Effect of Miricorilant, a Selective Glucocorticoid Receptor Modulator, on Olanzapine-Associated Weight Gain in Healthy Subjects

A Proof-of-Concept Study

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Abstract:

Purpose: Antipsychotic medications, including olanzapine, are associated with substantial weight gain and metabolic disturbances. We sought to determine whether coadministration of miricorilant, a selective glucocorticoid receptor modulator, with olanzapine can ameliorate these effects.

Methods: Sixty-six healthy men were enrolled in a 2-week, randomized, double-blind, placebo-controlled trial. The primary objective was to evaluate changes in body weight after 14 days coadministration of olanzapine (10 mg) + miricorilant (600 mg) compared with olanzapine (10 mg) + placebo. Secondary objectives included evaluating (a) the safety and tolerability of the combination; (b) the effects of the combination on glucose, insulin, insulin resistance, and triglycerides; and (c) the impact of the combination on hepatic enzymes.

Results: Subjects administered olanzapine + miricorilant gained less weight than subjects administered olanzapine + placebo (mean weight gain on day 15, 3.91 kg vs 4.98 kg; difference between groups, −1.07 kg; 95% confidence interval, −1.94 to −0.19; $P = 0.017$]). Compared with the placebo group, coadministration of miricorilant with olanzapine was associated with smaller increases in insulin (difference, −3.74 mIU/L; $P = 0.007$), homeostatic model assessment of insulin resistance (difference, −0.47; $P = 0.007$), triglycerides (difference, −0.29 mmol/L; $P = 0.057$), aspartate aminotransferase (difference, −32.24 IU/L; $P = 0.009$), and alanine aminotransferase (difference, −49.99 IU/L; $P = 0.030$).

Conclusions: Miricorilant may provide a promising option for ameliorating the detrimental effects of olanzapine, and investigation of this medication in patients affected by antipsychotic-induced weight gain is warranted. Two phase 2 studies of miricorilant in patients with recent and long-standing antipsychotic-induced weight gain are currently in progress.

Key Words: olanzapine, antipsychotic medication, glucocorticoid, weight gain, miricorilant

Antipsychotic drugs are widely prescribed to control schizophrenia and bipolar disorders, as well as other psychiatric disorders, such as dementia and major depression. First-generation antipsychotics were introduced more than 60 years ago. Atypical antipsychotic medications, also called second-generation antipsychotics (SGAs), were initially developed to overcome the extrapyramidal effects (eg, tardive dyskinesia) associated with first-generation antipsychotic medications. Although efficacious, SGAs often cause significantly more weight gain in patients than first-generation antipsychotics. Among the commonly used SGAs, clozapine and olanzapine, followed by risperidone and quetiapine, appear to cause the most weight gain.[1–3] In 1 study, standard doses of olanzapine or clozapine caused between 4.0 and 4.5 kg of weight gain over the course of 10 weeks.[4] In addition to weight gain, patients taking SGAs develop drug-induced metabolic changes, including increased insulin resistance and elevated levels of cholesterol and serum triglycerides, which significantly increase their risk for cardiovascular disease.[5,6] Consequently, patients with schizophrenia have a 2- to 3-fold increased risk of mortality compared with the general population, corresponding to a 10- to 25-year reduction in life expectancy.[7] Furthermore, weight gain is also associated with discontinuation of antipsychotic medications, leading to a decrease in their effectiveness.[3]

There are currently no approved treatments for antipsychotic-induced weight gain (AIWG). Adjunctive pharmacologic treatment, behavioral therapy, and switching antipsychotic medication have shown limited improvement in patients with schizophrenia.[8–10] Dietary counseling and exercise programs have shown only modest effects on weight in these patients.[5] Several medications have been evaluated for their ability to ameliorate the effects of antipsychotics, but with limited success.[11] ALK S3831, a combination of olanzapine and samidorphan (an opioid antagonist), has shown potentially promising results in a phase 3 study in patients with schizophrenia, inducing less weight gain than olanzapine alone.[12]

The mechanism by which antipsychotics cause weight gain and metabolic disturbances remains poorly understood. Antipsychotic medications act on multiple hormones, peptides, and neuroreceptors, and may increase appetite, increase preference for high-calorie carbohydrate foods, and decrease energy expenditure.[11,13–15] Roles for dopaminergic, serotoninergic, histaminergic, cholinergic, and adrenergic receptors have been proposed.[11,16] Insulin resistance can result either directly or indirectly from the use of antipsychotic medications.[11]

Dysregulation of the hypothalamic-pituitary-adrenal axis has been implicated with the use of atypical antipsychotics.[17] For example, rats treated with clozapine showed an increase in corticosterone.[18] In humans, there is evidence for a role for the glucocorticoid receptor (GR) in the deleterious effects of antipsychotics. In healthy subjects treated with either olanzapine or risperidone, mifepristone, a GR antagonist, ameliorated the weight gain caused by the antipsychotic medication.[19,20] In addition to potent GR antagonism, mifepristone demonstrates potent antagonism of the progesterone receptor (PR), and, as a result of this activity, it is the active ingredient in the "abortion pill." This

lack of selectivity for the GR makes the development of mifepristone to treat AIWG problematic. Miricorilant, also known as CORT118335, is an investigational mixed agonist/antagonist of the GR and a mineralocorticoid receptor antagonist with no progesterone activity that has shown efficacy in a rat model of olanzapine-induced weight gain.[21]

To assess the suitability of miricorilant to reduce AIWG, we undertook an exploratory proof-of-concept study in healthy volunteers who were administered olanzapine for 14 days. The design of the study was based on a previous study conducted with mifepristone.[19] We conducted the study at Quotient Sciences, a single clinical unit in the United Kingdom. The study design was parallel groups, randomized, and double-blinded, with a 1:1 randomization to coadministration of olanzapine and miricorilant or to olanzapine and appearance-matching placebo. We planned to enroll 64 subjects to provide 60 evaluable subjects, all of whom would receive a daily dose of study medications for 14 days. The dose of olanzapine (10 mg) selected for this study is the recommended daily dose for the treatment of patients with schizophrenia. Miricorilant was available as 100-mg tablets and we selected a dose of 600 mg, with all 6 tablets given once a day in the morning. The dose was selected based on the results of a previous phase 1 trial (NCT03315338), which showed that this dose would be safe and well tolerated. The primary endpoint was the difference in mean change in absolute body weight from baseline following 14 days of coadministration of olanzapine and miricorilant, compared with olanzapine and placebo. Secondary objectives included evaluation of effects on glucose, insulin, homeostatic model assessment of insulin resistance (HOMA-IR), and triglycerides. Information on safety and tolerability was also obtained, and we included a comparison of the effects of miricorilant and placebo on the incidence and degree of raised aspartate aminotransferase (AST) and alanine aminotransferase (ALT) as a secondary endpoint.

MATERIALS AND METHODS

Participants

This study, which was sponsored by Corcept Therapeutics (NCT03877562), was approved by the Health and Social Care Research Ethics Committee (Lisburn, Northern Ireland) and the Medicines and Healthcare products Regulatory Agency (London, UK). The study was conducted at a phase 1 research facility that specializes in recruiting healthy volunteers for interventional studies. Subjects were included if they met the inclusion and exclusion criteria specified in the protocol. The safety and wellbeing of the subjects was continually monitored by qualified medical personnel. Written informed consent was obtained from all participants after receiving a complete description of the study and before any procedures were performed. Subjects were healthy men, aged 18 to 55 years, with a body mass index of 18.0 to 25.0 kg/m^2 as measured at screening and stable body weight (weight predose on day 1 within ±2% of screening weight). Exclusion criteria included a history of drug or alcohol abuse, alcohol consumption greater than 21 units per week, current smokers, the need for prescribed or over-the-counter medication, and any condition that would be aggravated by glucocorticoid and/or mineralocorticoid antagonism.

Design

The study was a single-site, randomized, double-blind (sponsor and investigator site) placebo-controlled trial. Participants were assigned, in a 1:1 randomization ratio, to receive olanzapine (10 mg) and miricorilant (600 mg as 6 × 100 mg tablets) or olanzapine (10 mg) and appearance-matched placebo (6 tablets) once daily under fed conditions. For logistical reasons, the study was conducted in cohorts of approximately 10 to 12 subjects.

All participants were confined to the clinical unit from the day before dosing (day −1) until the day after the final dose (day 15). No smoking or alcohol consumption was allowed during the study. There was a follow-up visit approximately 14 days after the last dose. Food was available *ad libitum* throughout the study except for a minimum 8-hour fasting period before assessment of pharmacodynamic (PD) effects on days 1, 8, and 15. Subjects were provided with a choice of foods for all meals and could choose healthy or less healthy options. Food intake was not measured in this study.

Dosing of subjects was discontinued if there was a serious adverse event (AE) that was considered related to miricorilant, or a serious or severe AE where continued dosing with miricorilant put the safety of the participant at risk, or that confounded the assessment of the safety of miricorilant. Such AEs included meeting the criteria for drug-induced liver injury or clinical features of excessive GR or mineralocorticoid receptor antagonism that were considered to represent a clinical concern. Safety assessments were carried out throughout the study. Body weight, insulin, glucose, and triglycerides were measured before dosing, after an overnight fast, and on days 1 (baseline), 8, and 15.

PD Assessments

Body weight was measured using a single set of scales under consistent conditions (ie, same clothing, removal of all personal items before weighing). Venous blood samples were withdrawn via an indwelling cannula or by venipuncture according to the schedule presented in Table 1. Glucose, insulin, and triglycerides were measured using standard techniques. Homeostatic model assessment of insulin resistance was calculated using the HOMA (HOMA2 model) calculator (Oxford University 2013) application programming interface for SAS. All safety laboratory tests, including the liver enzymes AST and ALT, were conducted using standard techniques.

Statistical Analyses

A sample size of 30 subjects per group was estimated to provide 80% power to detect a 50% reduction (ie, a 1-kg reduction) in olanzapine-induced weight gain (2 group t-test; 2-sided a = 0.05) assuming a mean weight gain of 2.0 kg with standard deviation 1.35.

The safety population included all enrolled subjects who received at least 1 dose of investigational product (ie, either miricorilant or placebo). The safety population was used for the analysis of demographic and baseline characteristics and all safety variables. The intent-to-treat population included all enrolled subjects who received at least 1 dose of investigational product and at

TABLE 1. Baseline Characteristics for All Enrolled Subjects (N = 66)

	Olanzapine + Miricorilant (n = 33)	Olanzapine + Placebo (n = 33)
Age: mean (SD), y	33.5 (11.6)	29.0 (8.9)
Range	20–54	19–51
Body weight: mean (SD), kg	71.95 (5.57)	71.43 (7.1)
Range	59.9–87.2	57.8–92.4
Height: mean (SD), cm	179.4 (5.4)	176.6 (7.3)
Range	170–191	163–197
BMI, mean (SD)	22.35 (1.48)	22.89 (1.57)
Range	19.7–25.0	18.9–24.9

least 1 dose of olanzapine, and who had at least 1 valid predose and postdose PD measurement, and was used for the analysis of weight and PD laboratory endpoints.

The following imputation strategies were used to impute values for missing observations (ie, early withdrawal subjects): missing day 8 data were imputed using last observation carried forward; missing day 15 data were imputed using the day 8 value multiplied by the mean ratio of endpoint (day 15/day 8) calculated within the treatment group.

The statistical analysis was performed on the changes from baseline for weight (primary endpoint) and secondary PD laboratory endpoints using a mixed model with repeated measures model, which included terms for treatment, day, and treatment by day as fixed effects, and the corresponding baseline value fitted as a covariate. The model included subjects within treatment arm as random effects. A compound symmetry covariance structure was used to model the within-subject error. This phase 1 study was a clinical hypothesis–generating study in a limited number of subjects. Statistical tests for several hypotheses were conducted, and nominal *P*-values are presented in the results section for the tests of hypotheses. In this manuscript, an experiment-wise control of the type 1 error rate across the PD endpoints was implemented: a hierarchical testing was used to proceed from primary endpoint (weight) to secondary PD endpoints (insulin, HOMA-IR, and triglycerides decrease) and a Bonferroni adjustment was applied across the 3 PD endpoints (the significance threshold is presented in Table 2).

RESULTS

Baseline Characteristics

Two subjects withdrew consent for personal reasons and were replaced, such that 66 subjects were enrolled in the study. The baseline clinical characteristics of these 66 participants are summarized in Table 1. The 2 groups were comparable.

In total, 8 subjects were withdrawn from the study. Two subjects withdrew consent for personal reasons (1 in the placebo group and 1 in the miricorilant group), and 6 subjects were withdrawn because of the elevated ALT and AST, 5 subjects in the placebo group, and 1 subject in the miricorilant group (Fig. 1). Further details are provided in a subsequent section.

Body Weight Gain

As anticipated, administration of olanzapine for 14 days resulted in an increase in mean body weight (Table 2). Mean increases in body weight on both days 8 and 15 were higher in the placebo group than in the miricorilant group. In the placebo group, body weight increased by 3.49 kg and 4.98 kg on day 8 and day 15, respectively, while in the miricorilant group, body weight increased by 2.59 kg and 3.91 kg on day 8 and day 15, respectively. The estimated differences between treatment arms for change from baseline on day 8 and day 15 were −0.90 kg and −1.07 kg, respectively, with each difference being significant at the 5% level ($P = 0.044$ and $P = 0.017$ for day 8 and day 15, respectively).

Insulin and HOMA-IR

Administration of olanzapine for 14 days resulted in an increase in plasma insulin and HOMA-IR, as expected (Table 2). The mean increase in insulin in the placebo group was 9.14 mIU/L on day 8 and 9.65 mIU/L on day 15. For the miricorilant group, the increases were 5.65 mIU/L on day 8 and 5.91 mIU/L on day 15. The estimated difference between treatment arms on both days was significant ($P = 0.013$ on day 8 and $P = 0.007$ on day 15). Homeostatic model assessment of insulin resistance increased by 1.15 on day 8 and by 1.21 on day 15 in the placebo group. In the miricorilant group, the corresponding increases were 0.71 and 0.74, respectively. The estimated difference between the placebo and treated groups was statistically significant on both days ($P = 0.012$ on day 8 and $P = 0.007$ on day 15).

Triglycerides

Plasma triglycerides were increased by the administration of olanzapine for 14 days, and this effect was inhibited by the coadministration of miricorilant (Table 2). In the placebo group, triglycerides increased by 1.09 mmol/L on day 8 and 0.62 mmol/L on day 15. In the miricorilant group, the increases were 0.56 mmol/L and 0.34 mmol/L on days 8 and 15, respectively. The estimated

TABLE 2. Body Weight, Insulin, HOMA-IR, and Triglyceride Change From Baseline

	Olanzapine + Miricorilant	Olanzapine + Placebo	Difference (95% CI)	*P*
Primary endpoint*				
Body weight increase, kg				
Day 8	2.59	3.49	−0.90 (−1.77 to −0.02)	0.044
Day 15	3.91	4.98	−1.07 (−1.94 to −0.19)	0.017
Secondary endpoints†				
Insulin increase, mIU/L				
Day 8	5.65	9.14	−3.50 (−6.24 to −0.75)	0.013
Day 15	5.91	9.65	−3.74 (−6.47 to −1.01)	0.007
HOMA-IR increase				
Day 8	0.71	1.15	−0.44 (−0.78 to −0.10)	0.012
Day 15	0.74	1.21	−0.47 (−0.81 to −0.22)	0.007
Triglycerides increase, mmol/L				
Day 8	0.56	1.09	−0.52 (−0.82 to −0.22)	<0.001
Day 15	0.34	0.62	−0.29 (−0.59 to 0.01)	0.057

Based on a mixed model with repeated measures model with treatment, day, and treatment by day as fixed effects and baseline value as a covariate.

*The nominal *P* value is compared with 0.05.

†Bonferroni multiplicity adjustment applied; the nominal *P* value is compared with 0.0166.
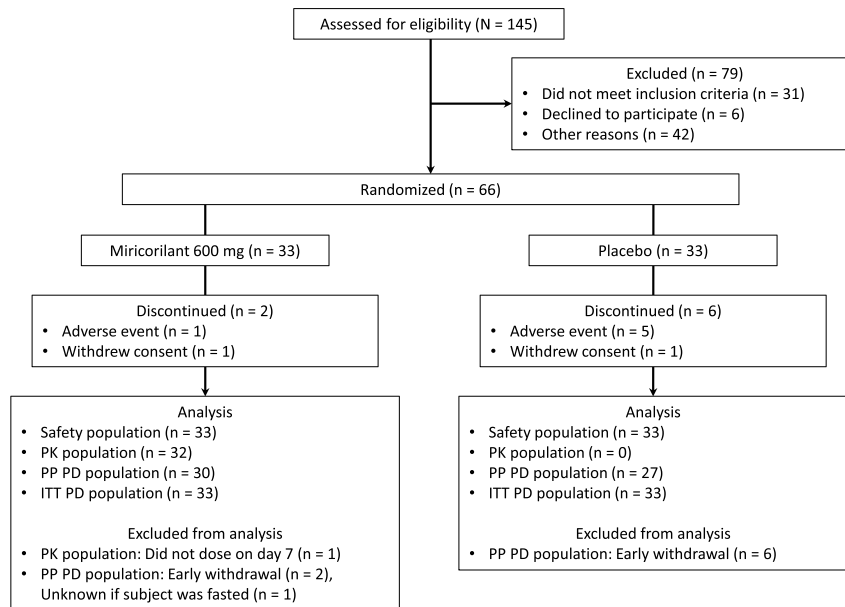
FIGURE 1. Patient disposition. ITT, intent-to-treat; PK, pharmacokinetic; PP, per protocol.

difference between the miricorilant group and the placebo group was statistically significant on day 8 ($P < 0.001$) and close to achieving significance on day 15 ($P = 0.057$).

Glucose

Administration of olanzapine for 14 days had no significant impact on plasma glucose concentrations.

Safety and Tolerability

No serious AEs were reported. One severe AE of increased liver enzymes was reported for a subject in the placebo group. All subjects in each group reported at least 1 AE during the study, most of which were considered to be possibly related or related to the administration of olanzapine as they were consistent with the known side effects of olanzapine [Zyprexa (olanzapine). Summary of product characteristics. Eli Lilly, 2006; Zyprexa (olanzapine). prescribing information. Eli Lilly; 2020]. Some of the AEs were assessed as possibly related to the administration of miricorilant, and a relationship to miricorilant could not be excluded. The most frequently reported AEs were somnolence and elevated liver enzymes (ALT and AST). Other AEs reported by >10% of subjects were abnormal dreams, fatigue, dry mouth, dizziness, headache, and epistaxis. Miricorilant appeared to reduce the incidence of

fatigue, with 8 subjects (24.2%) in the placebo group reporting fatigue compared with 5 subjects (15.2%) in the miricorilant group. Arthralgia was reported by 4 (12.1%) subjects receiving placebo, but not in the miricorilant-treated group.

Six subjects were withdrawn from the study because of elevated ALT and AST: 5 in the placebo group and 1 in the miricorilant group. Administration of miricorilant reduced both the incidence and degree of ALT and AST elevations. As shown in Table 3, the mean changes from baseline for ALT and AST to day 7 and day 12 were higher in the placebo group than in the miricorilant group, with ALT increasing by 51.22 IU/L and 165.01 IU/L on day 7 and day 12, respectively, in the placebo group and by 33.08 IU/L and 115.02 IU/L in the miricorilant group. The difference between treatment arms was significant on day 12 ($P = 0.030$). Aspartate aminotransferase increased by 31.17 IU/L and 77.07 IU/L on days 7 and 12, respectively, in the placebo group, and by 16.61 IU/L and 44.83 IU/L in the miricorilant group. The difference between treatment arms was significant on day 12 ($P = 0.009$).

DISCUSSION

We conducted this study to determine whether miricorilant is able to ameliorate the detrimental effects of olanzapine on body weight, insulin resistance, and plasma triglycerides. As anticipated,

TABLE 3. ALT and AST Change From Baseline

	Olanzapine + Miricorilant	Olanzapine + Placebo	Difference (95% CI)	*P*
ALT increase, IU/L				
Day 7	33.08	51.22	−18.15 (−63.53 to 27.23)	0.430
Day 12	115.02	165.01	−49.99 (−95.01 to −4.97)	0.030
AST increase, IU/L				
Day 7	16.61	31.17	−14.56 (−39.37 to 10.25)	0.250
Day 12	44.83	77.07	−32.24 (−56.16 to −8.33)	0.009

Based on a mixed model with repeated measures model with treatment, day, and treatment by day as fixed effects and baseline value as a covariate. Missing values at day 15 were imputed using last observation carried forward.

administration of olanzapine for 14 days was associated with increased body weight, increased serum insulin and HOMA-IR (indicative of insulin resistance), and elevated serum triglycerides. Coadministration of 600 mg miricorilant with olanzapine ameliorated these changes, with all comparisons between active and placebo achieving statistical significance.

Administration of olanzapine was also associated with substantial increases in ALT and AST. Although not widely recognized, transient increases in these enzymes are commonly associated with the administration of olanzapine, especially early in treatment[22,23] (Zyprexa [olanzapine]. Summary of product characteristics. Eli Lilly, 2006; Zyprexa [olanzapine]. prescribing information. Eli Lilly; 2020). In addition, elevated liver enzymes have been reported in subjects consuming high-calorie, high-carbohydrate diets while their physical activity was restricted in a phase 1 trial.[24] Subjects in our study had unlimited access to food, including high-calorie, high-fat, and high-carbohydrate foods, and physical activity was limited. Food intake and diet were not monitored during the study, so any effects of miricorilant on food intake and food choice cannot be assessed. Coadministration of miricorilant reduced the number of subjects withdrawn from the study due to elevated ALT and AST, and reduced the increases in these enzymes compared with the placebo group.

One limitation of this study is that we did not evaluate the effects of miricorilant alone. However, we had previously conducted an extensive phase 1 study in healthy volunteers (NCT03315338) and did not observe any effects of miricorilant on body weight, insulin, HOMA-IR, triglycerides, or liver enzymes. This suggests that miricorilant selectively affects these parameters in the context of olanzapine administration. Our data are currently limited to healthy male volunteers over a short period of time. The effects in male and female patients taking antipsychotic medications to treat mental health disorders are being assessed in larger studies (NCT03818256 and NCT04524403), in which mood and the longer-term effects will be systematically assessed.

The results observed in this study are similar to those noted with the nonselective GR antagonist, mifepristone, when coadministered with olanzapine.[19] Although the attenuation of weight gain was similar between miricorilant and mifepristone, the effects of miricorilant on serum insulin and triglycerides were more marked than the effects of mifepristone. Another potential advantage of miricorilant over mifepristone appears to be a reduction in the olanzapine-induced increases in ALT and AST. Miricorilant also provides a substantial benefit compared with mifepristone because it does not antagonize the PR and thus will not cause unwanted effects associated with PR antagonism, such as endometrial thickening and irregular vaginal bleeding.

The effects of miricorilant noted in this study can be compared with the effects of samidorphan, an opioid antagonist. Samidorphan was evaluated in healthy subjects[25] using a very similar study design to that described here for miricorilant. After administration of olanzapine and samidorphan for 3 weeks, mean body weight gain in the olanzapine-treated subjects was 3.1 kg, and in the olanzapine + samidorphan-treated subjects it was 2.2 kg. Samidorphan did not significantly ameliorate the olanzapine-induced increase in fasting insulin or triglycerides.

In summary, we have conducted an exploratory, proof-of-concept study in healthy male volunteers to evaluate the potential for miricorilant, a novel selective GR modulator, to ameliorate the detrimental metabolic effects of the antipsychotic medication olanzapine. Despite the short duration of the study (2 weeks), we observed a significant benefit of miricorilant on body weight gain and metabolic parameters such as insulin and triglycerides. These positive results support the development of miricorilant for the treatment of patients with AIWG. Two phase 2 studies of miricorilant in patients with recent and long-standing AIWG are currently in progress (NCT03818256 and NCT04524403).

REFERENCES

1. Haddad P. Weight change with atypical antipsychotics in the treatment of schizophrenia. *J Psychopharmacol*. 2005;19(suppl 6):16–27.

2. Henderson DC. Weight gain with atypical antipsychotics: evidence and insights. *J Clin Psychiatry*. 2007;68(suppl 12):18–26.

3. Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotic drugs in patients with chronic schizophrenia. *N Engl J Med*. 2005;353:1209–1223.

4. Allison DB, Casey DE. Antipsychotic-induced weight gain: a review of the literature. *J Clin Psychiatry*. 2001;62(suppl 7):22–31.

5. Dayabandara M, Hanwella R, Ratnatunga S, et al. Antipsychotic-associated weight gain: management strategies and impact on treatment adherence. *Neuropsychiatr Dis Treat*. 2017;13:2231–2241.

6. Stubbs B, Vancampfort D, De Hert M, et al. The prevalence and predictors of type two diabetes mellitus in people with schizophrenia: a systematic review and comparative meta-analysis. *Acta Psychiatr Scand*. 2015;132:144–157.

7. Laursen TM, Munk-Olsen T, Vestergaard M. Life expectancy and cardiovascular mortality in persons with schizophrenia. *Curr Opin Psychiatry*. 2012;25:83–88.

8. Maayan L, Vakhrusheva J, Correll CU. Effectiveness of medications used to attenuate antipsychotic-related weight gain and metabolic abnormalities: a systematic review and meta-analysis. *Neuropsychopharmacology*. 2010;35:1520–1530.

9. Mukundan A, Faulkner G, Cohn T, et al. Antipsychotic switching for people with schizophrenia who have neuroleptic-induced weight or metabolic problems. *Cochrane Database Syst Rev*. 2010;CD006629.

10. Mizuno Y, Suzuki T, Nakagawa A, et al. Pharmacological strategies to counteract antipsychotic-induced weight gain and metabolic adverse effects in schizophrenia: a systematic review and meta-analysis. *Schizophr Bull*. 2014;40:1385–1403.

11. Marteene W, Winckel K, Hollingworth S, et al. Strategies to counter antipsychotic-associated weight gain in patients with schizophrenia. *Expert Opin Drug Saf*. 2019;18:1149–1160.

12. Correll CU, Newcomer JW, Silverman B, et al. Effects of olanzapine combined with samidorphan on weight gain in schizophrenia: a 24-week phase 3 study. *Am J Psychiatry*. 2020;177:1168–1178.

13. Gothelf D, Falk B, Singer P, et al. Weight gain associated with increased food intake and low habitual activity levels in male adolescent schizophrenic inpatients treated with olanzapine. *Am J Psychiatry*. 2002;159:1055–1057.

14. Graham KA, Perkins DO, Edwards LJ, et al. Effect of olanzapine on body composition and energy expenditure in adults with first-episode psychosis. *Am J Psychiatry*. 2005;162:118–123.

15. Chen J, Huang XF, Shao R, et al. Molecular mechanisms of antipsychotic drug-induced diabetes. *Front Neurosci*. 2017;11:643.

16. Shen WW. A history of antipsychotic drug development. *Compr Psychiatry*. 1999;40:407–414.

17. Baptista T, Zárate J, Joober R, et al. Drug induced weight gain, an impediment to successful pharmacotherapy: focus on antipsychotics. *Curr Drug Targets*. 2004;5:279–299.

18. Tulipano G, Rizzetti C, Bianchi I, et al. Clozapine-induced alteration of glucose homeostasis in the rat: the contribution of hypothalamic-pituitary-adrenal axis activation. *Neuroendocrinology.* 2007;85:61–70.

19. Gross C, Blasey CM, Roe RL, et al. Mifepristone treatment of olanzapine-induced weight gain in healthy men. *Adv Ther.* 2009;26:959–969.

20. Gross C, Blasey CM, Roe RL, et al. Mifepristone reduces weight gain and improves metabolic abnormalities associated with risperidone treatment in normal men. *Obesity.* 2010;18:2295–2300.

21. Hunt HJ, Ray NC, Hynd G, et al. Discovery of a novel non-steroidal GR antagonist with in vivo efficacy in the olanzapine-induced weight gain model in the rat. *Bioorg Med Chem Lett.* 2012;22:7376–7380.

22. Beasley CM Jr., Tollefson GD, Tran PV. Safety of olanzapine. *J Clin Psychiatry.* 1997;58(suppl 10):13–17.

23. Pae CU, Lim HK, Kim TS, et al. Naturalistic observation on the hepatic enzyme changes in patients treated with either risperidone or olanzapine alone. *Int Clin Psychopharmacol.* 2005;20:173–176.

24. Purkins L, Love ER, Eve MD, et al. The influence of diet upon liver function tests and serum lipids in healthy male volunteers resident in a phase I unit. *Br J Clin Pharmacol.* 2004;57:199–208.

25. Silverman BL, Martin W, Memisoglu A, et al. A randomized, double-blind, placebo-controlled proof of concept study to evaluate samidorphan in the prevention of olanzapine-induced weight gain in healthy volunteers. *Schizophr Res.* 2018;195:245–251.