Assessment of Treatment Algorithms Including Amantadine, Metformin, and Zonisamide for the Prevention of Weight Gain With Olanzapine: A Randomized Controlled Open-Label Study

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ABSTRACT

Objective: This 22-week, open-label study, conducted between November 2006 and September 2008 in a community setting, was designed to determine if weight gain during olanzapine treatment can be prevented or mitigated with adjunctive treatment algorithms that include amantadine, metformin, and zonisamide.

Method: Outpatients with schizophrenia or schizoaffective disorder (*DSM-IV-TR* criteria) were randomly assigned to olanzapine alone (n = 50), olanzapine plus algorithm A (olanzapine + A [amantadine 200 mg/d with possible switches to metformin 1,000–1,500 mg/d and then to zonisamide 100–400 mg/d; n = 76]), or olanzapine plus algorithm B (olanzapine + B [metformin 1,000–1,500 mg/d with possible switches to amantadine 200 mg/d and then to zonisamide 100–400 mg/d; n = 73]). Brief weight management education was provided at baseline. The primary outcome measure was comparison of mean weight gain between olanzapine and pooled olanzapine + A and olanzapine + B results.

Results: Least squares mean ± SE weight gain was 2.76 ± 0.75 kg for olanzapine, 2.40 ± 0.65 kg for olanzapine + A, and 0.65 ± 0.63 kg for olanzapine + B. Mean weight gain during olanzapine treatment did not differ significantly from pooled results for olanzapine + A and olanzapine + B ($P = .065$). Participants treated with olanzapine + B experienced significantly less mean weight gain than olanzapine-treated participants ($P = .036$).

Conclusions: Pooled treatment algorithm results were not significantly different from olanzapine monotherapy in mitigating weight gain. However, participants who received treatment with metformin with possible progression to amantadine and then zonisamide had significantly less mean weight gain than participants treated with olanzapine alone. Progression of some participants through the algorithm indicated that a single therapy solution may not be adequate for every patient. Patients treated with olanzapine should receive regular weight monitoring.

Trial Registration: clinicaltrials.gov Identifier: NCT00401973

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Olanzapine is approved for the treatment of schizophrenia and acute mixed or manic episodes associated with bipolar disorder and as maintenance therapy for bipolar disorder. Olanzapine compares favorably with other treatments for efficacy in treating schizophrenia and other psychiatric disorders.[1,2] However, weight gain has been very commonly reported during olanzapine treatment.[3,4] During short-term clinical trials (median time, 6 weeks), olanzapine-treated participants gained an average of 2.6 kg; 22% of olanzapine-treated participants gained at least 7% of their baseline weight.[3] During long-term studies (≥ 48 weeks), olanzapine-treated participants gained an average of 5.6 kg; 64% of olanzapine-treated participants gained at least 7% of their baseline weight.[3] While some studies have shown that early weight change can help clinicians predict which patients will and which will not experience clinically significant weight gain,[5–7] clinicians need information that helps them not only to anticipate weight gain but also to prevent or mitigate it.

Several studies have reported some success with weight gain mitigation/prevention or weight loss strategies for psychiatric patients treated with antipsychotics,[8–12] including treatment with amantadine,[13–16] metformin,[17–20] or zonisamide.[21] Amantadine, which is indicated for the treatment of Parkinson's disease and extrapyramidal symptoms associated with antipsychotic agents as well as for influenza A, is a weak noncompetitive agonist of the *N*-methyl-D-aspartate receptor.[22] Amantadine blocks uptake of dopamine, norepinephrine, and serotonin. Amantadine treatment has been associated with slight mean weight loss without adversely affecting efficacy of olanzapine treatment[14–16]; however, a small open-label study showed no significant effect on weight.[13] Metformin, an antihyperglycemic drug used in treating type 2 diabetes, decreases hepatic glucose production and intestinal absorption of glucose while increasing peripheral glucose uptake and utilization.[23] Some studies have shown that metformin was effective in preventing or reversing weight gain during antipsychotic treatment,[17,19,20] but other studies reported no significant effect.[24–26] Most studies of metformin have been short term (≤ 12 weeks); longer term studies are needed.[27] Zonisamide, used primarily as an anticonvulsant, increases dopaminergic and serotonergic neurotransmission.[28] In a noncontrolled, open-label study of bipolar disorder, participants treated with zonisamide experienced a significant mean decrease in body mass index (BMI) over 25 weeks.[21] Because these 3 drugs may prevent or mitigate weight gain, because amantadine and zonisamide are familiar to mental health professionals, and because amantadine and metformin are among the more affordable treatments for patients, we chose to examine 2 treatment algorithms combining these drugs for their effect on weight change during olanzapine treatment. Treatment algorithms are better models of clinical practice than monotherapy; clinicians commonly switch patients from treatments that are not working to others that might be effective. This study

Clinical Points

- Weight gain has been very commonly reported during olanzapine treatment.
- We observed no significant difference on the primary outcome measure for this study: difference in weight gain between olanzapine monotherapy and the pooled results for the 2 weight gain treatment algorithms.
- Participants who initiated on metformin (500–1,500 mg/d), progressing as needed to amantadine (200 mg/d) and then to zonisamide (100–400 mg/d), experienced significantly less weight gain than participants on olanzapine monotherapy.

was designed to test the hypothesis that weight gain during olanzapine treatment can be prevented or mitigated with adjunctive pharmacologic algorithms that include amantadine, metformin, and zonisamide.

METHOD

This was a 22-week, randomized, open-label clinical trial comparing adjunctive pharmacologic algorithms plus weight management education to weight management education alone for prevention/mitigation of weight gain during treatment with olanzapine in participants with schizophrenia or schizoaffective disorder. The trial is registered at clinicaltrials.gov (identifier: NCT00401973). Written informed consent was obtained from all participants after the procedures and possible adverse events were fully explained. All procedures were approved by institutional review boards for all study sites and were conducted in compliance with the Declaration of Helsinki. The study was conducted between November 7, 2006, and September 3, 2008, at 19 study centers in Israel, Mexico, the Republic of Korea, Russian Federation, and the United States. One study site closed for reasons unrelated to the study. Data from the 2 participants at this site, who had enrolled but not completed, were excluded from these analyses.

Participants were men and women aged 18 to 65 years with *schizophrenia* or *schizoaffective disorder*, defined as 295.XX according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision,[29] with BMI (kg/m^2) between 20 and 35, inclusive. Weight gain during olanzapine treatment has been shown to be influenced by baseline BMI.[30] Therefore, to reduce potential confounding factors, enrollment of participants with BMI < 23 or > 30 was limited to a maximum of 25% of total enrollment. Participants were excluded if, in the opinion of the investigator, they were treatment resistant to olanzapine or if they had a diagnosis of substance dependence (other than nicotine and caffeine) within 30 days prior to visit 1; a plasma prolactin concentration greater than 200 ng/mL at visit 1; a history of *eating disorders*, defined as 307.XX according to *DSM-IV-TR*[29]; current treatment with amantadine, metformin, or zonisamide; or had a known glucose-6-phosphate-dehydrogenase deficiency. Participants diagnosed with diabetes or who were receiving treatment or nutritional therapy for diabetes were also excluded. Such treatments could affect patient weight, and, thus, could confound study results. In addition, people with diabetes may metabolize or respond to study medications differently.

Measures

The primary outcome measure was change in weight from baseline to endpoint. Effectiveness of treatment algorithms was assessed by comparing time to gain of 7% baseline weight, time to switch from first to second treatment within each algorithm, and time to switch to zonisamide. The Brief Psychiatric Rating Scale (BPRS),[31] Montgomery-Asberg Depression Rating Scale (MADRS),[32] and the Clinical Global Impressions-Severity of Illness Scale (CGI-S)[33] were also used to assess efficacy.

Adverse events were collected at each visit by nondirected inquiry.

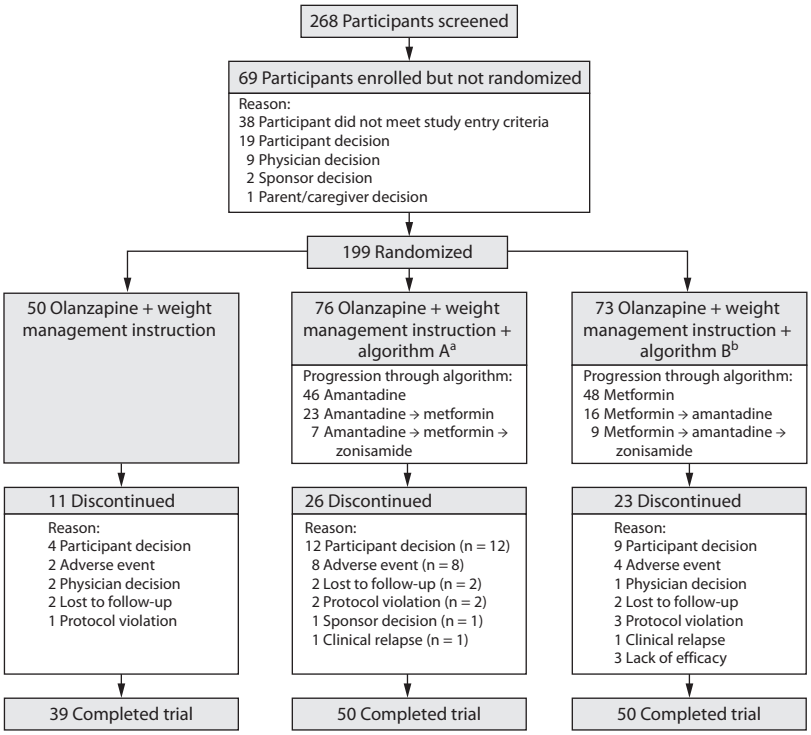
Study Design

Participants were randomly assigned to olanzapine (5–20 mg/d) alone, olanzapine plus algorithm A (olanzapine + A), or olanzapine plus algorithm B (olanzapine + B). The initial olanzapine dose and titration schedule for each participant were determined by study clinicians. All participants were provided with weight management information (1 double-sided page) on the importance of continuing antipsychotic therapy, and the potential for weight gain during antipsychotic treatment, as well as weight management tips, with an optional checklist for recording diet and exercise choices at baseline and throughout the study. At the first study visit, clinicians briefly discussed weight management tips with participants.

Participants in the olanzapine + A treatment group received amantadine, with possible switches first to metformin and then to zonisamide. Participants in the olanzapine + B treatment group initiated treatment on metformin, with possible switches to amantadine and then to zonisamide. Amantadine treatment (100 mg twice daily) was not titrated. Treatment with metformin began at 500 mg twice daily and was increased to 500 mg 3 times a day after 2 weeks. Zonisamide was initiated at 100 mg/d. At the discretion of the clinician, zonisamide could be increased by 100 mg/d every 2 weeks, to a maximum dose of 400 mg/d.

Because early weight gain of 3 kg has been shown to predict later substantial weight gain during olanzapine treatment,[6,7] the algorithms were designed so that comparatively small degrees of weight gain could trigger an alteration in treatment. Under both treatment algorithms, participants remained on their initial treatment as long as weight gain from baseline stayed below 1.5 kg. When weight gain was between 1.5 and 3.0 kg, inclusive, the treating physician had the option of switching the participant to the second treatment in the algorithm. If participants gained more than 3 kg from baseline, they were required to progress to the

Figure 1. Participant Disposition Diagram



[a]Participants in the olanzapine + A treatment group received olanzapine plus amantadine, with the potential to switch from amantadine first to metformin and then to zonisamide.
[b]Participants in the olanzapine + B treatment group received olanzapine plus metformin, with the potential to switch from metformin first to amantadine and then to zonisamide.

second treatment. Participants who gained less than 1.5 kg after switching remained on that second treatment for the remainder of the study. If weight gain after the switch was between 1.5 kg and 3.0 kg, inclusive, the treating physician had the option of switching the participant to zonisamide. If participants gained more than 3 kg after switching to the second treatment, they were required to progress to zonisamide. For participants who did not tolerate medication, the treating physicians could decide to decrease medication dose, return the participant to previous medication in the algorithm, or advance the participant to the next step in the algorithm. Participants who did not tolerate the initial dose of the first medication in the algorithm were discontinued from the study.

Statistical Analyses

Based on a hypothesized difference in weight change of approximately 3 kg between olanzapine monotherapy and olanzapine augmented with the pharmacologic algorithms, a common standard deviation of 5.75 kg, and the sample sizes obtained, the power of this study was estimated at 89%.

All analyses were performed using statistical software (SAS Drug Development; SAS Institute Inc, Cary, North Carolina). Treatment effects were tested at a 2-tailed α level of .05. Analysis of the primary objective comparing olanzapine monotherapy to olanzapine plus adjunctive pharmacologic treatment was performed using a mixed-effects model repeated-measures (MMRM) analysis on a qualified subset of randomized participants (participants with at least 1 postbaseline weight assessment who did not meet criteria for diabetes during the study based on a new diagnosis of diabetes, having 2 confirmed fasting serum glucose levels of ≥ 126 mg/dL (7 mmol/L), or initiation of treatment for diabetes other than metformin per the protocol). The MMRM model included fixed, categorical effects of treatment group, investigator, visit, and treatment group-by-visit interaction, as well as fixed continuous covariates of baseline weight and baseline weight-by-visit interaction. An unstructured covariance matrix was employed to model within-participant error. Treatment differences for each visit were tested using a single degree of freedom contrast based on least squares means from the model. Inference from the MMRM analyses was based on the restricted maximum likelihood solution and on *F* tests and *t* tests using denominator degrees of freedom estimated by the Kenward-Roger approximation.

Additional continuous outcomes were assessed by analysis of variance models using the last-observation-carried-forward method. Categorical outcomes, including baseline demographics, participant disposition, treatment-emergent adverse events, and treatment-emergent changes in laboratory analytes (based on National Cholesterol Education Program Adult Treatment Panel and American Diabetes Association criteria) were analyzed using Fisher exact test. Kaplan-Meier analyses and the associated log rank tests were used to compare treatment groups for time-to-event data. To examine the relationship between weight gain and measures of efficacy, Pearson correlations are reported.

RESULTS

Of 268 participants screened, 199 were randomly assigned to treatment, and 139 completed the study (Figure 1). Immediately prior to study entry, 85 participants (42.7%) reported receiving antipsychotic treatment: 60 (30.2%) with atypical antipsychotics and 39 (19.6%) with typical antipsychotics. The most commonly reported treatment was risperidone (33 participants; 16.6%). Only 2 participants (1.0%) reported receiving olanzapine treatment immediately prior to study entry.

Sixty participants discontinued before study completion; the most common reasons were participant decision (n = 25) and adverse events (n = 14). There were no significant differences among treatment groups in frequency of reasons for study discontinuation.

Three participants, all in the olanzapine + A group, discontinued the study due to serious adverse events; these were

Table 1. Participant Demographics and Baseline Characteristics[a]

Variable	Olanzapine Only (n = 50)		Olanzapine Plus Algorithm A (n = 76)		Olanzapine Plus Algorithm B (n = 73)	
	n	%	n	%	n	%
Men	31	62.0	46	60.5	43	58.9
Ethnicity						
African origin	2	4.0	10	13.2	4	5.5
Caucasian	23	46.0	30	39.5	34	46.6
East Asian	10	20.0	15	19.7	14	19.2
Hispanic	14	28.0	20	26.3	18	24.7
Native American	…	…	…	…	1	1.4
West Asian	1	2.0	1	1.3	2	2.7
Smokers	24	49.0	47	62.7	41	56.2
Diagnosis						
Schizophrenia	42	84.0	61	80.3	55	75.3
Schizoaffective disorder	8	16.0	15	19.7	18	24.7
	Mean	SD	Mean	SD	Mean	SD
Age, y	38.7	12.9	38.2	11.4	38.7	12.0
Age at onset of illness, y	24.35	8.42	26.44	9.98	24.40	9.18
No. of previous episodes	1.53	1.02	2.19	5.90	2.22	5.77
Baseline weight, kg	77.0	16.3	79.1	17.3	76.2	16.2
Baseline BMI (kg/m^2)	27.0	4.5	27.3	4.7	27.0	4.8
BPRS total score	49.0	16.0	45.6	12.8	46.8	14.2
CGI-S score	4.1	1.2	4.1	1.1	4.0	1.1
MADRS score	13.0	8.6	14.3	10.9	15.3	9.2

[a]There were no statistically significant differences in any pairwise between-group comparisons.
Abbreviations: BMI = body mass index, BPRS = Brief Psychiatric Rating Scale, CGI = Clinical Global Impressions-Severity of Illness scale, MADRS = Montgomery-Asberg Depression Rating Scale.

panic attack, akathisia, and hallucination (1.3% each). Ten additional participants continued in the study despite the following serious adverse events: 3 (olanzapine, 6.0%) due to worsened schizophrenia, 2 (olanzapine + B, 2.7%) due to hallucination, 1 each (olanzapine, 2.0%) due to psychotic disorder and suicidal ideation, 1 (olanzapine + A, 1.3%) due to squamous cell carcinoma, and 1 each (olanzapine + B, 1.4%) due to suicide attempt and chest pain. Eleven participants discontinued the study due to nonserious adverse events: 2 (olanzapine, 4.0%) for overdose; 1 each (olanzapine + A, 1.3%) for anxiety, increased blood glucose, dry mouth, paresthesia, and sedation; and 1 each (olanzapine + B, 1.4%) for depression, dizziness, stomach discomfort, and treatment noncompliance.

Participants had similar baseline demographics and disease characteristics across all treatment groups (Table 1). There were no significant differences among treatment groups in any baseline characteristics, although the olanzapine + A and olanzapine + B treatment groups had larger proportions of participants diagnosed with schizoaffective disorder than the olanzapine treatment group.

During the 22-week study, mean modal doses of olanzapine were 13.33 mg/d (olanzapine), 12.89 mg/d (olanzapine + A), and 13.48 mg/d (olanzapine + B). Kaplan-Meier curves of time to switch to the second and third treatments in each algorithm are shown in Figure 2A and 2B. A total of 30 olanzapine + A–treated participants (42.3%) and 25 olanzapine + B–treated participants (34.7%) switched to the second treatment within their algorithm ($P = .153$). Estimated time to switch to second algorithm treatment by 25% of participants was 42 days (95% CI, 28–69) for the olanzapine + A group and 66 days (95% CI, 29–110) for the olanzapine + B group. A total of 7 olanzapine + A–treated participants (9.9%) and 9 olanzapine + B–treated participants (12.5%) switched to zonisamide ($P = .707$). Time to switch to zonisamide by 25% of participants could not be estimated for either treatment group due to the low occurrence of the event.

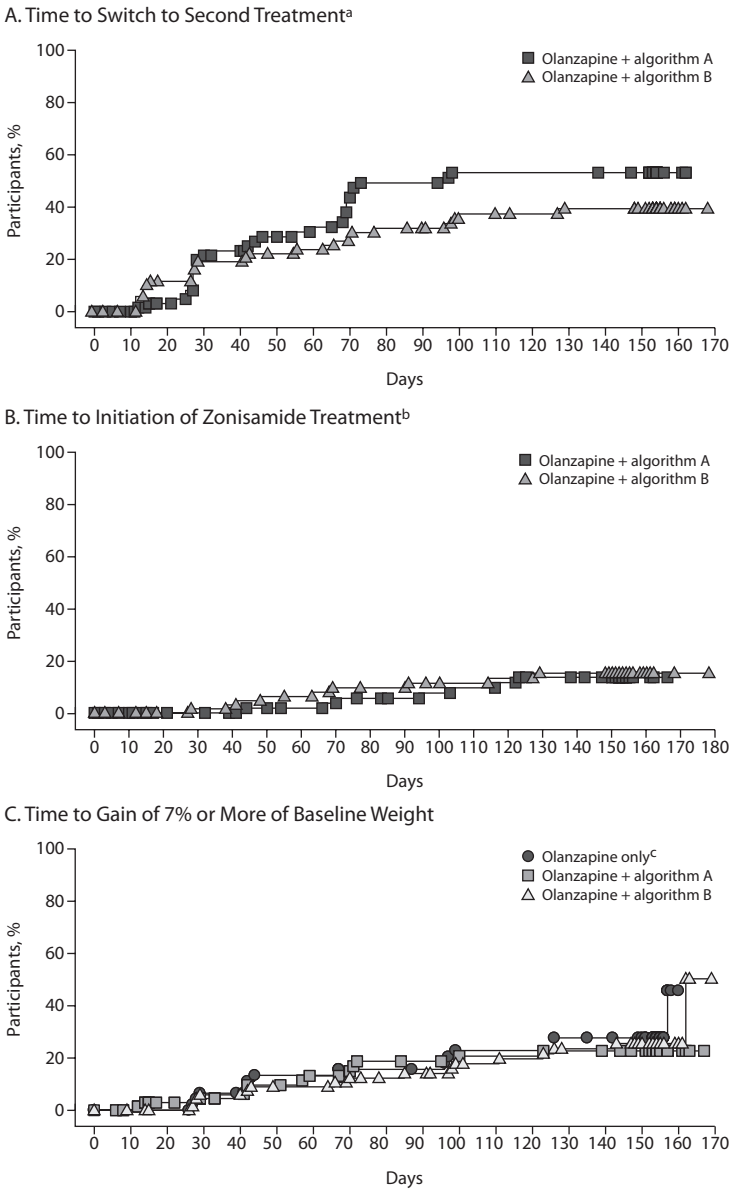
The protocol-defined primary outcome for this study, comparison between olanzapine and pooled results for olanzapine + A and olanzapine + B in mean weight gain, was not significant ($P = .065$). However, the olanzapine + B–treated participants experienced significantly less mean weight gain than those in the olanzapine-treated group, while the olanzapine + A–treated participants had least squares mean weight gain comparable to that of olanzapine-treated participants (Figure 3; Table 2). Within-group least squares mean weight gain from baseline was significant for olanzapine- and olanzapine + A–treated participants at each postbaseline time point ($P \leq .008$). The olanzapine + B treatment group did not have a significant least squares mean gain from baseline weight at any time point ($P \geq .064$). Effect sizes for differences in weight gain compared to olanzapine were 0.07 for olanzapine + A, 0.43 for olanzapine + B, and 0.26 for the pooled olanzapine + A and olanzapine + B treatment arms.

For the olanzapine and olanzapine + A treatment groups, peak least squares mean weight gain occurred at endpoint (Figure 3). While the rates of weight gain appeared to slow, further weight gain may have been observed over a longer time period. For olanzapine + B–treated participants, least squares mean weight gain peaked at week 14 (0.97 ± 0.52 kg) and decreased slightly thereafter.

Time to clinically significant weight gain (≥ 7% of baseline weight) was comparable among treatment groups (Figure 2C). There were no significant difference in participants with clinically significant weight gain across treatment groups (olanzapine, n = 13 [27.7%]; olanzapine + A, n = 13 [18.3%]; olanzapine + B, n = 16 [22.2%]; $P = .725$). Estimated time to clinically significant weight gain was 126 days for the olanzapine group and 143 days for the olanzapine + B group. Upper limit of 95% confidence interval could not be estimated for these values, but the lower limits were 67 days and 98 days, respectively. Time to clinically significant weight gain by 25% of participants could not be estimated for the olanzapine + A group because the proportion of participants who gained clinically significant weight was too small. There was no difference across groups in the number of participants with a clinically significant weight loss (≥ 7% of baseline weight) (olanzapine, n = 2 [4.3%]; olanzapine + A, n = 4 [5.6%]; olanzapine + B, n = 5 [6.9%]; $P = 1.000$).

Change in BMI was not significantly different between olanzapine and olanzapine + A treatment groups, but the olanzapine + B treatment group had a smaller mean increase in BMI than the olanzapine treatment group (Table 2). Within-group BMI change was significant for the olanzapine

Figure 2. Kaplan-Meier Analyses in Participants Assigned to Olanzapine Plus Algorithm A (n = 76) and B (n = 73)



[a]For algorithm A, time to switch from amantadine to metformin. For algorithm B, time to switch from metformin to amantadine.
[b]Time from start of treatment to switch to zonisamide.
[c]n = 50.

and olanzapine + A treatment groups (both *P* values < .001), but not for olanzapine + B (*P* = .166).

There were no significant differences in change in BPRS and CGI-S scores when the olanzapine + A and olanzapine + B treatment groups were compared to the olanzapine treatment group. However, the olanzapine + A and olanzapine + B treatment groups showed a significantly smaller improvement in MADRS score compared to the olanzapine group (Table 2).

The most commonly reported treatment-emergent adverse events were somnolence, diarrhea, and insomnia. Somnolence occurred in 17 participants (olanzapine, n = 4 [8.0%]; olanzapine + A, n = 5 [6.6%]; olanzapine + B, n = 8 [11.0%]); pairwise comparisons between treatment groups showed no significant differences ($P \geq .395$). Diarrhea occurred significantly more often among olanzapine + B–treated participants (n = 10 [13.7%]) than in olanzapine-treated (n = 0, *P* = .005) or olanzapine + A–treated participants (n = 3 [3.9%], *P* = .044). Insomnia occurred significantly more often in olanzapine-treated participants (n = 5 [10.0%]) than in olanzapine + B–treated participants (n = 1 [1.4%], *P* = .040). Insomnia occurred in 4 olanzapine + A–treated participants (5.3%), which was not significantly different from the olanzapine (*P* = .481) or olanzapine + B (*P* = .367) treatment groups. No other significant differences among participant groups occurred in frequency of treatment-emergent adverse events. Adverse events reported in 5% or more of participants in any group are shown in eTable 1.

We compared weight gain among participants with and those without gastrointestinal adverse events because such events may have affected eating behaviors among participants. Gastrointestinal adverse events did not appear to contribute to reduced weight gain (Table 2).

Changes in laboratory values potentially relevant to changes in weight and metabolic parameters are shown in Table 2, as are any mean changes in laboratory values that were both statistically and clinically significant. Within- or between-group differences in mean changes in fasting glucose, insulin, or leptin concentrations were not significant (although *P* values for comparison of olanzapine + A and olanzapine + B treatment groups were .056 and .051 for insulin and leptin, respectively). Because leptin concentrations differ between men and women, we divided leptin values by participant sex and repeated the analysis. A significant difference between olanzapine + A and olanzapine + B treatment groups was observed in men (*P* = .017) but not in women (*P* = .875).

Eight of the olanzapine-treated participants who had normal total fasting cholesterol (less than 200 mg/dL [5.2 mmol/L]) at baseline (34.8%) had a categorical increase to borderline high cholesterol (between 200 mg/dL [5.2 mmol/L] and 240 mg/dL [6.2 mmol/L]) at endpoint, compared with 8 olanzapine + A–treated participants (29.6%; *P* = .77) and 2 olanzapine + B–treated participants (6.3%; *P* = .01). Among all participants who had borderline high cholesterol at baseline, 6 (42.9%) in the olanzapine treatment group had a categorical increase to high (greater than or equal to 240 mg/dL [6.2 mmol/L) at endpoint compared with no participants in the olanzapine + A group (*P* = .01) and 1 patient (7.7%) in the olanzapine + B group (*P* = .08).

Change in hemoglobin A_{1c} was significantly different between the olanzapine + B treatment group and the other treatment groups ($P \leq .049$). The olanzapine treatment group

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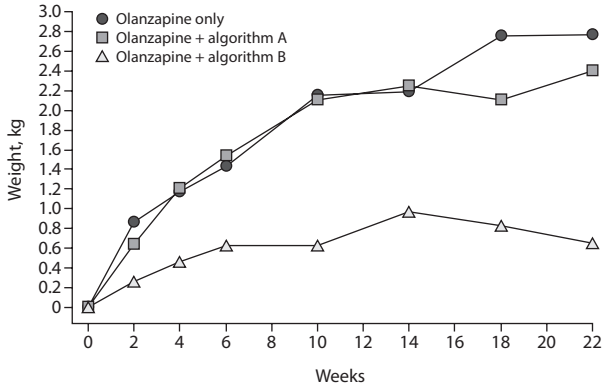
Figure 3. Least Squares Mean Change in Weight Over Time[a]



[a]Olanzapine only, n = 47; olanzapine + algorithm A, n = 71; olanzapine + algorithm B, n = 72.

had a significant within-group increase in total cholesterol ($P = .008$), while the olanzapine + A and olanzapine + B treatment groups had significant within-group decrease in high-density lipoprotein cholesterol ($P = .002$ and $P = .006$, respectively). Treatment-emergent high (≥ 105 mm Hg with an increase ≥ 15 mm Hg) and low (≤ 50 mm Hg with a decrease ≥ 15 mm Hg) diastolic blood pressure occurred in 3 and 1 participants, respectively. Treatment-emergent high (≥ 180 mm Hg with an increase ≥ 20 mm Hg) and low (≤ 90 mm Hg with a decrease ≥ 20 mm Hg) systolic blood pressure occurred in 2 and 7 participants, respectively. There were no significant differences across treatment groups for frequency of these events.

DISCUSSION

The protocol-defined primary outcome for this study, comparison of olanzapine treatment alone and pooled treatment algorithm groups for mean change in weight from baseline, did not demonstrate a significant difference. However, participants treated with an algorithm that initiated treatment on metformin had significantly less weight gain than participants treated with an algorithm that initiated treatment on amantadine or participants who received no adjunctive pharmacologic treatment.

Interestingly, there were no significant differences between treatment groups in the proportion of participants who experienced clinically significant weight gain. However, substantial weight gain was less common in this study than in others, even in the olanzapine treatment group.[3] In addition, mean weight gain observed for olanzapine monotherapy was somewhat less than what has typically been reported.[3] Since all participants received weight management education, definite conclusions cannot be drawn, but learning about the potential for weight gain during antipsychotic treatment, and ways to prevent or mitigate such weight gain, may have helped participants to manage their weight during antipsychotic treatment.

There were no significant differences across treatment groups in study discontinuation or frequency or type of

Table 2. Change in Weight, BMI, Relevant Laboratory Values Efficacy Measures at Endpoint

Variable	Olanzapine Only	Olanzapine Plus Algorithm A	Olanzapine Plus Algorithm B	Olanzapine Versus Olanzapine Plus Algorithm A, *P* Value	Olanzapine Versus Olanzapine Plus Algorithm B, *P* Value	Olanzapine Versus Olanzapine Plus Algorithm A and Olanzapine Plus Algorithm B, *P* Value
Weight, LS mean (SE), kg	2.76 (0.75)	2.40 (0.65)	0.65 (0.63)	.113	.036	.065
Weight, no gastrointestinal adverse events, LS mean (SE), kg[a]	2.63 (0.79)	2.16 (0.70)	0.34 (0.71)	.656	.032	.145
Weight, with gastrointestinal adverse events, LS mean (SE), kg[a]	3.10 (2.55)	5.09 (1.74)	1.26 (1.26)	.535	.533	.844
BMI (kg/m^2), mean (SD)	0.90 (1.51)	0.72 (1.66)	0.25 (1.52)	.482	.019	.88
Total cholesterol, mean (SD), mmol/L	0.36 (0.84)	0.01 (1.06)	−0.08 (0.92)	.173	.016	.029
HDL cholesterol, mean (SD), mmol/L	0.00 (0.23)	−0.11 (0.25)	−0.08 (0.24)	.015	.071	.017
LDL cholesterol, mean (SD), mmol/L	0.16 (0.60)	−0.04 (0.95)	−0.02 (0.84)	.350	.123	.152
Prolactin, mean (SD), µg/L	−16.2 (35.7)	−13.7 (33.1)	−7.2 (21.4)	.995	.190	.453
Insulin, mean (SD), µIU/mL	2.43 (7.57)	1.93 (17.54)	3.04 (13.51)	.752	.141	.495
Glucose, mean (SD), mmol/L	0.26 (0.99)	0.10 (0.48)	0.01 (0.58)	.833	.339	.499
Hemoglobin A_{1c}, mean (SD), %	0.09 (0.45)	0.10 (0.37)	−0.03 (0.25)	.976	.049	.278
Triglycerides, mean (SD), mmol/L	0.33 (1.01)	0.35 (0.88)	0.06 (0.64)	.637	.125	.498
Adiponectin, mean (SD), ng/mL	−677 (2,109)	−1,417 (2,847)	−174 (3,470)	.693	.306	.707
Leptin, mean (SD), ng/mL	1.9 (9.8)	4.1 (17.3)	0.70 (15.32)	.211	.600	.696
Leptin, mean (SD), ng/mL, women only[b]	3.2 (12.4)	3.6 (25.1)	1.9 (23.2)	.707	.811	.730
Leptin, mean (SD), ng/mL, men only[c]	1.0 (7.5)	4.5 (9.8)	−0.1 (5.2)	.085	.616	.509
BPRS score, mean (SD)	−13.9 (18.6)	−9.9 (11.2)	−9.7 (14.2)	.225	.124	.122
CGI score, mean (SD)	−1.0 (1.1)	−0.7 (1.1)	−0.8 (1.0)	.404	.652	.474
MADRS score, mean (SD)	−6.4 (8.4)	−4.1 (7.2)	−4.4 (7.5)	.037	.038	.020

[a]Gastrointestinal adverse events were defined as diarrhea, nausea, and constipation.
[b]For women, *n*'s for olanzapine, olanzapine + A, and olanzapine + B are 18, 24, and 26, respectively.
[c]For men, *n*'s for olanzapine, olanzapine + A, and olanzapine + B are 25, 37, and 37, respectively.
Abbreviations: BMI = body mass index, BPRS = Brief Psychiatric Rating Scale, CGI = Clinical Global Impressions-Severity of Illness Scale, LS = least squares, MADRS = Montgomery-Asberg Depression Rating Scale.

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serious adverse events. There were significant differences between groups for insomnia, which occurred significantly more frequently in participants treated with olanzapine monotherapy than in participants who initiated therapy on metformin, and for diarrhea, which occurred most frequently in participants who initiated on metformin. It is possible that use of an extended-release formulation of metformin[34] would have lessened the occurrence of diarrhea.

Participants who initiated therapy on metformin had a significant decrease in total cholesterol compared to participants treated with olanzapine monotherapy, an effect that was not observed in previous, smaller studies of metformin in olanzapine-treated participants.[19,35] The present study did not find a consistent pattern of changes in weight, lipids, glucose, and hemoglobin A_{1c} across groups.

Because weight gain and improvement in psychiatric symptoms may be correlated,[36–38] we also assessed change in symptomatology. Both treatment algorithms were comparable to olanzapine monotherapy in mean improvement in schizophrenia symptoms, but showed less improvement in depressive symptoms, although this difference may not be clinically significant.

The exclusion of participants with BMI > 35 or with diabetes must be considered a limitation of this study. While these exclusions made sense from the standpoint of the clinical trial, in clinical practice many patients in need of weight gain intervention will have diabetes or have BMIs above 35. The 22-week study may also have been too short; weight gain may not have plateaued in all treatment groups and longer term assessments of metabolic laboratory values such as prolactin and adiponectin would have been valuable. The allowed window for weight gain before switching treatments may have been too conservative, especially as weight measurements were collected as they would be in usual practice in a physician's office, rather than by a more stringent method. In addition, medication compliance was not analyzed.

Future studies might benefit from a randomization scheme that balanced representation of ethnicity, diagnosis, and BMI category across treatment groups, with large enough participant populations to allow subgroup analyses within these categories.

Strengths of this study include use of treatment algorithms instead of drug monotherapy to better represent real-world treatment options.

It is possible the dose of amantadine used in this study, 100 mg twice daily, was not optimal for weight management in this population. Three previous studies that found amantadine to be effective in weight management for mental health patients used doses up to 300 mg/d.[14–16] The one study that did not find a significant difference reported a mean amantadine dose of 160 mg/d.[13]

This study did not assess all possible treatments available for mitigating weight gain during olanzapine treatment. Other options, including intensive medical nutritional treatment and switching antipsychotics, have been shown to mitigate treatment-emergent weight gain.[8,11] This study does not provide a final, one-solution-fits-all answer to clinicians' questions regarding weight gain mitigation strategies during olanzapine treatment. However, the progression of some participants through the algorithm illustrated that a single therapy solution may work for some patients, but is not adequate for every patient. Patients treated with olanzapine should receive regular weight monitoring.

In conclusion, there was no significant difference on the primary outcome measure for this study: difference in weight gain between olanzapine monotherapy and the pooled results for the 2 weight gain treatment algorithms. However, participants who initiated on metformin (500–1,500 mg/d) progressing, as needed, to amantadine (200 mg/d) and then to zonisamide (100–400 mg/d) experienced significantly less weight gain than participants on olanzapine monotherapy. Further research should focus on longer term double-blind studies of monotherapy treatment with metformin, zonisamide, and higher dose amantadine.

Drug names: metformin (Glucophage and others), olanzapine (Zyprexa), risperidone (Risperdal and others), zonisamide (Zonegran and others).

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Supplementary Material

Article Title: Assessment of the Safety, Efficacy, and Practicality of Treatment Algorithms Including Amantadine, Metformin, and Zonisamide for the Prevention of Weight Gain During Treatment With Olanzapine in Outpatients With Schizophrenia

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List of Supplementary Material for the article

1. eTable 1 Treatment-Emergent Adverse Events Reported in ≥5% of Participants in Any Group

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eTable 1. Treatment-Emergent Adverse Events Reported in ≥5% of Participants in Any Group

Treatment-Emergent Adverse Event	OLZ (N=50) n (%)	OLZ/A (N=76) n (%)	OLZ/B (N=73) n (%)	p-value, Fisher's Exact Test OLZ vs. OLZ/A	OLZ vs. OLZ/B	OLZ/A vs. OLZ/B
Somnolence	4 (8.0%)	5 (6.6%)	8 (11.0%)	.740	.760	.395
Diarrhea	0	3 (3.9%)	10 (13.7%)	.276	.005	.044
Insomnia	5 (10.0%)	4 (5.3%)	1 (1.4%)	.481	.040	.367
Nausea	2 (4.0%)	3 (3.9%)	5 (6.8%)	1.000	.700	.489
Weight Increased	2 (4.0%)	4 (5.3%)	4 (5.5%)	1.000	1.000	1.000
Akathisia	2 (4.0%)	4 (5.3%)	2 (2.7%)	1.000	1.000	.681
Headache	2 (4.0%)	2 (2.6%)	4 (5.5%)	.649	1.000	.436
Increased Appetite	3 (6.0%)	1 (1.3%)	3 (4.1%)	.300	.686	.360
Dry Mouth	2 (4.0%)	4 (5.3%)	0	1.000	.163	.120
Sedation	0	4 (5.3%)	2 (2.7%)	.151	.514	.681
Vomiting	0	1 (1.3%)	5 (6.8%)	1.000	.079	.112
Nasopharyngitis	0	4 (5.3%)	0	.151	--	.120

Abbreviations: HDL = high-density lipoprotein; LDL = low-density lipoprotein; OLZ = olanzapine only; OLZ/A = olanzapine plus treatment algorithm A; OLZ/B = olanzapine plus treatment algorithm B.