for metabolic abnormalities.
- In the current study, modest changes in metabolic parameters occurred with aripiprazole or lithium treatment for up to 1 year.
- All patients with bipolar disorder should undergo regular metabolic health monitoring.

potential for weight gain and a low risk for diabetes or adverse effects on lipid profiles.[9,11,14,29–33] In bipolar disorder, results from a randomized, double-blind, 12-week study have shown no clinically meaningful differences in metabolic parameters or overall weight gain between aripiprazole and lithium during short-term treatment,[24] and results from a long-term, placebo-controlled, maintenance study have shown no significant differences in mean weight gain or glucose and lipid levels between aripiprazole and placebo over a 100-week study period.[28]

The primary objective of the current analyses was to assess the long-term metabolic effects of aripiprazole monotherapy relative to lithium monotherapy. Patients completing a 12-week controlled trial[24] could enter an extension phase in which they continued to receive their assigned medication, aripiprazole or lithium, for an additional 40 weeks in a blinded fashion. We report the metabolic findings from this long-term dataset.

METHOD

Study Design

This was a long-term, multicenter, double-blind, controlled trial evaluating safety and efficacy of aripiprazole relative to lithium for treatment of bipolar I disorder, mixed or manic, with or without psychotic features. The study consisted of a 12-week acute treatment phase followed by a 40-week extension phase. The study was conducted at 46 study centers in the United States, although only 31 study centers enrolled patients into the 40-week extension phase. Patients were enrolled in the 12-week acute treatment phase between April 2004 and July 2006; the first patient entered extension treatment in October 2004, and the last patient completed treatment in May 2007. The study was conducted in compliance with the Declaration of Helsinki and Good Clinical Practice. Institutional review board/independent ethics committee approval was received prior to study initiation. The trial is registered in clinicaltrials.gov (Identifier: NCT00095511).

Patients who completed the 12-week, randomized, double-blind, placebo-controlled study, and for whom continued participation in the study was indicated per investigator judgment, had the option to enter a 40-week extension phase. Full details of the double-blind, placebo-controlled study have been published previously.[24] Briefly, patients with acute bipolar I mania (*DSM-IV-TR* criteria)[34] experiencing an acute manic or mixed episode requiring hospitalization and a Young Mania Rating Scale score ≥ 20 were randomly assigned to double-blind aripiprazole, lithium, or placebo treatment for 3 weeks. Patients receiving aripiprazole or lithium continued to receive blinded treatment for an additional 9 weeks, while placebo patients were blindly switched to double-blind aripiprazole for the remaining 9 weeks of the study; data from these patients are not included in the aggregate analyses presented here. Patients whom the investigator deemed would benefit from continued treatment entered the 40-week extension phase and continued to receive the same treatment in a double-blind fashion that they were receiving at week 12.

Study Treatments

All patients entering the extension phase continued to receive the same study medication that they were receiving at the end of the 12-week treatment phase (aripiprazole 15 or 30 mg/d or lithium 900 or 1,200 or 1,500 mg/d). Patients who received placebo during the first 3 weeks of the 12-week treatment phase and who were blindly switched to aripiprazole after week 3 continued to receive the same dose of aripiprazole during the extension phase. Aripiprazole was administered once daily; lithium was administered 3 times daily. Lithium doses could be altered based on serum lithium concentrations to ensure that patients were maintained within the target therapeutic serum level of 0.60–1.20 mEq/L. As lithium-treated patients required regular blood sampling, false (sham) levels of lithium were reported for patients receiving aripiprazole or placebo in order to maintain the treatment blinding.

Concomitant antidepressants were not permitted during this study. Concomitant benzodiazepines, sleep aids, benztropine, and propranolol were permitted as previously reported.[24]

Assessments and Statistical Analyses

Efficacy and safety findings of this long-term extension study have been reported previously.[35] This article reports the metabolic effects of aripiprazole relative to lithium and includes measurement of body weight and body mass index (BMI) and laboratory assessment of fasting levels of total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides, plasma glucose, and insulin. Laboratory tests and weight measurements were assessed at screening, baseline, and weeks 3, 12, and 52 or at the time of study discontinuation. Criteria for defining clinically significant changes in metabolic parameters were as follows: fasting total cholesterol ≥ 240 mg/dL, fasting glucose ≥ 115 mg/dL, fasting HDL-C ≤ 30 mg/dL, fasting LDL-C ≥ 160 mg/dL, and fasting triglycerides ≥ 120 mg/dL for females or ≥ 160 mg/dL for males. Clinically significant weight gain or loss was an increase or decrease ≥ 7% from baseline, respectively.

Analyses were performed on the safety sample, which included all patients originally randomly assigned to aripiprazole or lithium treatment who received at least 1

dose of study medication during the double-blind treatment phase, and the extension-phase safety sample, which included all patients randomly assigned to aripiprazole or lithium who received at least 1 dose of study medication during the 40-week extension phase.

The mean change from baseline in patient weight and metabolic parameters at week 52 was analyzed using analysis of covariance (ANCOVA), with treatment as main effect and baseline measure as a covariate, using both the safety sample and the extension phase safety sample, whereas the percentage of patients showing clinically relevant weight gain/loss from baseline to week 52 was analyzed with the Cochran-Mantel-Haenszel procedure using the extension phase safety sample.

The mean change from baseline in patient weight and metabolic parameters at week 52 was also investigated stratified by baseline BMI using ANCOVA, with treatment as main effect and baseline measure as a covariate. For this analysis, the following criteria were used: underweight/normal = BMI < 25 kg/m^2, overweight = BMI ≥ 25 kg/m^2 and < 30 kg/m^2, and obese = BMI ≥ 30 kg/m^2.

RESULTS

Patient Characteristics and Demographics

In total, 480 patients were initially randomly assigned to treatment (lithium, n = 160; aripiprazole, n = 155; placebo, n = 165), of whom 99 entered the double-blind extension phase; 33 of these patients received placebo and were not included in the aggregate analyses presented here, leaving 28 patients entering extension treatment taking aripiprazole and 38 patients entering extension treatment taking lithium. Overall, 20 of these patients completed the 40-week extension phase: 7 patients in the aripiprazole group and 13 patients in the lithium group. Full details of patient disposition have been reported previously.[35]

The safety sample consisted of 159 patients from the lithium group and 154 patients from the aripiprazole group; 1 patient in each group did not receive study medication. Three aripiprazole patients entered the 40-week extension phase but discontinued prior to starting the 40-week extension phase study medication; thus, the extension phase safety sample included 38 patients from the lithium group and 25 patients from the aripiprazole group.

Baseline patient demographics for the extension phase are shown in Table 1. Overall, the demographic characteristics were similar across treatment groups with the exception of race and type of current episode; a higher proportion of white subjects were treated with lithium than aripiprazole, and more lithium than aripiprazole patients were experiencing a mixed episode. The demographic characteristics of patients entering the extension phase were also similar to those of the randomized patient population.

Stratification of the safety sample by BMI revealed that a larger proportion of patients had a baseline BMI ≥ 30 kg/m^2 (lithium 41.8%, aripiprazole 43.4%) compared with those with a BMI < 25 kg/m^2 (lithium 27.2%, aripiprazole 27.6%) and those with a BMI ≥ 25 kg/m^2 and < 30 kg/m^2 (lithium 31.0%, aripiprazole 28.9%).

Table 1. Patient Demographic Characteristics of the Extension Phase Safety Sample

Variable	Lithium (n = 38)	Aripiprazole (n = 25)
Age, y		
Mean (SD)	41.21 (9.84)	37.50 (11.85)
Range	18–63	22–69
Gender, n (%)		
Male	19 (50)	10 (40)
Female	19 (50)	15 (60)
Race, n (%)		
White	31 (82)	15 (60)
Black	5 (13)	10 (40)
Asian	1 (3)	0
Other	1 (3)	0
Weight, kg		
Mean (SD)	82.2 (16.6)	87.8 (20.0)
Range	53.1–115.7	51.9–144.2
Body mass index, kg/m^2		
Mean (SD)	28.4 (5.3)	30.5 (6.9)
Range	17.8–43.8	20.1–45.6
Current episode, n (%)		
Bipolar manic	20 (53)	16 (64)
Bipolar mixed	18 (47)	9 (36)
Psychotic symptoms present, n (%)	5 (13)	7 (28)

Study Treatments and Concomitant Medications

For the aripiprazole-treated patients, the mean daily dose of aripiprazole during the last 4 weeks of the acute phase (weeks 9–12) was 24.7 mg/d (days 57–84). From then to the end of week 52, the mean 4-weekly daily dose was between 20.8 mg/d and 23.9 mg/d. During the last 4 weeks of the extension phase, the mean daily dose of aripiprazole was 21.7 mg/d. For the lithium-treated patients, the mean daily dose during the last 4 weeks of the acute phase was 1,188.5 mg/d (days 57–84). Thereafter, to the end of week 52, the mean 4-weekly daily dose of lithium was between 1,119.5 mg/d and 1,211.7 mg/d.

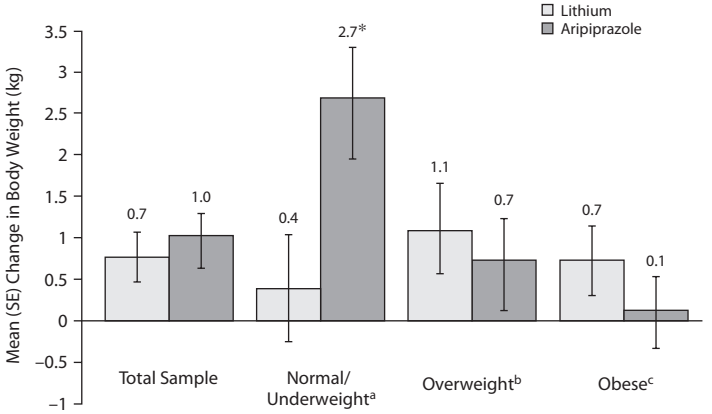
Weight

Weight gain was moderate and not statistically significantly different between treatments over 1 year of treatment. At week 52 (last observation carried forward [LOCF] safety sample), the mean weight change from baseline was 0.74 kg (1.6 lb) in the lithium group and 0.97 kg (2.1 lb) in the aripiprazole group ($P = .60$). Similarly, for patients who remained on treatment at week 52 (observed cases [OC] extension phase safety sample), the mean weight change was 2.71 kg (6.0 lb) in the lithium group (n = 9) and 5.66 kg (12.5 lb) in the aripiprazole group (n = 7, $P = .46$).

Mean change in weight stratified by baseline BMI is shown in Figure 1. There were no significant differences between treatment groups in mean weight change from baseline to week 52 (LOCF safety sample), with the exception of patients with a baseline BMI < 25 kg/m^2 (underweight/normal), who showed a greater increase in mean weight when treated with aripiprazole.

For patients who remained on treatment at week 52 (OC extension phase safety sample), there were no statistically

Figure 1. Mean (SE) Change in Weight From Baseline to End of Week 52 for Total Safety Sample and Stratified by Baseline BMI (last observation carried forward)



Baseline Weight (kg)

Lithium	88.8 (n = 136)	66.1 (n = 37)	83.9 (n = 39)	106.0 (n = 60)
Aripiprazole	88.3 (n = 127)	66.6 (n = 35)	82.4 (n = 37)	106.0 (n = 55)

[a]Normal/underweight = BMI < 25 kg/m^2.
[b]Overweight = BMI ≥ 25 kg/m^2 and < 30 kg/m^2.
[c]Obese = BMI ≥ 30 kg/m^2.
*Aripiprazole vs lithium: $P = .02$.
Abbreviations: BMI = body mass index, SE = standard error.

significant differences between the lithium and aripiprazole groups in the numbers and percentages of patients showing clinically relevant weight gain (20.0% vs 42.9%, $P = .323$) or weight loss (10.0% vs 0%, $P = .403$).

Metabolic Parameters

There were no significant differences between the lithium and aripiprazole treatment groups in mean changes from baseline to week 52 in fasting levels of total cholesterol, HDL-C, LDL-C, plasma glucose, triglycerides, or insulin (LOCF, Figure 2A). Similar results were obtained for the OC analysis (Figure 2B).

Mean change from baseline in fasting metabolic measures stratified by baseline BMI is shown in Table 2. After stratification by baseline BMI, there were no significant differences from baseline to week 52 in fasting levels of total cholesterol, HDL-C, LDL-C, plasma glucose, triglycerides, or insulin levels with the exception of total cholesterol for the normal/underweight (BMI < 25 kg/m^2) group and insulin levels for the overweight (≥ 25 kg/m^2 and < 30 kg/m^2) group. In both groups, the significant differences between the treatment groups were the result of mean decreases with lithium treatment compared to aripiprazole (total cholesterol: −13.64 vs 3.50 mg/dL, $P = .05$ and insulin levels: −0.22 vs 0.54 μU/mL, $P = .04$).

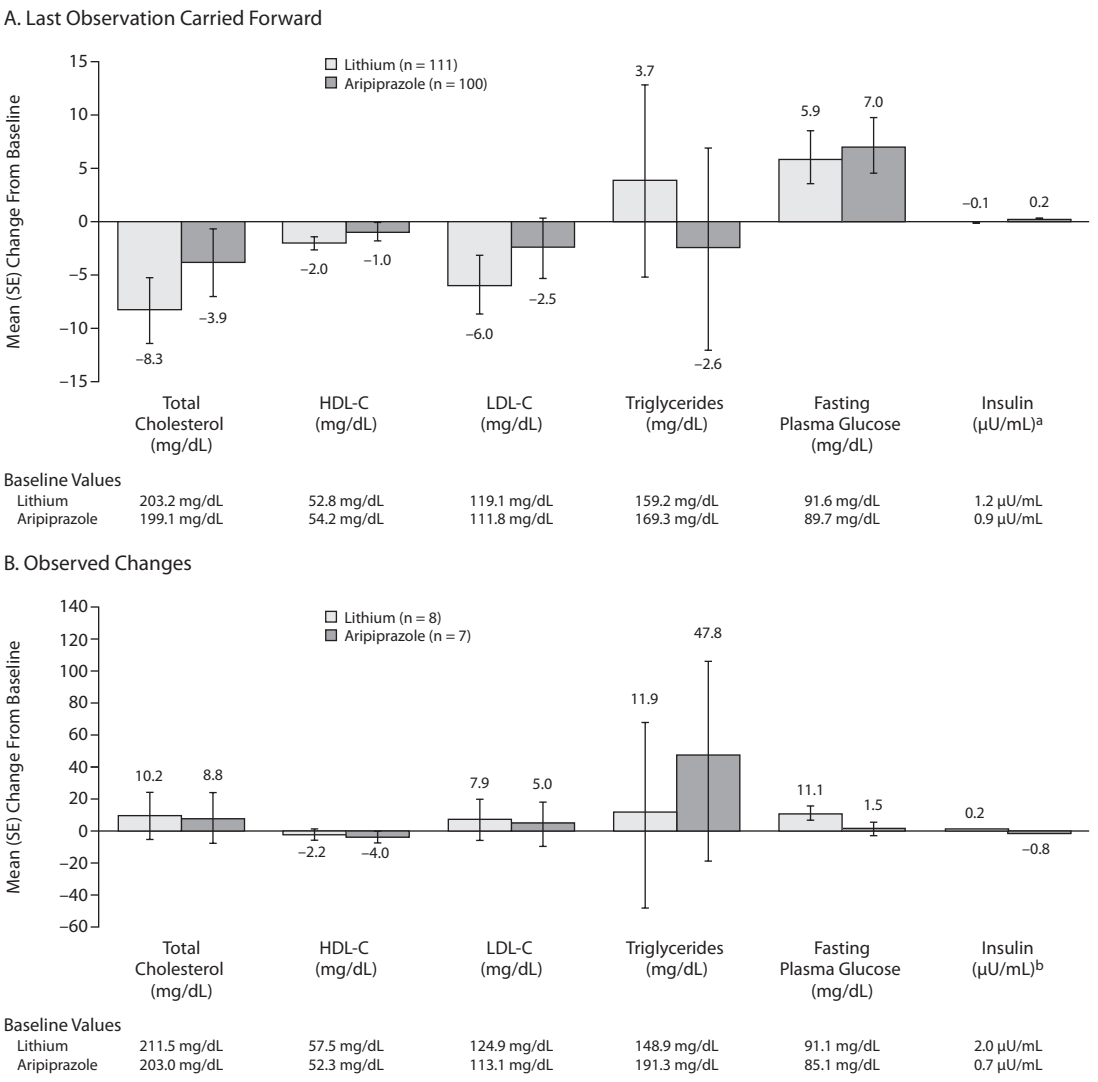
The proportions of patients with potentially clinically significant metabolic abnormalities (see Method for definitions) during the 40-week extension phase were as follows for lithium (n = 38) and aripiprazole (n = 25), respectively: fasting total cholesterol, 16.1% vs 28.6%; fasting glucose, 13.3% vs 14.3%; fasting HDL-C, 0% vs 7.1%; fasting LDL-C, 17.2% vs 14.3%; and fasting triglycerides, 63.3% vs 50.0%.

DISCUSSION

Results from this double-blind, long-term extension study found modest changes in metabolic parameters in patients with bipolar disorder treated with either aripiprazole or lithium for up to 1 year. Taken together, the tolerability data presented herein are aligned with the previously reported study, demonstrating that aripiprazole monotherapy is effective in the long-term treatment of bipolar disorder compared to lithium monotherapy.[35]

In this study, both aripiprazole and lithium treatment were associated with a modest increase in weight. For both treatments, the observed weight changes in this study differ to some extent from previous reports. For aripiprazole, previous long-term studies with aripiprazole monotherapy in patients with schizophrenia, schizoaffective disorder, or bipolar disorder have generally demonstrated minimal weight gain with similar exposures.[28,30,36,37] For example, mean weight change was + 0.4 kg (0.9 lb, LOCF) over 100 weeks of treatment with aripiprazole in patients with bipolar disorder[28] and was + 0.3 kg (0.7 lb) (random regression model analysis) following 52 weeks of treatment with aripiprazole in patients with schizophrenia,[38] both of which are lower than the weight gain with aripiprazole reported here (+ 0.97 kg [2.1 lb], LOCF). Conversely, the magnitude of weight gain over 52 weeks of treatment with lithium reported here (0.74 kg [1.6 lb], LOCF) is lower than that reported in previous studies. Lithium treatment resulted in a mean change in weight at week 52 of + 2.2 kg (4.8 lb, mixed-model repeated-measures analysis) in analysis of data from 2 double-blind, placebo- and lamotrigine-controlled, 18-month studies in patients with bipolar I disorder,[39] whereas older data suggest mean weight gain of 4 kg (8.8 lb) over 1 year of treatment.[7]

Figure 2. Mean (SE) Change in Fasting Metabolic Measures From Baseline to Week 52 for the Total Safety Sample



[a]Lithium: n = 87, aripiprazole: n = 80.
[b]Lithium: n = 7, aripiprazole: n = 5.
Abbreviations: HDL-C = high-density lipoprotein cholesterol, LDL-C = low-density lipoprotein cholesterol, SE = standard error.

Analysis of weight gain by baseline BMI revealed that weight gain was greatest with aripiprazole in patients who were in the normal/underweight BMI category at baseline. This is similar to findings in schizophrenia for which weight gain was predominantly observed in patients with a low BMI.[30] Although weight gain with lithium appeared to be similar across the baseline BMI categories in this study, previous data have shown higher mean changes in weight with lithium over 52 weeks in obese patients (+6.1 kg [13.5 lb]) than in nonobese patients (+1.1 kg [2.4 lb]).[41] Thus, the differential effects of weight gain by baseline BMI should be interpreted with caution. Regardless, it is notable that, at baseline, just over 40% of the population enrolled in this study were obese (BMI > 30 kg/m^2), which is consistent with the known risk of obesity in patients with bipolar disorder.[41,42]

The effect of both treatments on metabolic laboratory tests was minimal. No clinically meaningful differences were reported between lithium and aripiprazole in the incidence of potentially clinically relevant laboratory abnormalities or in the mean change in laboratory measures during long-term treatment. There were also no overall differences in mean change in lipid, glucose, or insulin levels in the total population. Although there were statistically significant differences in total cholesterol and insulin levels between treatment groups in the normal/underweight and overweight groups, respectively, these differences were driven by a decrease in levels with lithium treatment over the course of treatment. In both groups, elevated fasting triglyceride levels was the most frequently reported potentially clinically relevant lipid abnormality.

All patients receiving treatment with atypical antipsychotics, including those with bipolar disorder, should be monitored for weight gain and metabolic disturbances in accordance with current guidelines and proactively

Table 2. Mean Change From Baseline to Week 52 in Fasting Metabolic Measures Stratified by Baseline Body Mass Index: Underweight/Normal, Overweight, and Obese (safety sample, last observation carried forward)

	Underweight/Normal			Overweight			Obese		
Measure	Lithium (n = 29)	Aripiprazole (n = 25)	*P* Value	Lithium (n = 31)	Aripiprazole (n = 28)	*P* Value	Lithium (n = 50)	Aripiprazole (n = 45)	*P* Value
Total cholesterol (mg/dL)									
Baseline, mean	190.00	176.96	…	216.58	212.39	…	203.50	203.42	…
Mean (SE) change at wk 52	−13.64 (5.8)	3.50 (6.3)	.05	−11.75 (5.9)	−7.77 (6.2)	.65	−4.31 (4.5)	−5.18 (4.7)	.89
HDL-C (mg/dL)									
Baseline, mean	56.41	60.04	…	50.87	54.93	…	51.70	50.07	…
Mean (SE) change at wk 52	−1.47 (1.9)	0.70 (2.0)	.44	−2.87 (1.3)	−1.60 (1.4)	.51	−1.96 (1.0)	−1.57 (1.0)	.78
LDL-C (mg/dL)									
Baseline, mean	110.27	96.72	…	133.16	121.68	…	116.66	114.44	…
Mean (SE) change at wk 52	−13.3 (5.0)	−1.38 (5.4)	.11	−7.51 (5.2)	−5.47 (5.5)	.79	−1.79 (3.9)	−1.14 (4.1)	.91
Triglycerides (mg/dL)									
Baseline, mean	120.28	103.56	…	165.45	181.03	…	178.38	200.73	…
Mean (SE) change at wk 52	3.75 (19.9)	21.57 (21.4)	.55	−5.63 (13.2)	−6.66 (13.9)	.96	9.36 (14.4)	−11.82 (15.1)	.31
Glucose (mg/dL)									
Baseline, mean	88.03	85.48	…	90.06	85.32	…	95.06	95.29	
Mean (SE) change at wk 52	2.99 (3.3)	−1.63 (3.5)	.34	3.86 (2.1)	8.65 (2.2)	.12	8.71 (5.1)	9.55 (5.4)	.91
Insulin (μU/mL)[a]									
Baseline, mean	1.13	0.70	…	0.95	0.99	…	1.34	1.04	…
Mean (SE) change at wk 52	−0.26 (0.11)	−0.39 (0.13)	.45	−0.22 (0.25)	0.54 (0.26)	.04	0.12 (0.19)	0.21 (0.19)	.74

[a]Underweight/normal: n = 26 for lithium, n = 19 for aripiprazole; overweight: n = 24 for lithium, n = 22 for aripiprazole; obese: n = 36 for lithium, n = 45 for aripiprazole.
Abbreviations: HDL-C = high-density lipoprotein cholesterol, LDL–C = low-density lipoprotein cholesterol, SE = standard error.
Symbol: … = no data.

managed should it occur.[11,43] In fact, there is increasing awareness among psychiatrists that medical therapies beyond antipsychotics for bipolar disorder have the potential to cause metabolic abnormalities, and this growing recognition has prompted many clinicians to regularly monitor weight and other metabolic parameters in their patients and to initiate intervention where necessary.[6] With this in mind, waist circumference, triglyceride to HDL-C ratio, or BMI have all been shown to be sensitive to the prediction of metabolic syndrome in antipsychotic-treated patients, and abnormalities in any of these parameters should prompt a full evaluation for metabolic syndrome.[44]

This study had several limitations. The number of patients completing the full 52 weeks of treatment was small, although high discontinuation rates are not uncommon in long-term trials in patients with bipolar mania. Furthermore, although this study provides a useful insight into the comparable effects of lithium and aripiprazole treatment on metabolic parameters, the study was not powered to statistically compare the 2 active treatments during the initial 12 weeks of treatment or during the extension phase of the study. The study was also not prospectively designed to examine the metabolic effects of treatment. Finally, the high attrition rate, coupled with the exclusion of patients with rapid-cycling bipolar mania, indicates that the results should be generalized with caution to a wider population of patients with bipolar mania. It should also be considered that the impact of clinical trial participation on the weight and metabolic findings of this study is unknown.

In conclusion, it is now widely recognized that patients with bipolar disorder are at an increased risk of long-term metabolic health problems. Although this study revealed only modest changes in metabolic parameters for up to 1 year of treatment with either aripiprazole or lithium, all patients treated with atypical antipsychotics or lithium should be monitored appropriately for changes in metabolic parameters given their implications for overall patient health.

Drug names: aripiprazole (Abilify), benztropine (Cogentin and others), clozapine (Clozaril, FazaClo, and others), haloperidol (Haldol and others), lamotrigine (Lamictal and others), lithium (Lithobid and others), olanzapine (Zyprexa), propranolol (Inderal, InnoPran, and others), ziprasidone (Geodon).

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Potential conflicts of interest: **Dr McIntyre** has received grant/research support from AstraZeneca, Eli Lilly, Janssen-Ortho, National Alliance for Research on Schizophrenia and Depression, Shire, Stanley Medical Research Institute, and Pfizer; has served on the advisory boards of AstraZeneca, Biovail, Bristol-Myers Squibb, Eli Lilly, France Foundation, GlaxoSmithKline, Janssen-Ortho, Lundbeck, Merck, Organon, Pfizer, Schering-Plough, Shire, and Solvay/Wyeth; has served on the speaker's bureaus for AstraZeneca, Biovail, Eli Lilly, Janssen-Ortho, Lundbeck, and Merck; has received income from CME activities from AstraZeneca, Bristol-Myers Squibb, CME Outfitters, Eli Lilly, France Foundation, I3CME, Merck, Optum Health, Physicians Postgraduate Press Inc., Schering-Plough, and Solvay/Wyeth; and has received travel support from Bristol-Myers Squibb. **Dr McElroy** has served as a consultant to and is a member of the scientific advisory boards for Alkemes, Eli Lilly, and Shire and is a principal or coinvestigator on research studies sponsored by the Agency for Healthcare Research and Quality (AHRQ), Alkermes, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Forest, GlaxoSmithKline, Jazz, Marriott Foundation, National Institute of Mental Health, Orexigen Therapeutics, Shire, and Takeda. **Dr Carlson** and **Mr Eudicone** are employees of Bristol-Myers Squibb. **Dr Baker** was an employee of Bristol-Myers Squibb at the time of the study and is currently an employee of Otsuka Pharmaceutical Development & Commercialization, Inc. **Dr Forbes** is an employee of Otsuka Pharmaceutical Development & Commercialization, Inc.

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