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Ziprasidone with Adjunctive Mood Stabilizer in the Maintenance Treatment of Bipolar I Disorder: Long-term Changes in Weight and Metabolic Profiles

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Abstract

This analysis was conducted to compare the effects of adjunctive ziprasidone or placebo on metabolic parameters among patients receiving maintenance treatment with lithium or valproate. We also tested whether metabolic syndrome (MetS) and other risk factors were associated with baseline characteristics and treatment response. In the stabilization phase (Phase 1), 584 bipolar I disorder (DSM-IV) patients received 2.5-4 months of open label ziprasidone (80-160 mg/d) plus lithium or valproic acid (ZIP+MS). Patients who achieved at least 8 weeks of clinical stability were subsequently randomized into Phase 2 to 6-months of double-blind treatment with ZIP+MS (N=127) vs. placebo+MS (N=113). At baseline of Phase 1, MetS was found in 111 participants

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(23%). Participants with MetS (vs. non-MetS participants) were more likely to be aged 40 years or older, had significantly more severe manic symptoms, higher abdominal obesity, and higher BMI. Increase in abdominal obesity was associated with lower manic symptom improvement ($p<0.05$, as assessed by MRS change score) during Phase 1, while symptom improvement differed across racial groups. In the Phase 2 double-blind phase, the ZIP+MS group had similar weight and metabolic profiles compared to the placebo+MS group across visits. These results corroborate existing findings on ziprasidone which exhibits a neutral weight and metabolic profile in the treatment of schizophrenia and bipolar patients. Our findings suggest that MetS is highly prevalent in patients with bipolar disorder, may be associated with greater manic symptom severity, and may predict treatment outcomes.

Keywords

Metabolic syndrome; medical comorbidity; treatment remission; ziprasidone

1. Introduction

The proliferation of an increasingly obese population in both developed and emerging countries, with associated cardiovascular and metabolic risk factors, is becoming the focus of health improvement efforts not only for the general public but now also for those with mental disorders. The cardiovascular risk factor cluster, commonly known as metabolic syndrome (MetS), is characterized by elevated blood pressure, elevated triglycerides, low HDL cholesterol levels, hyperglycemia, and central obesity. Approximately 34% of US adults have MetS (Ford 2005). The prevalence in both males and females increases with BMI and age, reaching a 3-fold increase in the 40-59 year age group compared to those 20-39 years (Ervin et al., 2009). MetS is highly prevalent (>75%) in patients with type 2 diabetes or impaired glucose tolerance and is detected in approximately 50% of patients with coronary heart disease (Fauci et al., 2008).

Among patients with schizophrenia, the risk of MetS rises dramatically in comparison to the general population (138 % for males and 251% for females) (McEvoy et al., 2005). Similar percentages are seen for bipolar disorder patients. Patients with bipolar disorder are at increased risk of cerebrovascular diseases, late-onset diabetes and liver diseases associated with MetS. Such increased risks for MetS have been documented in at least twelve countries from Europe, Australia, Asia, North and South America (McIntyre et al., 2010). More problematic, the increase in cardiometabolic risk factors among patients with bipolar disorder translates into a near doubling of the death rates from cardiovascular causes (Osby et al., 2001; Angst et al., 2002).

Combination therapies with currently marketed second generation antipsychotics (SGAs) are increasingly used for the treatment of bipolar disorder, especially for patients with psychotic manifestations, with inadequate response to initial monotherapy with a mood stabilizer (lithium or valproate), or who are in long-term maintenance treatment (Fountoulakis et al., 2005; Smith et al., 2007; Yatham et al., 2009). In addition, there is growing concern that several SGAs currently marketed for the treatment of schizophrenia and bipolar disorder are associated with significant weight gain and other cardiometabolic risk factors, including elevated blood glucose levels and undesirable lipid (cholesterol and triglycerides) profiles (Sanger et al., 2001; Newcomer, 2005; Suppes et al., 2005; Lieberman et al., 2005). The untoward metabolic changes associated with some SGAs may account in part for the startling high prevalence rates of MetS among patients with psychiatric disorders. Compounding these side effect burdens, some studies show that combination treatment with an antipsychotic and a mood stabilizer results in greater weight gain than monotherapy with

either an antipsychotic or a mood stabilizer (Kim et al., 2008), and that short-term differences in weight gain among typical and atypical antipsychotics may become less pronounced with extended treatment (Perez-Iglesias et al., 2008). Furthermore, pharmacoepidemiological and case-control studies suggest the mood stabilizers as a class display different tolerability and side-effect profiles (Henner et al., 2004), including a differential propensity among antipsychotic agents for the risk of developing diabetes (Guo et al., 2006; Yood et al., 2009) .

In this post-hoc analysis, we investigated the prevalence of MetS and associated risk factors in patients with bipolar I disorder using baseline data obtained at the screening visit of a multi-center, randomized, double-blind, placebo-controlled maintenance trial. The associations of MetS risk with symptom severity and relapse (intervention for mood episode) as well as clinical and demographic characteristics including age, gender, race, and body mass index (BMI) were also investigated. We further explored the effect of ziprasidone therapy adjunctive to a mood stabilizer on weight and metabolic abnormalities over 6 months of double-blind maintenance treatment.

2. Experimental Procedures

2.1 Study Design

This was a post-hoc analysis of metabolic parameters and associated risk factor data from a double-blind, placebo-controlled trial designed to evaluate the maintenance of effect of ziprasidone (ZIP) plus adjunctive lithium (Li) or valproate/valproic acid (VAL) therapy in symptomatic subjects with a recent or current manic or mixed episode of bipolar I disorder. The trial consisted of an open-label stabilization period of up to 16 weeks (Period 1) followed by a 6 month, double-blind maintenance period (Phase 2). The study design has been described in detail elsewhere (Bowden et al., 2010).

In the stabilization period (Phase 1), open-label ZIP (40-80 mg, taken with food twice daily for a total daily dose of 80-160 mg) was added to Li (0.6 - 1.2 mEq/L) or VAL (50-125 μg/ml) after the mood stabilizer had been maintained within this therapeutic blood level for at least 2 weeks. Subjects who achieved symptomatic stability for 8 consecutive weeks on the open-label adjunctive regimen (as assessed by a CGI-I score ≤3) and who were on a stable treatment regimen during the final 4 weeks of the 8 weeks of stability were randomized into Phase 2 in a 1:1 ratio to ZIP+MS or PBO+MS to evaluate the maintenance of effect for up to an additional 6 months. During the open-label stabilization period, serum Li and VAL levels were examined at screening, baseline, Weeks 2, 4, 8, 12, and 16 or end of treatment. During the double-blind maintenance period, serum Li and VAL levels were measured at Week 2, 4, 8, 12, 16, and 24. The study was approved by the Institutional Review Board and/or Independent Ethics Committee at each center and was conducted in compliance with the ethical principles of the Declaration of Helsinki and with all guidelines of the International Conference on Harmonization's Good Clinical Practice. The study was conducted at 118 centers: 68 in the United States, 41 in Asia/Europe, and 9 in Latin America from December 2005 to May 2008 (clinicaltrials.gov identifier: NCT00280566).

Clinical laboratory tests were performed under fasting conditions at multiple visits during the trial. During the open-label stabilization period, the laboratory tests conducted included high density lipoprotein cholesterol (HDL), low density lipoprotein cholesterol (LDL), triglycerides, and glucose; measured under fasting conditions at screening baseline, Weeks 4, 12, and 16 or at the end of open-label treatment. During the double-blind maintenance period, fasting levels were obtained for HDL, LDL, triglycerides, and glucose at Weeks 4, 12, and 24.

2.2 Analysis Methods

The presence of MetS was assessed using the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATPIII) criteria (Grundy et al., 2005) as meeting at least 3 of the following 5 criteria: waist circumference > 102 cm (males) or > 88 cm (females); triglycerides ≥ 150 mg/dL; HDL-C < 40 mg/dL (males) or < 50 mg/dL (females); systolic blood pressure (BP) ≥ 130 mm Hg and diastolic BP ≥ 85 mm Hg; blood glucose ≥ 100 mg/dL (Table 1).

In this post-hoc analysis, adjusted odd ratios of MetS for gender were obtained using logistic regression analysis, adjusting for age and race. For the open-label stabilization period (Phase 1), we applied analysis of covariance method to estimate the effect of adjunctive MS on metabolic risks. We applied logistic regression method to test the significance of association between MetS risk and symptom severity as well as baseline clinical and demographic characteristics including age, gender, race, and body mass index (BMI). The predictive value of metabolic risk factors measured during the stabilization phase (Phase 1) for predicting relapse in the subsequent double-blind Phase 2 was also investigated using a Cox regression model. We used time course data from the double-blind, placebo-controlled, adjunctive phase (Phase 2) to estimate the effect of ziprasidone plus a mood stabilizer (MS, lithium or valproic acid) on metabolic risk factors in bipolar disorder maintenance treatment. The time courses for weight changes and metabolic lipid parameters over time were analyzed using mixed model repeated measures (MMRM) method. A p-value of ≤ .05 was considered statistically significant.

3. Results

3.1 Prevalence of obesity and metabolic risks at screening baseline

Baseline demographic characteristics of participants collected at the screening visit are provided in Table 2. Baseline body weight data were available on 955 subjects (407 males; 548 females) and indicated a high overall prevalence (625/955; 65%) of overweight subjects (BMI ≥25). The prevalence was similar in males and females: 259/407 (64%) males and 366/548 (67%) females (n=548). Obesity (BMI ≥30) was found in 362/955 (38%) subjects in the overall sample; and the prevalence was significantly higher in females (n=231, 42%) than in males (n=131, 32%) ($p<0.05$) (Figure 1).

Of the 482 subjects with fasting laboratory measurement data available at screening baseline, MetS was identified in 111 subjects (23%), 44 in males vs. 67 in females ($p=0.8104$, adjusting for age and race). The prevalence rates were significantly higher in females than males in abdominal obesity (waist circumference: males >102 cm, females >88 cm) ($p<0.001$), and suboptimal HDL (males <40 mg/dL, females <50 mg/dL) ($p=0.033$), after adjusting for age and race. High blood pressure was more prevalent in males than females ($p=0.002$). No significant differences were observed between male and female subjects in elevated levels of triglycerides ($p=0.3441$) and glucose ($p=0.8741$).

In multifactor logistic regression analysis, participants with MetS at screening baseline were more likely to be older ($p=0.011$; 57% > 40 years in the MetS vs. 38% in the non-MetS group,), had more severe symptoms as assessed by MRS ≥ 18 ($p=0.027$; 79% vs. 69%,), and higher BMI ($p<0.001$; 95% vs. 55%) (c-statistics=0.82, $p<0.001$) (Figure 2). Gender ($p=0.155$) and race ($p=0.388$) were not significant in the model.

3.2 Pre-randomization open-label stabilization phase

During the open-label period, the median number of treatment days for all subjects enrolled was 59.5 days, while the median number of treatment days for subjects who were ultimately randomized into the double-blind period was higher at 77 days.

During Phase 1 with ZIP+MS treatment, the rate of shift from a normal to a MetS state (incidence rate 9%) was numerically lower than from MetS to normal (13%). Rates of transition from normal to elevated risks were, however, higher than transition from high risk to normal for triglycerides (13% vs. 8.4%) and glucose (9.6% vs. 7.4%). Overall, from screening baseline, there were significant reductions (after Bonferroni adjustment for multiple testing) in total cholesterol ($p=0.004$) and LDL ($p<0.001$) when ZIP was combined with a MS adjunct therapy; whereas, no significant changes in body weight and other metabolic risk factors were observed (Table 3). We found neutral weight gain and no significant differences in changes in individual metabolic risk factors between the adjunctive (ZIP+Li and ZIP+VAL) groups (Table 3), with the exception of glucose levels favoring ZIP +VAL group ($p=0.047$) but the difference was not significant after multiplicity adjustment.

3.3 Associations between metabolic risk and symptom severity

In multifactor regression analysis, increase in abdominal obesity was associated with lower manic symptom improvement ($p<0.05$, as assessed by MRS change score) during Phase 1, while symptom improvement differed across racial groups (blacks fared worse, and Asians fared better, than whites) (Figure 3) after adjustment for age, gender, and mood-stabilizer received. Associations of manic symptom improvement with changes in other risk factors (HDL, glucose, triglycerides, hypertension status) were not significant (all $p > 0.1$). Furthermore, the change in triglyceride level during stabilization Phase 1 was a significant baseline predictor of relapse risk (defined as intervention for a mood episode) in the double-blind maintenance phase, with increase in triglyceride level associated with higher relapse rate (−2.4, SE 5.7 mg/dL in non-relapse group vs. +25.0, SE 15.7 mg./dL in the relapse group) ($p<0.05$). Overall MetS status at randomization and the shift in risk status of other risk factors (waist circumference, HDL, glucose, and hypertension) from screening baseline were not significant predictors for risk of relapse in survival analysis (all $p > 0.05$).

3.4 Randomized double-blind adjunctive maintenance phase

Table 2 provides the demographics for subjects randomized in the double-blind period. A total of 240 subjects were randomized (127 to ZIP+Li/VAL and 113 to PBO+ Li/VAL) into the double-blind adjunct maintenance phase; 232 (111 males and 121 females) had fasting laboratory data available for analysis. The mean (SD) age was comparable for ZIP+ Li/VAL (39.6 years, SD 12.3) and the PBO+Li/VAL groups (38 years, SD 11.6). The proportion of subjects with an index episode of manic vs. mixed was 57.9% in the ZIP + Li/VAL group and 53.1% in the PBO+Li/VAL group. The mean (median) modal dose of ZIP at Week 24 was 111.4 mg/d (120 mg/d). The median treatment duration was 167 days for ZIP + Li/VAL group, compared to 141 days for PBO + Li/VAL group ($p=0.0047$, log-rank test). Discontinuation rate for any reason was significantly lower in the ZIP + Li/VAL group (33.9%, 43/127) compared to the PBO + Li/VAL group (51.4%, 57/111) ($p=0.0047$). Relapse rate in the ZIP + Li/VAL group (19.7%, 25/127) was also significantly lower than in the PBO + Li/VAL group (32.4%, 36/111) ($p=0.0104$, log-rank test).

Figure 4 shows the ZIP+MS adjunctive therapy group had a similar weight and metabolic syndrome risk profile compared to the PBO+ MS group across all visits in Phase 2, with the exception of greater worsening of HDL at Week 4 in the PBO+MS group. Change in total cholesterol levels in Phase 2 was also not significantly different between ziprasidone (mean 0.1 mg/dL, 95%CI −1.28, 1.48 mg/dL) and placebo (mean −2.1 mg/dL, 95%CI −5.37, 1.17

mg/dL). Similarly, non-significant changes were observed for LDL with mean 1.6 mg/dL (95%CI −2.05, 5.25) for ziprasidone versus 0.4 (95%CI −4.88, 5.68) for placebo.

4. Discussion

This post-hoc analysis of a 6-month, multi-center, randomized, placebo-controlled study investigated the efficacy of adjunctive ziprasidone in delaying the time to intervention for a mood episode. Our findings confirmed that among this sample of patients with a recent or current manic or mixed episode of bipolar I disorder, almost two-thirds of participants were overweight or obese, and close to a quarter had MetS at screening These results suggest that MetS is extremely common in bipolar patients and is associated with older age, higher manic symptom severity, and higher BMI. The results also confirm previous findings that the baseline prevalence rates surpassed corresponding prevalence rates of overweight/obesity and MetS among similarly-aged individuals in the general population. This once again draws attention to the growing public health concern that individuals with serious mental illness represent a vulnerable population for whom clinicians should more closely conduct metabolic monitoring and consider the potential for long-term metabolic side effects when selecting pharmacologic treatments.

In this study, ziprasidone plus mood stabilizer (lithium or valproic acid/divalproex) adjunctive therapy in the open-label, stabilization period resulted overall in small, non-significant changes in weight and other metabolic risk factors, but with significant reductions in total cholesterol ($p<0.01$) and LDL ($p<0.001$) when compared to enrollment baseline levels. In the randomized, double-blind, placebo-controlled maintenance treatment period, overall changes in weight and other metabolic parameters were relatively small when compared to the end of open-label period. These results corroborate existing findings on ziprasidone as one of the few SGAs exhibiting a neutral weight, lipid and related metabolic profile in the treatment of psychiatric patients (Newcomer 2005; Lieberman et al., 2005; Torrent et al., 2008; Unger and Scherer, 2010). In other bipolar disorder trials, maintenance treatment with olanzapine monotherapy (Tohen et al., 2006) or quetiapine adjunctive therapy to lithium or valproate (Suppes et al., 2009; Vieta et al., 2008) was associated with clinically meaningful weight gain, dyslipidemia, and diabetes-related adverse events. During maintenance treatment with aripiprazole monotherapy, clinically significant weight gain (≥ 7% increase from baseline) occurred more commonly with aripiprazole than with placebo (Keck et al., 2006). However, the rate of MetS did not significantly differ between treatment arms, suggesting that aripiprazole did not compromise the metabolic status of patients with bipolar disorder over 26 weeks of treatment (Kemp et al., 2010a).

Even over extended follow-up, ziprasidone appears to have minimal effects on body weight in patients with schizophrenia. Analysis of an integrated trials database found that patients receiving maintenance treatment over 1-year experienced a similar incidence of weight gain with ziprasidone (17%) as when taking a placebo (13%) (Parsons et al., 2009). Moreover, in patients switching from typical and/or atypical antipsychotics to ziprasidone, significant improvements in total cholesterol, LDL, HDL, and triglycerides have been shown to occur (Rossi et al., 2008). In another study, the observed reduction in body weight when switching to ziprasidone was even more remarkable, as patients lost a mean 9.8 kg and 6.9 kg when switching from olanzapine and risperidone, respectively, over 52 weeks of treatment (Weiden et al., 2008).

In the present study, the findings suggest that patients with bipolar disorder will be unlikely to experience any untoward changes in weight or metabolic risk factors during the long-term treatment of bipolar disorder when ziprasidone is used in combination with Li or VAL. This is noteworthy, as the combination of mood stabilizers and/or SGAs has generally been

associated with increased metabolic risk. Some authors have found that the greater the number of mood stabilizers taken by bipolar patients, the higher the likelihood of meeting criteria for MetS (Garcia-Portilla et al., 2008; Correll et al., 2006).

This lack of significant change may reflect the continuing neutral weight change effects of ziprasidone over time or alternatively reflect observations that bipolar disorder patients are at greater risk for weight gain during acute treatment, reaching a plateau over time (Gergerliouglu et al., 2006). It could also be interpreted that for those patients previously treated with medications prone to causing metabolic disturbances, switching to adjunctive ziprasidone treatment with a mood stabilizer showed little evidence of major improvement in these parameters over time when compared to placebo. Results from previous studies on switching antipsychotic treatment in psychiatric patients have suggested that antipsychotic-associated metabolic adverse effects such as weight gain may be difficult to reverse even after switching to a metabolically neutral agent (Kim et al., 2007; Karayal et al., 2011). The most important pharmacological mechanisms contributing to weight gain are not fully understood. Current clinical and experimental evidence suggests that antagonism of 5-HT2C receptors and H1 receptors as well as resistance to leptin signaling may be involved in raising the propensity for weight gain. Pharmacological aspects of ziprasidone that may protect against weight gain include its partial agonism at 5-HT1A receptors and antagonism or weak partial agonism at 5-HT1B receptors (Reynolds and Kirk, 2010).

Our findings corroborate previous observations that metabolic abnormalities may adversely affect psychiatric outcomes, as cardiometabolic illnesses in bipolar disorder have been linked to greater rates of attempted suicide (Fagiolini et al., 2006), greater baseline symptom severity (Thompson et al., 2006), earlier likelihood of relapse (Fagiolini et al., 2003), and lower rates of acute response and remission to conventional mood stabilizers (Kemp et al., 2010b). We found that an increase in abdominal obesity was negatively associated with symptom improvement ($p<0.05$, as assessed by MRS change score) during Phase 1. While race did not predict the prevalence of MetS at baseline, it was shown to have a significant moderating effect on symptom improvement in adjunctive stabilization treatment (Blacks fared worse, and Asians fared better, than Whites). We did not investigate differences attributable to countries of origin. An increase in central adiposity has previously been linked to the development of depressive symptoms, even more consistently than overall obesity (Vogelzangs et al., 2010). Mechanisms potentially explaining the link between abdominal obesity and mood symptoms include greater production of inflammatory cytokines from visceral adipose tissue as opposed to subcutaneous adipose tissue (Fried et al., 1998) and dysregulation of the hypothalamic-pituitary-adrenal axis, given the high density of glucocorticoid receptors within visceral fat (Bronnegard et al., 1990; Bjorntorp, 2001).

Increase in triglycerides levels during stabilization Phase 1 predicted increased risk of relapse in the double-blind maintenance phase. It has been suggested that alterations in lipids may influence mood symptoms through a variety of mechanisms, including effects on membrane-bound serotonergic structures, reduced membrane fluidity, and promotion of vascular lesions contributing to changes in angiogenesis and endothelial function (Papakostas et al., 2003a; Papakostas et al., 2003b).

Metabolic abnormalities may mediate psychopathology by contributing to oxidative stress, inflammatory activation, and autonomic dysregulation. It has been hypothesized that these cumulative physiologic insults serve to increase ‘allostatic load’, rendering patients with bipolar disorder more vulnerable to the effects of stress and the development of cognitive impairment and psychiatric comorbidities (Kapczinski et al., 2008). Given the complex interactions between metabolic risk factors and mood symptoms, the use of psychotropic

treatments that mitigate, or at the very least do not worsen cardiometabolic risk factors, is highly desirable.

The findings of this analysis should be considered in light of several limitations. Although the study duration of 6 months represents the longest randomized controlled trial data available with ziprasidone in bipolar disorder, it is shorter than other maintenance studies of SGAs that have extended up to 2 years (Suppes et al., 2009). As patients with bipolar II disorder were excluded, we cannot determine whether patients with bipolar II disorder or bipolar spectrum conditions will experience similar change in weight and metabolic profiles. The study also excluded patients with a BMI > 35. This may have served to reduce the overall prevalence of obesity and MetS in the sample, and may have also limited our ability to detect a reduction in body weight during open stabilization. Prior research suggests that patients experiencing the largest weight change on antipsychotic therapy are those whose baseline weight differs most from the population mean, a phenomenon in part reflecting regression to the mean (Allison et al., 2009). In addition, the prevalence of MetS may have been underestimated, as country- and ethnicity-specific criteria for abdominal obesity were not employed. This would be most applicable to enrolled participants of Asian descent, an ethnic group for which a lower threshold for abdominal obesity is advocated when determining metabolic risk (WHO Expert Consultation, 2004). The findings of a significant reduction in fasting glucose when ziprasidone was combined with VAL should be interpreted with caution, as the difference was not significant after correcting for multiple comparisons. Moreover, the allocation of lithium or valproate was not randomized.

The lack of adverse metabolic effects when combining ziprasidone with Li or VPA during the maintenance phase of bipolar I disorder should provide reassurance to prescribing clinicians that ziprasidone protects not only against the development of new mood episodes but also offers a safer alternative to mood stabilizers and SGAs that are associated with an increased risk of hyperglycemia and diabetes. In clinical practice, the adequate screening for diabetes and dyslipidemia in patients who are initiating treatment with SGA drugs is limited. Even when abnormal glucose and lipid values are detected at screening, there is some evidence that clinicians are unlikely to select or switch to a lower metabolic risk agent (Morrato et al., 2009). The results underscore the need for clinicians to incorporate abnormal body weight and laboratory findings into their prescribing decisions, especially for patients receiving long-term therapy.

For clinicians interested in minimizing the commonly seen increased risks in weight and metabolic adverse effects during maintenance treatment of bipolar disorder, ziprasidone may be a viable alternative in an adjunctive therapy regimen combining a SGA with a mood stabilizer.

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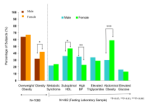
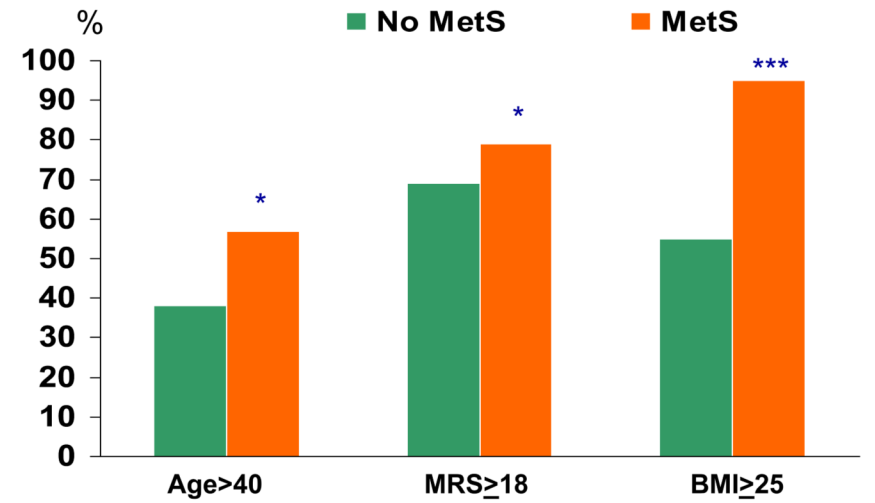


Figure 1.
Prevalence of Obesity/Overweight and Metabolic Syndrome Risks in Baseline Screening Subjects



Baseline metabolic syndrome status (NCEP ATP III) Model: Age (P=0.011), MRS severity (P=0.027), BMI (P<0.001). Gender (P=0.155) and race (P=0.388) are not significant. *P<0.05; **P<0.01; ***P<0.001

Figure 2.
Baseline Metabolic Syndrome Status and Associated Risk Factor: Screening Sample (N=482)

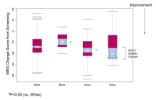


Figure 3.
MRS Improvement by Race group: 16-Week Open-Label Ziprasidone+Li/VAL Period

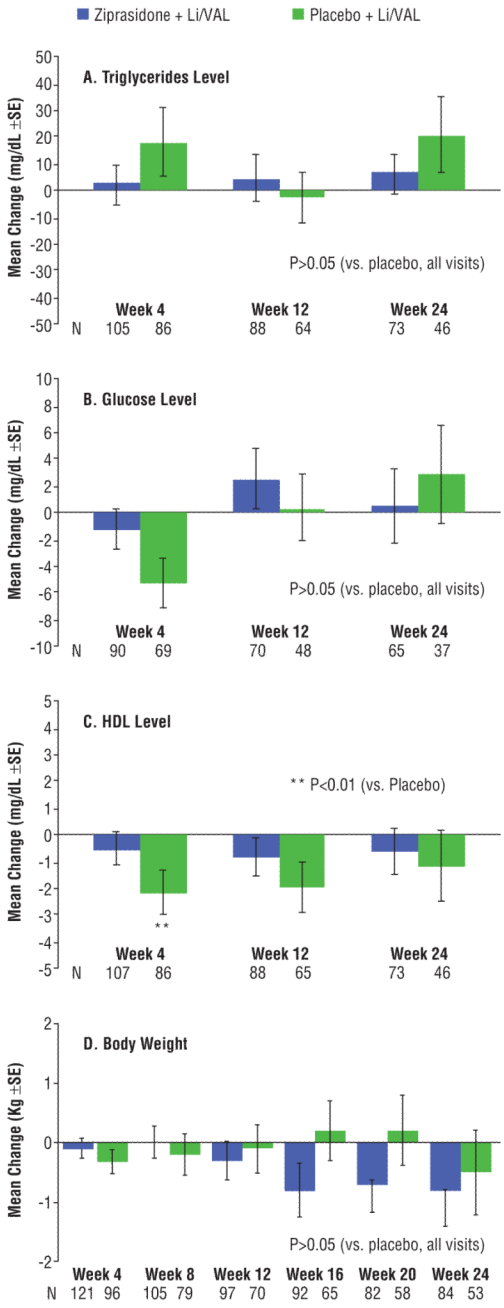


Figure 4.
Mean Change in Metabolic Variables and Body Weight Over Time in Double-Blind Phase

Table 1

ATP III A (AHA) Clinical Identification of the Metabolic Syndrome

Risk factor	Diagnosis Criteria (3 or more Criteria)
Abdominal Obesity	Waist Circumference
Men	>102 cm (> 40 in)
Women	>88 cm (>35 in)
Hypertriglyceridemia	Triglycerides
	≥150 mg/dL (≥1.69 mmol/L)
Abnormal HDL Level	HDL Cholesterol
Men	<40 mg/dL (<1.04 mmol/L)
Women	<50 mg/dL (< 1.29 mmol/L)
Elevated Blood Pressure	Blood Pressure
	≥130/≥85 mm Hg
Elevated Glucose Level	Fasting glucose ≥ 100 mg/dL (≥5.55 mmol/L)

Table 2

Demographics of Subjects Receiving Randomized Treatment

Parameter	Screening Phase (N=1088)	Randomization Phase (N=240)	
		Ziprasidone + Li/VAL (n = 127)	Placebo + Li/VAL (n = 113)
Males, n (%)	473 (43.5)	51 (40.2)	60 (53.1)
Age, years			
Mean (SD)	37.5 (11.4)	39.6 (12.3)	38.0 (11.6)
Range	18-71	18–64	18–71
Race, n (%)			
White	786 (72.2)	82 (64.6)	67 (59.3)
Black	100 (9,2)	5 (3.9)	6 (5.3)
Asian	123 (11.3)	31 (24.4)	29 (25.7)
Other	79 (7.3)	9 (7.1)	11 (9.7)

[a] Not recorded in 1 subject.

Table 3

Body Weight and Fasting Lipid Parameters: Change Score from Pre-treatment Baseline during Open-label 10 to 16 Weeks Stabilization Phase

	Lithium + Ziprasidone		Valproate + Ziprasidone			Ziprasidone + Mood Stabilizers (MS) ‡		
	Screening Baseline Mean (SD)	Change Score Mean (95% CI)	Screening Baseline Mean (SD)	Change Score Mean (95% CI)	Zip+Li vs. Zip+Val	Screening Baseline Mean (SD)	Change Score Mean (95% CI)	Zip + MS vs. Screening Baseline
Body Weight (kg)	n=225 78.6 (19.5)	n=225 0.23 (−0.46, 0.91)	n=268 83.0 (22.6)	n=268 0.54 (−0.09, 1.16)	P=0.513 F(1, 490) =0.43	n=507 81.0 (21.2)	n=507 0.39 (−0.06, 0.84)	P=0.09 t= 1.70 df=505
BMI	n=193 28.1 (6.0)	n=193 −0.08 (−0.27, 0.12)	n=228 29.1 (7.1)	n=228 0.12 (−0.06, 0.29)	P=0.152 F(1, 418) = 2.06	n=433 28.6 (6.6)	n=433 0.04 (−0.09, 0.17)	P=0.554 t= 0.59 df=431
LDL Cholesterol (Fasting), mg/dL	n=148 107.5 (31.3)	n=148 −4.8 (−8.3, −1.4)	n=160 106.5 (31.6)	n=160 −3.3 (−6.63, −0.04))	P=0.530 F(1,305)=0.4	n=316 106.8 (31.3)	n=316 −4.24 (−6.72, −1.77)	P<0.001 t= −3.38 df=314
HDL Cholesterol (Fasting). mg/dL	n=152 50.5 (13.1)	n=152 −0.16 (−1.37, 1.04)	n=162 49.4 (16.3)	n=162 0.34 (−0.82, 1.51)	P=0.553 F(1,311)=0.35	n=322 50.0 (14.8)	n=322 0.06 (−0.83, 0.94)	P=0.90 t= 0.13 df=320
Cholesterol (Fasting), mg/dL	n=152 185.9 (40.4)	n=152 −4.30 (−8.23, −0.37)	n=162 184.3 (41.0)	n=162 −3.48 (−7.28, 0.33)	P=0.767 F(1,311)=0.09	n=322 184.8 (40.5)	n=322 −4.2 (−7.0, −1.3)	P=0.004 t= −2.87, df=320
Triglycerides (fasting), mg/dL	n=146 138.3 (78.0)	n=146 4.40 (−6.27, 15.08)	n=161 142.1 (82.7)	n=161 −0.77 (−10.94, 9.39)	P=0.490 F(1,304)=0.48	n=315 139.5 (79.9)	n=315 1.32 (−6.37, 9.00)	P=0.74 t= 1.316 df = 313
Glucose (Fasting), mg/dL	n=153 95.4 (24.7)	n=153 2.05 (−0.70, 4.79)	n=162 90.3 (24.5)	n=162 −1.85 (−4.52, 0.82)	P=0.047 F(1,312)=3.98	n=323 93.3 (27.1)	n=323 −0.7 (−3.2, 1.9)	P=0.61 t= −0.52 df=321

‡14 subjects had unspecified mood stabilizer information. P-values were reported before Bonferroni adjustment for multiplicity comparisons.