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Reduction in Multiple Cardiometabolic Risk Factors With Combined Olanzapine/Samidorphan Compared With Olanzapine: Post Hoc Analyses From a 24-Week Phase 3 Study

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***Background and Hypotheses*: Weight gain and adverse cardiometabolic effects often limit the clinical utility of olanzapine. In ENLIGHTEN-2, combining olanzapine with the opioid receptor antagonist samidorphan (OLZ/SAM) mitigated olanzapine-associated weight gain. These analyses tested the hypothesis that OLZ/SAM would be associated with reduced adverse cardiometabolic effects compared with olanzapine. *Study Design*: This phase 3 double-blind study randomized adults with schizophrenia to OLZ/SAM or olanzapine for 24 weeks. Post hoc analyses assessed changes from baseline to week 24 in cardiometabolic risk parameters, including body mass index (BMI), risk of developing obesity (BMI ≥30 kg/m^2) or metabolic syndrome, waist circumference, along with mean and potentially clinically significant changes in blood pressure, glucose, and lipids. *Results*: After 24 weeks' treatment, compared with olanzapine, OLZ/SAM was associated with smaller least-squares mean (LSM) changes from baseline in systolic blood pressure (LSM difference, −2.63 mm Hg; 95% CI: −4.78, −0.47), diastolic blood pressure (LSM difference, −0.75 mm Hg; 95% CI: −2.31, 0.80), and BMI (LSM difference, −0.65 kg/m^2; 95% CI: −1.01, −0.28). OLZ/SAM treatment was also associated with reduced risk of shifting from normal blood pressure to stage 1/2 hypertension (odds ratio [OR], 0.48; 95% CI: 0.24, 0.96), becoming obese (OR, 0.52; 95% CI: 0.32, 0.82), and developing metabolic syndrome (OR, 0.55; 95% CI: 0.31, 0.99) compared with olanzapine. No treatment group differences were noted for risk of hyperglycemia or hyperlipidemia. *Conclusions*: OLZ/SAM treatment was associated with lower risk of worsening cardiometabolic risk factors related to obesity, hypertension, and metabolic syndrome relative to olanzapine. NCT02694328, https://clinicaltrials.gov/ct2/show/NCT02694328.**

Key words: 3-carboxamido-4-hydroxynaltrexone/dyslipidemia/hyperglycemia/hypertension/metabolic syndrome/schizophrenia

Introduction

Serious mental illness (SMI), including schizophrenia and bipolar I disorder, is associated with increased cardiometabolic risk.[1,2] This includes a higher risk for cardiovascular disease (in SMI) or stroke (in schizophrenia or bipolar disorder) compared with healthy matched controls.[1,3,4] Many psychiatric medications have adverse cardiometabolic effects that can further exacerbate the risk of cardiometabolic morbidity and mortality in patients with SMI.[1,5] Olanzapine is well-established as an effective antipsychotic for the treatment of schizophrenia and bipolar I disorder.[6–10] In long-term studies, olanzapine is associated with decreased rates of hospitalization, increased rates of remission, and increased time on treatment compared with certain other antipsychotics.[6,11,12] However, the clinical utility of olanzapine is often limited by the potential for substantial weight gain and associated adverse cardiometabolic effects.[13–18] Specifically, olanzapine is associated with increased central adiposity and risk for developing diabetes mellitus, dyslipidemia, and metabolic syndrome,[19–22] potentially adding to the greater risk for cardiovascular morbidity and mortality already observed in patients with SMI. Furthermore, weight gain and cardiometabolic side effects associated

with olanzapine treatment[23,24] may reduce medication adherence[6] and lead to treatment switches,[25] which, in turn, may increase the risk of relapse, hospitalization, and disease progression.[25,26]

Although the specific cause(s) of antipsychotic-associated weight gain remains unclear,[1,27] past studies have focused on receptor interactions within serotoninergic, dopaminergic, histaminergic, adrenergic, cannabinoid, and muscarinic neurotransmitter pathways.[28] Additionally, it is established that the endogenous opioid system plays a role in weight and metabolic regulation,[29,30] and evidence of this effect from both nonclinical and clinical studies supports the rationale for targeting this system to mitigate weight-related side effects of antipsychotic treatment.[30–34]

A combination of olanzapine and the opioid receptor antagonist samidorphan[35,36] (OLZ/SAM; Lybalvi, Alkermes, Inc.)[37] was approved in the United States in May 2021 for the treatment of adults with schizophrenia as a maintenance monotherapy treatment, and for adults with bipolar I disorder, where it is approved for the acute treatment of manic or mixed episodes, either as a monotherapy or as an adjunct to lithium or valproate. Based on phase 2 and 3 clinical trials, this combination provides efficacy similar to that of olanzapine[34,38,39] while mitigating olanzapine-associated weight gain in patients with schizophrenia.[34,38] In the phase 3 ENLIGHTEN-2 study, OLZ/SAM was associated with a significantly lower mean percent change in body weight at 24 weeks compared with olanzapine as well as a 50% reduction in the likelihood of clinically significant weight gain of ≥10% from baseline at week 24 (the coprimary endpoints) and in weight gain of ≥7% from baseline at week 24 (the key secondary endpoint).[34] Patients on OLZ/SAM also had significantly smaller increases in waist circumference at week 24 compared with olanzapine alone, a study measure serving as a proxy for central adiposity. Patients were less likely to experience an increase of ≥5 cm in waist circumference during treatment with OLZ/SAM, a threshold associated with increased mortality risk in males and females, regardless of body mass index (BMI).[34] Despite these differences in weight gain and in waist circumference increases, changes in lipid and glycemic measures were generally small for patients treated with either OLZ/SAM or olanzapine, with no clinically meaningful differences between treatment groups.[34]

To better understand the potential benefits of OLZ/SAM compared with olanzapine, post hoc analyses were conducted to evaluate their respective effects across multiple cardiometabolic risk factors.[40–42] Although mean between-group differences in lipid and glycemic parameters were not observed at 24 weeks, previously reported findings on weight and waist circumference suggest that differentiation on other measures of cardiometabolic risk could be detected within that 24-week time frame. We hypothesized that, compared with olanzapine alone, OLZ/SAM would be associated with reductions in some clinically relevant cardiometabolic risk factors, such as obesity, hypertension, and metabolic syndrome.

Methods

Study Design

In the phase 3, double-blind ENLIGHTEN-2 study (NCT02694328), patients diagnosed with schizophrenia were randomized 1:1 to receive OLZ/SAM or olanzapine for 24 weeks. Treatment was initiated with OLZ/SAM 10/10 mg (olanzapine 10 mg/samidorphan 10 mg) or olanzapine 10 mg daily. The olanzapine dosage was increased to 20 mg daily (olanzapine 20 mg/samidorphan 10 mg [20/10 mg] or olanzapine 20 mg) beginning at week 2 but could be lowered to 10 mg daily for tolerability reasons at the end of week 2, 3, or 4 at the investigator's discretion. Doses were fixed at week 4 and remained the same thereafter.[34]

Patients

Detailed eligibility criteria were reported previously.[34] In short, stable outpatients aged 18 to 55 years with a primary diagnosis of schizophrenia and a BMI from 18 to 30 kg/m^2 were enrolled. Patients were excluded if they had a history of treatment-resistant schizophrenia, had less than 1 year since the initial onset of symptoms, were antipsychotic treatment naïve, had active alcohol or substance use disorders (excluding nicotine), or any clinically significant or unstable medical illness (eg, diabetes mellitus, hypo- or hypertension, thyroid dysfunction, cardiac arrhythmia, cardiomyopathy, cardiac conduction defect, history of myocardial infarction or unstable angina within 6 months, and history of seizure disorder or brain tumor). There were a number of exclusion criteria based on baseline laboratory parameters, where total fasting cholesterol >280 mg/dL, fasting triglycerides >500 mg/dL, glycosylated hemoglobin (HbA1c) ≥6.0%, fasting plasma glucose ≥126 mg/dL, and/or a clinically significant electrocardiogram abnormality (ie, QT interval >450 ms for males and >470 ms for females, as corrected by the Fridericia formula) were exclusionary. All patients provided written informed consent to participate in the trial, which was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines. The study protocol and all amendments were approved by institutional review boards at each study site.

Assessments

Body weight and waist circumference measures (both conducted in triplicate), vital signs, electrocardiograms, adverse events, fasting (≥8 h by self-report) metabolic laboratory parameters (triglycerides, cholesterol, glucose,

and insulin), and HbA1c (fasting or nonfasting) were collected weekly through week 6 and then biweekly through week 24. Blood pressure was monitored after the patient had been supine for 5 min, preferably by automated measurement and using the same arm throughout the study.

Post Hoc Analysis of Cardiometabolic Risk

Post hoc analyses evaluated the mean change from baseline in BMI, waist circumference, and supine systolic and diastolic blood pressure at week 24. Additionally, blood pressure shifts from normal (<120/<80 mm Hg) or normal/elevated (120–129/<80 mm Hg) to stage 1 hypertension (130–139/80–89 mm Hg) or stage 2 hypertension (≥140/≥90 mm Hg) were evaluated at week 24. The proportion of patients who did not meet individual metabolic parameter criteria or the full definition for metabolic syndrome at baseline (defined as the presence of ≥3 of the criteria listed in supplementary table 1 [43]) but then went on to meet respective criteria for individual metabolic syndrome parameters or for the full metabolic syndrome at the last on-treatment assessment was also evaluated. Risk differences for shifts in metabolic laboratory parameters were based on sustained potentially clinically significant shifts (ie, the parameters met shift criteria at the last 2 on-treatment assessments).

Statistical Analyses

Least-squares mean (LSM) changes in continuous measures for OLZ/SAM and olanzapine were compared using an analysis of covariance model based on multiple imputation for missing data. For binary endpoints, including risk differences and odds ratios (ORs), a logistic regression model was used based on the same imputed data sets. Rubin's rule was used to combine results by applying the logistic regression model on imputed data sets. The proportions of patients who developed metabolic syndrome or who met individual metabolic syndrome criteria were based on observed data at each patient's last on-treatment assessment.

Results

Cardiometabolic effects were evaluated in a post hoc analysis of all patients who had at least one postbaseline weight assessment (n = 538).[34] Baseline patient characteristics are shown in table 1. The final dose level of olanzapine was 20 mg for the majority of patients (78.8% and 80.4% of patients for OLZ/SAM and olanzapine, respectively), and the overall mean olanzapine dose level (time-weighted average over the study) was 16.8 mg for the OLZ/SAM group and 16.9 mg for the olanzapine group.[34]

OLZ/SAM was associated with smaller increases in BMI from baseline to week 24 relative to olanzapine (LSM difference, −0.65 kg/m^2; 95% CI, −1.01, −0.28) (figure 1A). Additionally, OLZ/SAM was associated with a smaller proportion of patients (15.1%) who met criteria for obesity (ie, BMI ≥30 kg/m^2) at week 24 than was olanzapine (25.8%; OR, 0.52; 95% CI: 0.32, 0.82), with a number needed to treat (NNT) of 10.

At week 24, treatment with olanzapine was associated with an increase in supine systolic blood pressure (LSM

Table 1. Baseline Characteristics of Participants in the Post Hoc Analyses of Cardiometabolic Risk Factors in the ENLIGHTEN-2 Study

Parameter	OLZ/SAM	Olanzapine
Randomized and received ≥1 dose, *n*	274	276
Completed, *n* (%)	176 (64.2)	176 (63.8)
Had ≥1 postbaseline weight assessment, *n*	266	272
Age (years), *Mean* (*SD*)	40.3 (9.82)	40.1 (10.05)
Male, *n* (%)	188/266 (70.7)	203/272 (74.6)
Race, *n* (%)		
Black	193/266 (72.6)	190/272 (69.9)
White	61/266 (22.9)	64/272 (23.5)
BMI (kg/m^2), *Mean* (*SD*)	25.31 (3.1)	25.48 (3.2)
BMI <30 kg/m^2, *n* (%)	266/266 (100.0)	270/272 (99.3)
BMI ≥30 kg/m^2, *n* (%)	0/266	2/272 (0.7)
Body weight (kg), *Mean* (*SD*)	77.00 (13.7)	77.45 (13.5)
Waist circumference (cm), *Mean* (*SD*)	90.8 (10.9)	90.9 (10.6)
Waist circumference >80 cm (females) or >102 cm (males), *n* (%)	75/265 (28.3)	80/270 (29.6)
Metabolic syndrome, *n* (%)	33/265 (12.5)	23/270 (8.5)
Systolic blood pressure (mm Hg), *Mean* (*SD*)[a]	121.4 (12.7)	121.8 (11.9)
Diastolic blood pressure (mm Hg), *Mean* (*SD*)[a]	77.2 (9.1)	77.3 (9.6)
Hypertension, *n* (%)		
Stage 1 (130–139/80–89 mm Hg)	96/266 (36.1)	86/272 (31.6)
Stage 2(≥140/≥90 mm Hg)	35/266 (13.2)	38/272 (14.0)
Plasma glucose (mg/dL), *Mean* (*SD*)[b]	90.3 (11.6)	91.4 (12.0)
HbA1c (%), *Mean* (*SD*)[c]	5.40 (0.4)	5.40 (0.4)
HOMA-IR, *Mean* (*SD*)[d]	3.03 (6.4)	2.88 (4.1)
Total cholesterol (mg/dL), *Mean* (*SD*)[e]	183.4 (34.7)	185.2 (37.3)
LDL cholesterol (mg/dL), *Mean* (*SD*)[e]	109.6 (32.3)	112.7 (34.0)
HDL cholesterol (mg/dL), *Mean* (*SD*)[e]	62.4 (22.4)	62.1 (21.0)
Triglycerides (mg/dL), *Mean* (*SD*)[e]	114.4 (94.0)	107.1 (62.1)

[a]Measured in supine position after 5 min at rest.
[b]Upper reference value in an otherwise healthy population for fasting plasma glucose is 100 mg/dL.[62]
[c]Upper reference value in an otherwise healthy population for HbA1c concentration is 5.7%.[62]
[d]Upper reference value in an otherwise healthy population for HOMA-IR is 2.0.[63]
[e]Optimal lipid levels are <150 mg/dL total cholesterol, <100 mg/dL LDL cholesterol, and <150 mg/dL triglycerides; the reference range for HDL cholesterol varies by gender.[64]
BMI, body mass index; HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; LDL, low-density lipoprotein; OLZ/SAM, combination of olanzapine and samidorphan.

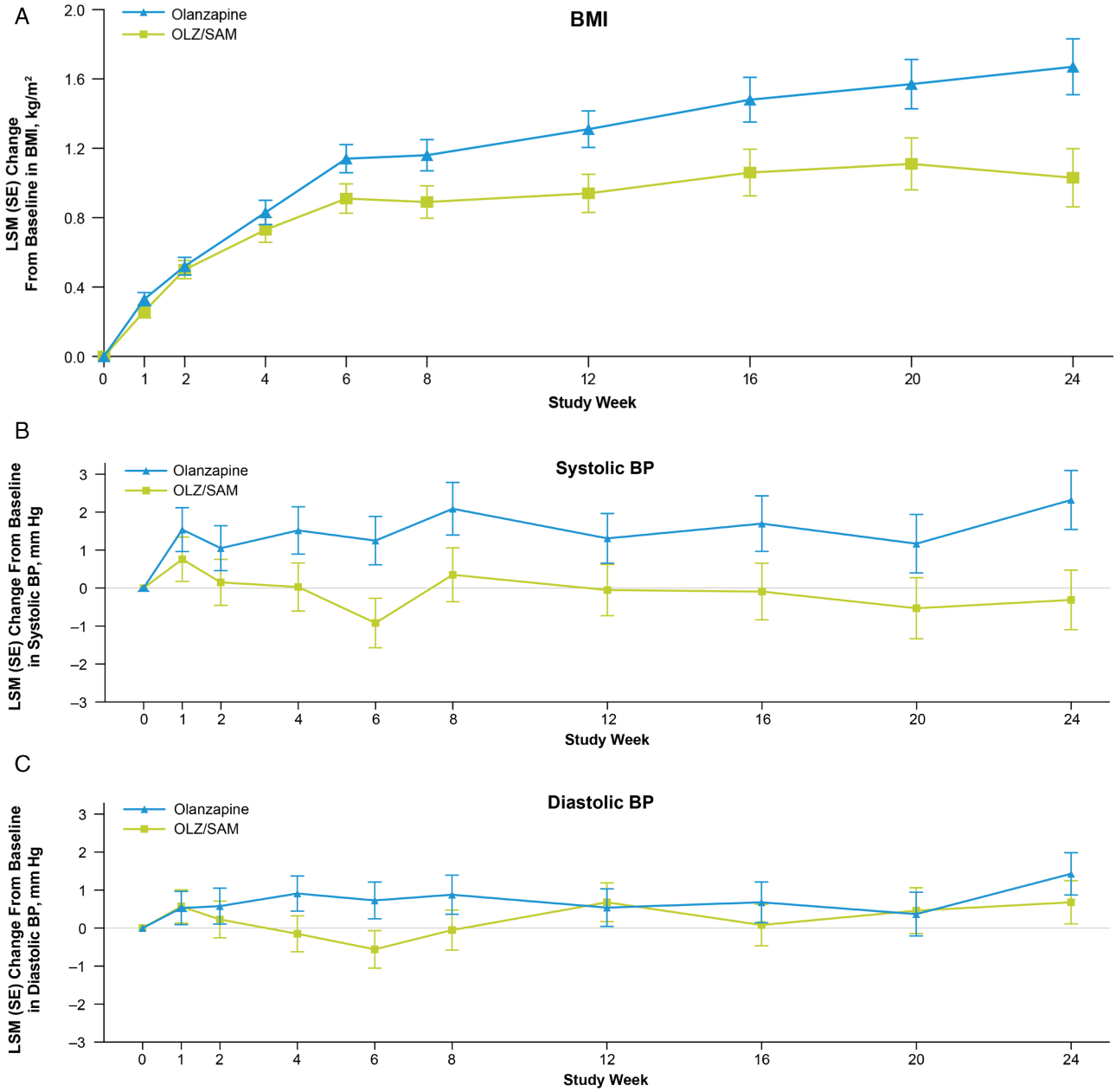

Fig. 1. By visit least-squares mean change from baseline in (A) body mass index,[a] (B) systolic blood pressure,[b] and (C) diastolic blood pressure[b] in ENLIGHTEN-2. [a]Based on an analysis of covariance approach using multiple imputation for missing post-baseline assessments. The model included treatment, race, and age group as factors and the baseline value as a covariate. LSM difference (95% CI) of OLZ/SAM versus olanzapine in BMI: −0.65 kg/m^2 (−1.01, −0.28). [b]Based on an analysis of covariance or logistic regression approach using multiple imputation for missing post-baseline assessments. The model included treatment group as a factor and the baseline value as a covariate. LSM difference (95% CI) for OLZ/SAM versus olanzapine in BP: systolic BP: −2.63 mm Hg (−4.78, −0.47); diastolic BP: −0.75 mm Hg (−2.31, 0.80). BMI, body mass index; BP, blood pressure; HbA1c, glycosylated hemoglobin; LDL, low-density lipoprotein; LSM, least-squares mean; MetS, metabolic syndrome; OLZ/SAM, combination of olanzapine and samidorphan

[95% CI] change, 2.32 [0.79, 3.85] mm Hg), whereas OLZ/SAM was not (LSM [95% CI] change, −0.31 [−1.84, 1.23] mm Hg) (figure 1B). The LSM difference for OLZ/SAM versus olanzapine for change in supine systolic blood pressure at week 24 was −2.63 mm Hg (95% CI: −4.78, −0.47). Diastolic blood pressure increased in both treatment groups (LSM [95% CI] change of 0.68 [−0.43, 1.79] mm Hg for OLZ/SAM and 1.43 [0.33, 2.52] mm Hg for olanzapine), with an LSM difference for OLZ/SAM vs olanzapine of −0.75 mm Hg (95% CI: −2.31, 0.80) (figure 1C). At baseline, 49.2% in the OLZ/SAM treatment group and 45.6% in the olanzapine treatment group had blood pressure readings in the hypertensive range. Among those with normal blood

pressure at baseline, the risk of shifting to stage 1/2 hypertension was reduced by approximately 50% with OLZ/SAM compared with olanzapine at week 24 (OR, 0.48; 95% CI: 0.24, 0.96) with an NNT of 7 (table 2). Among patients with normal/elevated blood pressure at baseline, the risk of shifting to stage 1 or 2 hypertension was reduced by approximately one third with OLZ/SAM compared with olanzapine at week 24 (OR, 0.66; 95% CI: 0.38, 1.17), with an NNT of 12.

Overall, 33/265 (12.5%) of patients randomized to OLZ/SAM and 23/270 (8.5%) of patients randomized to olanzapine met criteria for metabolic syndrome at baseline. The proportion of patients without metabolic syndrome at baseline who went on to develop metabolic syndrome by the time of their last assessment was smaller in the OLZ/SAM group (21/228; 9.2%) than the olanzapine group (42/248; 16.9%). This translates to an approximate 45% reduction in the risk of developing metabolic syndrome with OLZ/SAM (OR, 0.55; 95% CI: 0.31, 0.99; NNT = 20) compared with olanzapine (figure 2). Additionally, among patients without metabolic syndrome at baseline, a numerically smaller proportion of patients treated with OLZ/SAM went on to meet any individual component criterion of metabolic syndrome compared with those treated with olanzapine, although the differences did not reach statistical significance (NNT range: 20–23). Among patients without metabolic syndrome at baseline, the proportions of patients with waist circumference >80 cm (for females) or >102 cm (for males) at their last assessment were numerically smaller with OLZ/SAM treatment (64/228 [28.1%]) than with olanzapine treatment (91/248 [36.7%]; OR, 0.76; 95% CI: 0.49, 1.19; NNT = 21).

Risk differences for several factors known to be associated with increased cardiometabolic risk favored OLZ/SAM over olanzapine at week 24, including weight gain of ≥10% (absolute risk difference, −13.7%; 95% CI: −22.8%, −4.6%; NNT = 8), having a BMI ≥30 kg/m^2 (−10.6%; 95% CI: −18.0%, −3.2%; NNT = 10), waist circumference increases of ≥5 cm (−17.1%; 95% CI: −26.3%, −7.8%; NNT = 6), and progression to stage 1/2 hypertension (−14.8%; 95% CI: −28.5%, −1.2%; NNT = 7) (figure 3). Mean changes in lipid and glycemic parameters between baseline and week 24 were generally small, as previously reported.[34] No significant between-group LSM (SE) differences were observed for changes from baseline for HOMA-IR (LSM [SE] difference vs olanzapine, 0.08 [0.87]; 95% CI: −1.64, 1.80), insulin (LSM [SE] difference vs olanzapine, −0.68 [2.47]; 95% CI: −5.54, 4.18), or HbA1c (LSM [SE] difference vs olanzapine, −0.01 [0.03]; 95% CI: −0.06, 0.05) at week 24. No between-group differences were observed in the risk of developing sustained potentially clinically significant hyperglycemia (fasting glucose, ≥126 mg/dL and HbA1c ≥5.7%) or hyperlipidemia (total cholesterol ≥240 mg/dL, LDL cholesterol ≥160 mg/dL, and triglycerides ≥200 mg/dL) while on treatment (figure 3).

Table 2. Risk of Shifting From Normal or Normal/Elevated Blood Pressure Levels to Stage 1/2 Hypertension in ENLIGHTEN-2

Shift Category	Patients Meeting Criteria, n/m (%)		Odds Ratio[a] (95% CI)	NNT
	OLZ/SAM	Olanzapine		
Normal to stage 1/2 hypertension[b]	22/100 (21.6)	41/112 (36.6)	0.48 (0.24, 0.96)	7
Normal/elevated to stage 1/2 hypertension[b]	38/135 (28.2)	55/148 (37.3)	0.66 (0.38, 1.17)	12

[a]OLZ/SAM was compared with olanzapine using a logistic regression model and a multiple imputation approach for missing data. The model included treatment, race (black or African American, non-black or African American) and age group (age <30 years, age ≥30 years), and treatment as factors and baseline value as covariate.
[b]Blood pressure definitions: normal, <120/<80 mm Hg; normal/elevated, ≥120 to ≤129/<80 mm Hg; stage 1 hypertension, ≥130 to ≤139/≥80 to ≤89 mm Hg; and stage 2 hypertension, ≥140/≥90 mm Hg.
n/m, number of responders who met criteria at week 24/number of participants who met baseline criteria; NNT, number needed to treat; OLZ/SAM, combination of olanzapine and samidorphan.

Discussion

In the current analyses, OLZ/SAM mitigated olanzapine-associated increases in BMI and supine blood pressure and reduced the risk of developing stage 1/2 hypertension, obesity, and metabolic syndrome—all well-established risk factors for cardiovascular morbidity and mortality.[1,3,4] These post hoc analyses of the ENLIGHTEN-2 study build upon the primary results in which OLZ/SAM mitigated olanzapine-associated weight gain and increases in waist circumference.[34] In ENLIGHTEN-2, olanzapine was associated with continued weight gain over the course of the 24-week study, whereas with OLZ/SAM, after an initial period of weight gain over the first 4 to 6 weeks of treatment, weight stabilized for the remainder of the treatment period.[34] The significantly smaller increases in BMI and waist circumference and the reduced risk of obesity with OLZ/SAM vs olanzapine treatment are thus consistent with the pattern of weight gain mitigation observed in the primary analysis.[34] Moreover, the magnitude of risk reduction is consistent with that previously observed in ENLIGHTEN-2 in which, based on the calculated ORs, the risks of gaining ≥10% or ≥7% of baseline body weight, or of having a waist circumference increase of ≥5 cm at week 24, were each reduced by about 50% with OLZ/SAM vs olanzapine.[34] Similarly, in the current analyses, the risks of incident metabolic syndrome, obesity, or stage 1/2 hypertension were also reduced by about 50% with OLZ/SAM versus olanzapine.

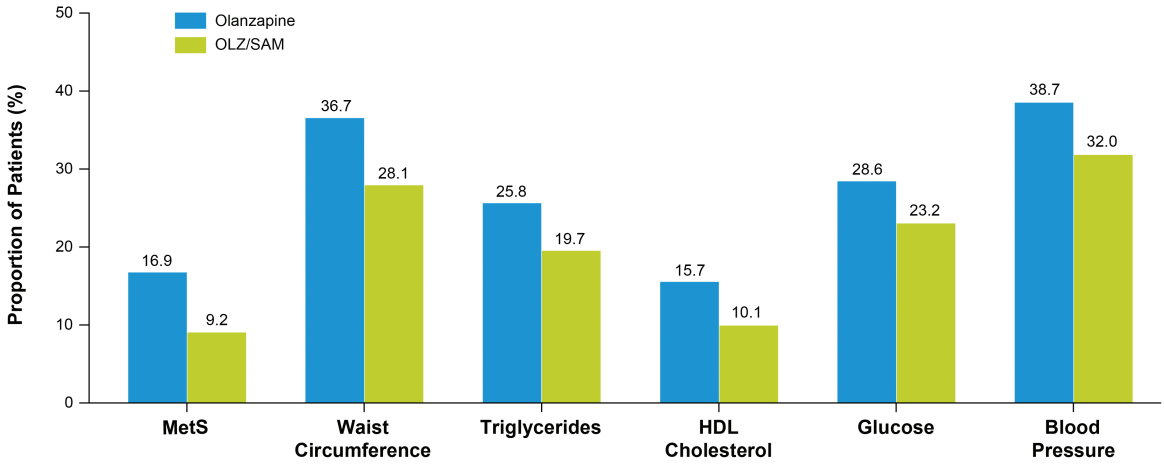

Fig. 2. Proportions of patients without metabolic syndrome at baseline who developed metabolic syndrome or any component criterion of metabolic syndrome.[a,b], [a]Odds ratio (95% CI) for the development of MetS during treatment with OLZ/SAM vs olanzapine, at the last on-treatment assessment, in those without MetS at baseline: 0.55 (0.31, 0.99). [b]The proportion of patients who developed metabolic syndrome or who developed individual metabolic syndrome parameter criteria were compared using a logistic regression model based on observed data at the patients' last on-treatment assessments. The model included treatment, race (black, non-black), and age group (<30 years, ≥30 years) as factors, and baseline body mass index as covariate. HDL, high-density lipoprotein; MetS, metabolic syndrome; OLZ/SAM, combination of olanzapine and samidorphan.

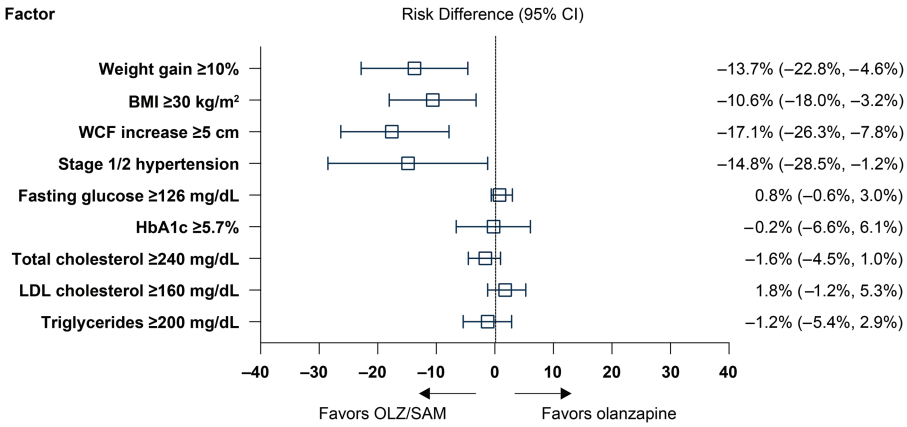

Fig. 3. Cardiometabolic parameter risk differences with OLZ/SAM compared with olanzapine.[a] [a]The odds ratio (95% CI) for developing obesity (BMI ≥30 kg/m^2) with use of OLZ/SAM versus olanzapine was 0.52 (0.32, 0.82). Risk differences for shifts in metabolic laboratory parameters were based on sustained potentially clinically significant shifts (ie, the parameters met shift criteria at the last 2 on-treatment assessments). BMI, body mass index; HbA1c, glycosylated hemoglobin; LDL, low-density lipoprotein; OLZ/SAM, combination of olanzapine and samidorphan; WCF, waist circumference.

Additionally, OLZ/SAM treatment was associated with reductions in cardiometabolic risk factors relative to olanzapine. At week 24, supine systolic blood pressure was 2.63 mm Hg lower in OLZ/SAM-treated patients than in olanzapine-treated patients, while supine diastolic blood pressure was generally similar between groups. These findings are consistent with experimental weight gain studies that suggested that even moderate weight gain (approximately 5% from baseline) can increase systolic blood pressure with minimal changes to diastolic blood pressure.[44–46] Because increased systolic blood pressure correlates most substantially with central fat accumulation,[44–46] the ability of OLZ/SAM to mitigate olanzapine-associated increases in waist circumference,[34] a proxy measure of central adiposity, may explain the observed reduction in supine systolic blood pressure with minimal effects on diastolic blood pressure in the current study. While other potential mechanisms contributing to this difference have not been evaluated, evidence suggests a continuous relationship between blood pressure and risk of cardiovascular mortality, such that incremental reductions as small as 2 mm Hg in systolic blood pressure are associated with long-term reduction in risk of death from stroke and ischemic heart disease.[41] Therefore, in

reducing the risk of an increase in supine systolic blood pressure observed with olanzapine treatment, the stability in blood pressure observed with OLZ/SAM may result in longer-term, clinically meaningful morbidity and mortality benefits.

Antipsychotic-associated weight gain is a common[17,18,21,22] and major concern for patients with schizophrenia for a host of psychological, biological, and mortality-related reasons. Weight gain often leads to central obesity, which, in turn, drives adverse metabolic consequences, such as hypertension, type 2 diabetes, and dyslipidemia.[1,27] Epidemiologic studies have reported that body weight increases of as little as 1 to 5 kg raise the risk of cardiovascular disease and diabetes mellitus.[47–49] Similarly, the risk of cardiovascular mortality increases exponentially as patients progress from being overweight to obese,[50] and an increased waist circumference also increases cardiometabolic risk.[51]

Patients with schizophrenia are already known to be at increased risk for cardiovascular disease and cardiovascular-related mortality compared with the general population, contributing to a 15- to 20-year shorter life expectancy.[52,53] Additionally, they have an increased prevalence of obesity, hyperglycemia, hypertension, and lipid abnormalities, leading to greater rates of metabolic syndrome compared with the general population.[1,18,21,22,54–56] In the primary ENLIGHTEN-2 analyses, treatment with OLZ/SAM was associated with a reduced risk of 2 important cardiometabolic risk factors: significant weight gain and waist circumference increase of ≥5 cm.[34] In the post hoc analyses, risk differences favoring OLZ/SAM over olanzapine were also observed with respect to the percentage of patients without obesity or hypertension at baseline who subsequently developed obesity or progressed to stage 1/2 hypertension, respectively, at week 24. Consistent with these findings, the proportion of patients who developed metabolic syndrome was reduced by nearly 50% for OLZ/SAM vs olanzapine, and fewer patients (among those who did not have metabolic syndrome at baseline) met any of the individual metabolic syndrome component criteria at study end. Interestingly, glycemic and lipid parameter changes were small and were similar between groups over the 24-week study,[34] with no differences in the proportion of patients who developed hyperglycemia or hyperlipidemia.

The explanation for why OLZ/SAM and olanzapine differed in their effects on some cardiometabolic risk measures and not others is unknown. Data from previous studies suggest that the observed impact of samidorphan on olanzapine-associated weight gain and cardiometabolic dysregulation may be due to samidorphan's effects on food reward centrally[57] and insulin resistance peripherally.[58] However, in the current study, measures of insulin levels and insulin resistance revealed no statistically significant differences between the olanzapine and OLZ/SAM groups, suggesting that other mechanisms may play a role. The lack of observed OLZ/SAM versus olanzapine differences in glycemic and lipid parameters may relate in part to the 24-week duration of the study, which would be sufficient to detect early, weight-independent effects on metabolic parameters[59,60] but perhaps not long enough to detect potential weight-dependent changes and, even further, the impact of mitigating weight gain.

The analyses presented here are limited by their post hoc nature. Additionally, overall study limitations include the fact that nearly 40% of patients discontinued treatment early (like other 6-month studies of antipsychotics in schizophrenia[61]), with greater dropout in the olanzapine group than in the OLZ/SAM group. Further limitations include that self-reported fasting status was not independently confirmed and that enrollment was limited to patients younger than 55 years. Additionally, the restrictive BMI entry criterion of 18 to 30 kg/m^2, and exclusion of patients with significant metabolic abnormalities, especially among patients with longstanding illness and antipsychotic treatment, could have enriched the population with patients less susceptible to antipsychotic-associated weight gain and metabolic dysregulation.[34] Also, blood pressure measurements in ENLIGHTEN-2 may not have been conducted under the same rigor as in a dedicated hypertension study. Finally, the 24-week randomized double-blind treatment period versus olanzapine alone is a limitation when weight gain and increasing risk of adverse metabolic effects are documented to continue with life-long olanzapine therapy. Further prospective research in larger populations in real-world settings is needed to corroborate these findings.

In conclusion, these post hoc analyses build on earlier findings from ENLIGHTEN-2, where OLZ/SAM mitigated olanzapine-associated weight gain. Patients with schizophrenia were less likely to experience worsening of certain cardiometabolic risk factors related to obesity, hypertension, and metabolic syndrome when treated with OLZ/SAM compared with olanzapine.

Supplementary Material

Supplementary material is available at https://academic.oup.com/schizophreniabulletin/.

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