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Effect of Continuing Olanzapine vs Placebo on Relapse Among Patients With Psychotic Depression in Remission: The STOP-PD II Randomized Clinical Trial

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Et al.

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Effect of Continuing Olanzapine vs Placebo on Relapse Among Patients With Psychotic Depression in Remission
The STOP-PD II Randomized Clinical Trial

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IMPORTANCE Psychotic depression is a severely disabling and potentially lethal disorder. Little is known about the efficacy and tolerability of continuing antipsychotic medication for patients with psychotic depression in remission.

OBJECTIVE To determine the clinical effects of continuing antipsychotic medication once an episode of psychotic depression has responded to combination treatment with an antidepressant and antipsychotic agent.

DESIGN, SETTING, AND PARTICIPANTS Thirty-six week randomized clinical trial conducted at 4 academic medical centers. Patients aged 18 years or older had an episode of psychotic depression acutely treated with sertraline plus olanzapine for up to 12 weeks and met criteria for remission of psychosis and remission or near-remission of depressive symptoms for 8 weeks before entering the clinical trial. The study was conducted from November 2011 to June 2017, and the final date of follow-up was June 13, 2017.

INTERVENTIONS Participants were randomized either to continue olanzapine (n = 64) or switch from olanzapine to placebo (n = 62). All participants continued sertraline.

MAIN OUTCOMES AND MEASURES The primary outcome was risk of relapse. Main secondary outcomes were change in weight, waist circumference, lipids, serum glucose, and hemoglobin A_{1c} (HbA_{1c}).

RESULTS Among 126 participants who were randomized (mean [SD] age, 55.3 years [14.9 years]; 78 women [61.9%]), 114 (90.5%) completed the trial. At the time of randomization, the median dosage of sertraline was 150 mg/d (interquartile range [IQR], 150-200 mg/d) and the median dosage of olanzapine was 15 mg/d (IQR, 10-20 mg/d). Thirteen participants (20.3%) randomized to olanzapine and 34 (54.8%) to placebo experienced a relapse (hazard ratio, 0.25; 95% CI, 0.13 to 0.48; $P < .001$). The effect of olanzapine on the daily rate of anthropometric and metabolic measures significantly differed from placebo for weight (0.13 lb; 95% CI, 0.11 to 0.15), waist circumference (0.009 inches; 95% CI, 0.004 to 0.014), and total cholesterol (0.29 mg/dL; 95% CI, 0.13 to 0.45) but was not significantly different for low-density lipoprotein cholesterol (0.04 mg/dL; 95% CI, −0.01 to 0.10), high-density lipoprotein cholesterol (−0.01 mg/dL; 95% CI, −0.03 to 0.01), triglyceride (−0.153 mg/dL; 95% CI, −0.306 to 0.004), glucose (−0.02 mg/dL; 95% CI, −0.12 to 0.08), or HbA_{1c} levels (−0.0002 mg/dL; 95% CI, −0.0021 to 0.0016).

CONCLUSIONS AND RELEVANCE Among patients with psychotic depression in remission, continuing sertraline plus olanzapine compared with sertraline plus placebo reduced the risk of relapse over 36 weeks. This benefit needs to be balanced against potential adverse effects of olanzapine, including weight gain.

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Major depressive disorder with psychotic features (psychotic depression) is a severely disabling disorder, with high risk of suicide.[1,2] Meta-analyses support the use of either electroconvulsive therapy or pharmacotherapy with the combination of an antidepressant with an antipsychotic agent for the acute treatment of psychotic depression.[3,4] Once an episode of major depression responds to antidepressant medication, the antidepressant needs to be continued to prevent relapse and recurrence of depression.[5] However, it is not known whether antipsychotic medication needs to be continued once an episode of psychotic depression has responded to combined antidepressant-antipsychotic treatment. This is a critical question because premature discontinuation of antipsychotic medication has the risk of relapse of a severe life-threatening disorder. In contrast, the unnecessary continuation of an antipsychotic agent exposes a patient to potentially serious adverse effects.

The Study of the Pharmacotherapy of Psychotic Depression (STOP-PD) was the first randomized clinical trial (RCT) funded by the National Institute of Mental Health (NIMH) to examine the efficacy and tolerability of combination pharmacotherapy using a serotonergic antidepressant and a second-generation antipsychotic agent for the acute treatment of psychotic depression.[6] Olanzapine plus sertraline was more efficacious than olanzapine plus placebo, but both treatments were associated with an increase in weight and lipids over the 12-week study.[6] The primary goal of the current STOP-PD II trial was to assess the risks and benefits of continuing antipsychotic medication in younger and older patients with psychotic depression, once the depressive episode had responded to treatment with sertraline plus olanzapine. The study tested the hypotheses that the combination of sertraline plus olanzapine is associated with lower risk of relapse and higher weight and total cholesterol and triglyceride levels than the combination of sertraline plus placebo.

Key Points

Question Does continuing antipsychotic medication reduce the risk of relapse among patients with psychotic depression in remission?

Findings In this 36-week randomized clinical trial that included 126 persons aged 18 years or older, 13 participants (20.3%) randomized to sertraline plus olanzapine and 34 (54.8%) to sertraline plus placebo experienced a relapse, a difference that was statistically significant.

Meaning For patients with psychotic depression in remission, continuing olanzapine reduced the 36-week risk of relapse.

Methods

The trial design and methods have been published previously.[7] The study protocol is provided in Supplement 1. This article reports the results of the first and second aims listed in the protocol that pertain to the benefits and risks of continuing antipsychotic medication among patients with psychotic depression in remission. Findings that pertain to additional aims listed in the protocol, namely the association between age and change in weight and metabolic measures and the association of genetic polymorphisms with outcomes, are not presented herein.

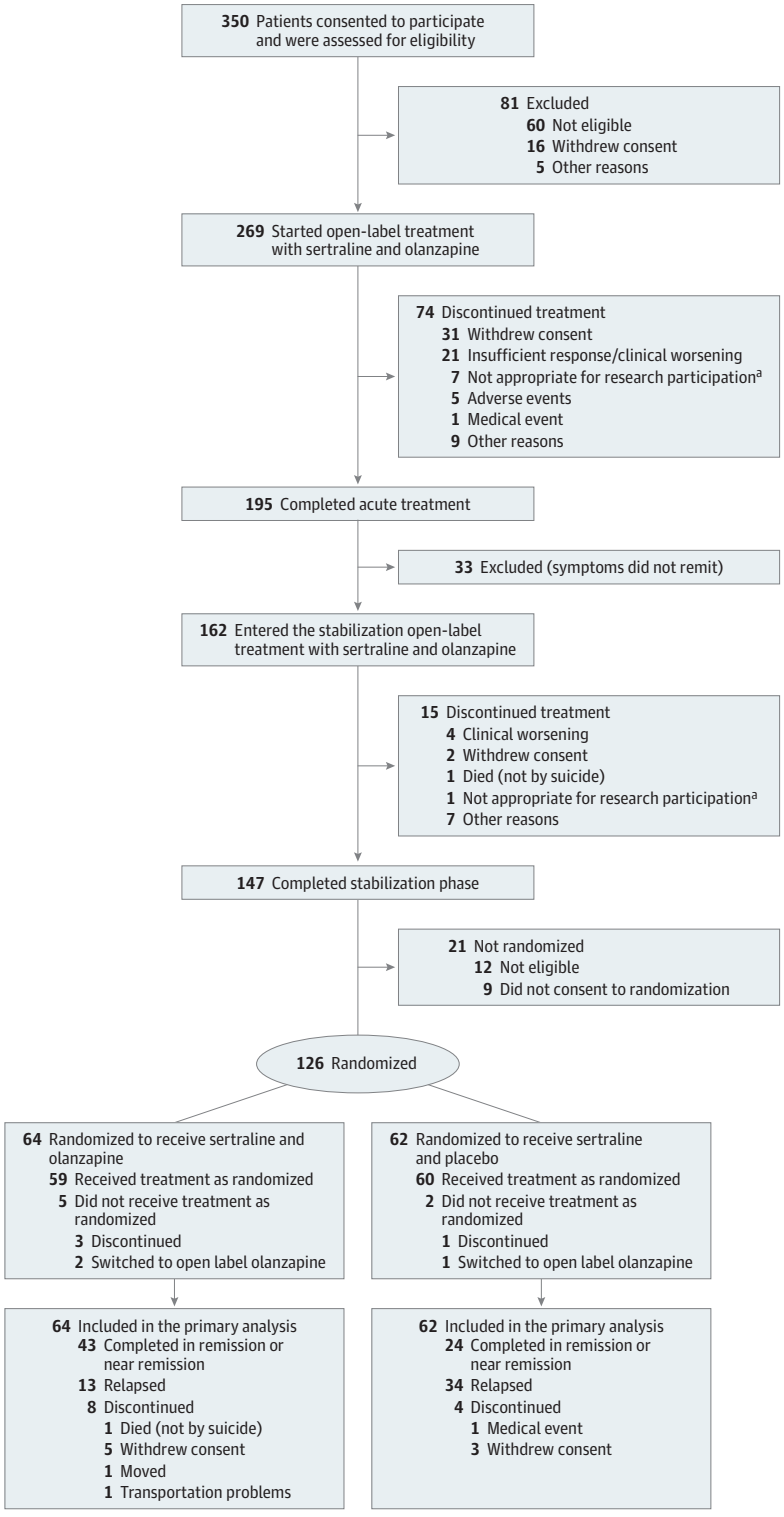
Participants

The study was conducted at 4 medical centers (University Health Network, Toronto; University of Massachusetts Medical School; University of Pittsburgh School of Medicine; and Weill Cornell Medical College) between November 2011 and June 2017, and the final date of follow-up was June 13, 2017 (**Figure 1**). Participant safety issues and quality assurance were overseen by a data and safety monitoring board appointed by the NIMH. Race/ethnicity were collected via participant self-report using fixed categories to satisfy the National Institutes of Health Policy and Guidelines on the Inclusion of Women and Minorities as Subjects in Clinical Research. Using procedures approved by local institutional review boards, written informed consent was obtained from all participants or their substitute decision maker prior to the initiation of any research procedures.

The study had 3 phases: acute, stabilization, and randomization. At the time of enrollment in the acute phase of the study, participants were between the ages of 18 and 85 years, met Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition, Text Revision) (*DSM-IV*-TR)[8] criteria for a current major depressive episode with at least one associated delusion (with or without hallucinations), and had a 17-item Hamilton Depression Rating Scale (HDRS)[9] total score of 21 or higher. Inclusion criteria for a delusion were a score of 3 or higher on the delusion severity item of the Schedule for Affective Disorders and Schizophrenia[10] (delusion definitely present) and a score of 2 or higher on any of the 3 conviction items of the Delusion Assessment Scale[11] (the participant is certain a belief is true and does not change the belief in response to reality testing by the interviewer). The study's exclusion criteria included current or lifetime *DSM-IV-TR* criteria for any other psychotic disorder, bipolar disorder, or intellectual disability; *DSM-IV-TR* criteria for current body dysmorphic disorder or obsessive-compulsive disorder; *DSM-IV-TR* defined dementia preceding the index episode of depression or a 26-item informant questionnaire on cognitive decline in the elderly (IQCODE)[12] mean score of 4 or higher at acute phase baseline; *DSM-IV-TR* defined substance abuse or dependence within the preceding 3 months; type 1 diabetes mellitus; neurologic disease that might affect neuromuscular function; and unstable physical illness, although many of the study participants had stable chronic physical problems.

In the open-label acute phase, participants received a combination of sertraline (target dose, 150-200 mg/d, dispensed in 50-mg pills) plus olanzapine (target dose, 15-20 mg/d, dispensed in 5-mg pills). Olanzapine was chosen because it is the only antipsychotic agent with established efficacy in combination therapy in both younger and older persons with psychotic depression.[3,4,6] Participants entered the open-label stabilization phase as soon as they met criteria for remission, defined as the absence of delusions and hallucinations and a 17-item HDRS score of 10 or less for 2 consecutive weeks. In addition, participants who met criteria for "near remission" following 12 weeks of acute treatment were also eligible to enter the stabilization phase. *Near remission* was defined as the absence of delusions

Figure 1. Flow of Participants in the Study of the Pharmacotherapy of Psychotic Depression II (STOP-PD II)



[a] Examples of "not appropriate for further research participation": repeated nonadherence with research assessments or repeated nonadherence with study medications during the "open-label" acute and stabilization phases of the study.

and hallucinations, an HDRS score of 11 to 15 with 50% or more reduction in baseline HDRS score, and being rated as "very much improved" or "much improved" on the Clinical Global Impression[13] scale. At the end of the 8-week stabilization phase, participants who still met full-remission or near-remission criteria following treatment with sertraline plus olanzapine and who had a Mini-Mental State Examination (MMSE)[14] score of 24 or higher were eligible for the 36-week RCT.

Randomization

Randomization was computer-generated with a 1:1 allocation ratio and a block size range of 4 to 8, stratified by age (18-59 years vs 60-85 years), remission vs near remission status at randomization, and study site.

Intervention

All participants continued to take open-label sertraline for the duration of the trial. They were randomized under double-blind conditions to either continue olanzapine or switch from olanzapine to identically appearing placebo pills over a 4-week taper of olanzapine. The double-blind taper was conducted according to a schedule for the substitution of blinded olanzapine or placebo for open-label olanzapine, based on the number of olanzapine pills that the participant was taking at the time of randomization (Supplement 1). Participants in the trial were assessed weekly for the first 8 weeks and once every 4 weeks thereafter until study completion at week 36, relapse, or early termination. If a participant chose to discontinue one or both study medications, including replacing study medication(s) with other psychotropic medication, every effort was made to continue research assessments for the entire course of randomized treatment or until relapse, whichever came first.

Outcomes

Primary Outcome: Relapse

Risk of relapse was the primary outcome. Relapse criteria were broad, to reflect a range of clinically relevant outcomes of psychotic depression. Declaring relapse required at least 1 of the following: (1) enough Structured Clinical Interview for the *DSM* (SCID)–rated symptoms to meet criteria for a *DSM-IV* major depressive episode; (2) 17-item HDRS score of 18 or higher; (3) SCID-rated psychosis (delusions or hallucinations); or (4) other significant clinical worsening, defined as having a suicide plan or attempting suicide, developing SCID-rated symptoms of mania or hypomania, or being hospitalized in a psychiatric unit. Although patients with a diagnosis of bipolar disorder were not eligible for the study, psychotic depression in younger adults may predict subsequent development of mania or hypomania.[1] Participants with relapse left the study and were treated under usual care conditions. Whenever possible, investigators remained blind to the randomization assignment of participants after they left the study.

Secondary Outcomes: Anthropometric and Metabolic Measures

Weight and waist circumference were measured at each study visit. Fasting cholesterol and triglycerides levels, as well as fasting glucose and hemoglobin A_{1c} (HbA_{1c}), were measured at the RCT baseline, once every 8 weeks thereafter, and at study termination.

Other Measures of Tolerability

Research psychiatrists measured RCT baseline extrapyramidal symptoms, every 4 weeks thereafter, and at study termination. Parkinsonism was measured with the Simpson-Angus Scale[15] (total score range, 0-40, with higher scores indicating greater severity), akathisia with the Barnes Akathisia scale[16] (score range on the global clinical assessment, 0-5, with higher scores indicating greater severity), and tardive dyskinesia with the Abnormal Involuntary Movements Scale[17] (score range, 0-5 on each of 10 items, with higher score on each item indicating greater severity). Incident akathisia was defined as a Barnes global clinical assessment score[16] of 0 at RCT baseline and 2 or higher at any subsequent assessment. Incident tardive dyskinesia was defined according to Schooler-Kane research criteria.[18]

Adverse effects were elicited from participants at each visit with the Udvalg for Kliniske Undersogelser[19] scale (score range, 0-3 on each of 48 items, with higher score on each item indicating greater severity). With the exception of weight gain and weight loss, an adverse effect was considered present if there was a 2-point increase from RCT baseline or a score of 3 or 4 and an increase from baseline. Adverse weight gain was operationalized as measured weight of more than 7% higher than premorbid weight and adverse weight loss was operationalized as measured weight more than 7% lower than premorbid weight. *Premorbid weight*, defined as the most recent known weight prior to onset of the current episode of depression, was used so that we could account for depression-related weight loss. Incident falls were queried at each study visit. In addition, we recorded serious adverse events that resulted in death, life-threatening problems including suicide attempts, persistent or significant disability or incapacity, or hospitalization.

Power Analysis

We calculated that a sample of 176 randomized participants would provide 80% power to detect a 20% difference in risk of relapse between randomized groups and up to 15% attrition. A 20% difference would mean that 5 patients would need to be treated with olanzapine to prevent 1 case of relapse, a figure that is consistent with 1 year of continuation of antidepressant treatment for nonpsychotic depression.[20] Three years after the start of recruitment, however, a revised sample size of 128 randomized participants was approved by NIMH and its data and safety monitoring board because of a higher than anticipated overall risk of relapse.

Statistical Analyses

Analyses included all randomized participants. The primary hypothesis was tested with a Cox proportional hazards model that compared risk of relapse across treatment groups. The Cox model included treatment group and the 3 aforementioned stratification variables as covariates. The proportional hazards assumption of the Cox models was confirmed by visual inspection of complementary log-log plots and tests of correlation of the Schoenfeld residual with time. In addition, a Cox model that excluded participants who had elected to discontinue either sertraline, olanzapine or placebo, or both but remained in the study for research assessments was performed as a post hoc sensitivity analysis.

Linear mixed models were used to analyze the anthropometric and metabolic measures. Each of these models included a participant-level random intercept and random slope (with continuous time) and fixed effects for site, time, treatment group, and treatment × time interaction. A Poisson mixed-effects regression with an overdispersion parameter was used to analyze Simpson-Angus Scale[15] scores. This model included

Table 1. Characteristics of Study Participants

Baseline Characteristics	No. (%) of Participants	
	Sertraline + Olanzapine (n = 64)	Sertraline + Placebo (n = 62)
Sociodemographic		
Age, mean (SD), y	55.0 (15.1)	55.7 (14.9)
18-59	36 (56.2)	36 (58.1)
≥60	28 (43.8)	26 (41.9)
Sex		
Men	27 (42.2)	21 (33.9)
Women	37 (57.8)	41 (66.1)
Race		
White	54 (84.4)	49 (79.0)
Black	6 (9.4)	9 (14.5)
Other[a]	4 (6.3)	4 (6.5)
Hispanic ethnicity	6 (9.4)	9 (14.5)
Marital		
Single	19 (29.7)	15 (24.2)
Married	28 (43.8)	35 (56.5)
Separated or divorced	12 (18.8)	7 (11.3)
Widowed	5 (7.8)	5 (8.1)
Education, mean (SD), y	14.4 (3.2)	13.4 (3.9)
Living arrangements		
With others	46 (71.9)	49 (79.0)
Alone	17 (26.6)	10 (16.1)
Senior residence	1 (1.6)	1 (1.6)
Clinical Characterstics at Acute Phase Baseline		
Inpatient status at acute phase enrollment	41 (64.1)	46 (74.2)
Study site		
Cornell University	16 (25.0)	15 (24.2)
University of Massachusetts	15 (23.4)	14 (22.6)
University of Pittsburgh	9 (14.1)	10 (16.1)
University Health Network, Toronto	24 (37.5)	23 (37.1)
≥2 Lifetime depressive episodes	47 (73.4)	47 (75.8)
Duration of current episode of depression, median (IQR), mo	5.5 (3-12)	5.5 (2-12) [n=60]
Age of onset of first major depressive episode, median (IQR), y	37 (24-50) [n=62]	35 (18-51) [n=61]
Suicide attempt in current episode	13 (20.3)	12 (19.4)
Treatment resistance in current episode[b]	3 (4.7)	5 (8.1)
Diagnoses		
Hyperlipidemia	18 (29.0)	19 (29.7)
Hypertension	17 (26.6)	22 (35.5)
Diabetes	12 (18.8)	15 (24.2)
Premorbid weight, mean (SD), lb[c]	166.6 (34.6) [n=60]	171.4 (40.2) [n=59]

Abbreviation: IQR, interquartile range.

SI conversion factor: To convert lb to kg, multiply by 0.45.

[a] Includes American Indian or Alaska Native, Asian, Native Hawaiian or other Pacific Islander, and unknown or not reported.

[b] Defined as an antidepressant plus antipsychotic combination rating score of 3 or higher on the Antidepressant Treatment History Form[23] or 7 or more treatments of electroconvulsive therapy during the current episode of psychotic depression.

[c] Defined as the most recent known weight before onset of the current episode of depression.

a participant-level random intercept and fixed effects for site, time, treatment group, and treatment × time interaction.

Because of relapse, the frequency of early termination was higher in the sertraline-placebo group than with the sertraline-olanzapine group resulting in missed outcomes. Our mixed models provide valid inference under the missing-at-random assumption. However, to investigate bias due to nonignorable missing patterns, pattern mixture modeling was performed for each outcome. They examined whether the treatment effect changed with the pattern of early termination and, if so, corrected for the bias due to this pattern. Pattern mixture models indicated that estimates from the linear mixed models and Poisson model were likely not biased, with the exception of triglycerides. In the case of triglycerides, pattern-mixture-averaged estimates[21] are reported.

To examine for the possible effect of a statin or hypoglycemic agent on linear mixed-model metabolic results, post hoc sensitivity analyses were performed, whereby if a drug in these categories was started or changed during the trial, pertinent metabolic data from that point on were excluded from the mixed model.

Table 2. Clinical Characteristics at Randomization

Randomized Baseline Characteristics	No. (%) of Participants	
	Sertraline + Olanzapine (n = 64)	Sertraline + Placebo (n = 62)
HDRS 17 total score, mean (SD)[a]	5.3 (3.6)	5.6 (3.6)
SADS		
Delusion score of 1[b]	64 (100)	62 (100)
Hallucination score of 1[c]	64 (100)	62 (100)
HADS anxiety score, median (IQR)[d]	5.0 (2.0-8.0)	4.0 (1.0-7.0) [n = 61]
CORE total score, median (IQR)[e]	1.0 (0-3.0)	1.0 (0-4.8)
CIRS-G total score, median (IQR)[f]	3.0 (1.0-6.0)	3.0 (2.0-5.8)
MMSE, mean (SD)[g]	28.1 (1.9)	27.9 (2.0)
DKEFS trail making test conditions 4 vs 5 scaled score, mean (SD)[h]	7.9 (3.5) (n = 61)	8.1 (3.6) (n = 59)
DKEFS color word interference condition 3 final weighted scaled score, mean (SD)[i]	8.6 (2.9) (n = 60)	7.6 (2.8) (n = 58)
Barnes Akathisia Rating Scale global score >0	3.0 (4.7)	2.0 (3.2)
AIMS overall severity score >0[j]	2.0 (3.1)	2.0 (3.2)
Simpson-Angus Scale Total score, median (IQR)[k]	1.0 (0-2.0)	1.0 (0-2.0)
Study Medication Dosage at Randomization Baseline, Median (IQR), mg/d		
Sertraline	150 (150- 200)	150 (150-200)
Olanzapine	15 (10-20)	15 (10-20)

Abbreviations: AIMS, Abnormal Involuntary Movement Scale[17]; CIRS-G, Cumulative Illness Rating Scale for Geriatrics[24]; CORE, CORE assessment of psychomotor change[25]; DKEFS, Delis-Kaplan Executive Function Scale[26]; HADS, Hospital Anxiety and Depression Scale[27]; HDRS 17, 17-item Hamilton Depression Rating Scale[9]; IQR, interquartile range; MMSE, Mini-Mental State Examination[14]; SADS, Schedule for Affective Disorders and Schizophrenia.[10]

[a] Range, 0 to 52; higher score indicates greater severity of depression (a mean score of 5, remission of depression).

[b] Range, 1 to 7; a higher score indicates greater delusional severity (1 indicates no delusion present).

[c] Range, 1 to 3; a score of 1 indicates no hallucination (3, definite hallucination).

[d] Range, 0 to 21; a higher score indicates greater severity of anxiety (≤7, normal range).

[e] Range, 0 to 54: a higher score indicates greater severity of psychomotor change (median score of 1, minimal psychomotor change).

[f] Excluding the psychiatric illness category, range, 0 to 52; a higher score indicates greater severity of cumulative illness (median score of 3, low level of cumulative physical illness).

[g] Range, 0 to 30; a higher score indicates better cognitive function (mean score of 28, normal range).

[h] Trail making test conditions 4 vs 5 scaled score measures cognitive flexibility and color word interference condition 3 final weighted scaled score measures inhibition (both are measures of executive brain function). For each of these tasks, scaled scores range, 1 to 19, with higher scores indicating better performance on the task (10 represents the normative population mean).

[i] Scores on the global clinical assessment item of the Barnes akathisia rating scale range from 0 to 5. A higher score indicates greater severity of akathisia. A score of 0 indicates that akathisia is not present.

[j] Measured tardive dyskinesia. Scores on the global severity of abnormal movements range from 0 to 4 (higher score, greater severity of abnormal movement; 0, no abnormal movements).

[k] Measure extrapyramidal adverse effects. Total score, excluding the head dropping item, ranges from 0 to 36 (higher score, greater severity; 0, no extrapyramidal effects).

Post hoc analyses compared randomized groups on the number of participants who experienced an incident high metabolic value.

The incidence of akathisia and tardive dyskinesia, the frequency of Udvalg for Kliniske Undersogelser[19] scale adverse effects, and the frequency of falls and serious adverse events are reported descriptively.

Analyses were conducted using SAS version 9.4 (SAS Institute Inc). All statistical tests were 2-sided, performed at an overall 5% level of significance for primary and secondary outcomes. *P* values for multiple secondary outcomes were adjusted using the Holm stepdown method.[22] Because these adjustments were post hoc, the interpretation of secondary outcomes should be considered exploratory.

(To convert cholesterol from mg/dL to mmol/L, multiply by 0.0259; glucose from mg/dL to mmol/L, multiply by 0.0555; triglycerides from mg/dL to mmol/L, multiply by 0.0113; lb to kg, multiply by 0.45; and in to cm, multiply by by 2.54.)

Results

Participant Characteristics

Of the 269 participants who enrolled in the study, 126 were randomized (64 to sertraline-olanzapine and 62 to sertraline-placebo) (Figure 1). Characteristics of the randomized groups are shown in **Table 1** and **Table 2.**

Primary Outcome

A relapse occurred in 13 of 64 participants (20.3%) in the sertraline-olanzapine group and 34 of 62 (54.8%) in the sertraline-placebo group. **Table 3** lists the relapse events in each randomized group. In the multivariable Cox proportional hazards model, there was a statistically significant difference in risk of relapse between randomized groups (hazard ratio [HR], 0.25 [95% CI, 0.13-0.48], $P < .001$), controlling for age group (HR, 0.78 [95% CI, 0.42-1.46], $P = .44$ for young vs old), remission

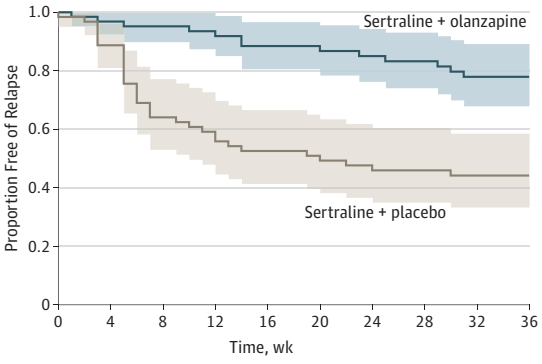
Table 3. Number of Relapse Events[a]

	Sertraline + Olanzapine	Sertraline + Placebo
Depression, no psychosis	5	18
Psychosis, no depression	0	1
Depression and psychosis	4	11
Suicide plan or attempt	0	3
Mania or hypomania	0	0
Psychiatric hospitalization[b]	6	11

[a] More than 1 event occurred in some cases of relapse.

[b] Psychiatric hospitalization for depression, psychosis, suicidality, or mania or hypomania.

Figure 2. Probability of Not Experiencing a Relapse



Median length of observation was 36 weeks (interquartile range [IQR], 24.8-36) for the sertraline plus olanzapine group and 19.5 weeks (IQR, 5.3-36) for the sertraline plus placebo group. For group comparison of the proportion free of relapse, log-rank test *P* value <.001. The shaded area represents the 95% CIs.

vs near-remission status at RCT baseline (HR, 2.45 [95% CI, 0.98-6.13], *P* = .06 for remission vs near-remission), and study site (HR, 1.53 [95% CI, 0.62-3.76], *P* = .36, for University of Massachusetts vs Cornell; HR, 1.09 [95% CI, 0.39-2.98], *P* = .88, for Pittsburgh vs Cornell; and HR, 1.80 [95% CI, 0.81-4.03], *P* = .15, for Toronto vs Cornell). **Figure 2** shows the Kaplan-Meier survival curves of the 2 randomized groups. Based on the HR, the number needed to treat with sertraline plus olanzapine to prevent 1 relapse was 2.8.

The results were similar in a post hoc sensitivity analysis that excluded 7 participants who had elected to discontinue either sertraline, olanzapine or placebo, or both but had remained in the study for research assessments (HR, 0.22 [95% CI, 0.11-0.43], *P* < .001).

Secondary Outcomes

The effect of olanzapine on the daily rate of anthropometric and metabolic measures (treatment × linear time interaction) was significantly higher than placebo for weight (0.13 lb [95% CI, 0.11-0.15], adjusted *P* < .001), for waist circumference (0.009 inches [95% CI, 0.004-0.014], adjusted *P* = .002), and for total cholesterol (0.29 mg/dL [95% CI, 0.13-0.45], adjusted *P* = .003). However, the daily rate was not statistically different for low-density lipoprotein cholesterol (0.04 mg/dL [95% CI, −0.01 to 0.10], adjusted *P* = .57), high-density lipoprotein cholesterol (−0.01 mg/dL [95% CI, −0.03 to 0.01], adjusted *P* = .99), triglyceride (−0.153 mg/dL [95% CI, −0.306 to 0.004], adjusted *P* = .25), glucose (−0.02 mg/dL [95% CI, −0.12 to 0.08], adjusted *P* = .99), or HbA_{1c} levels (−0.0002 mg/dL [95% CI, −0.0021 to 0.0016], adjusted *P* = .99). Because the linear mixed models include linear and quadratic effects of time, the daily rate of change of each of these variables cannot be extrapolated to cumulative linear change over the course of the clinical trial. eFigures 1 through 8 in Supplement 2 show the trajectory of each of these variables during the trial. **Table 4** shows post hoc analyses of the within-group change of each of these variables, based on the difference in raw means (or, where relevant, raw medians) between RCT baseline and termination.

During the course of the trial, statins were started or changed for 12 participants (6 olanzapine, 6 placebo) and hypoglycemic agents were started or changed for 3 participants (2 olanzapine, 1 placebo). The results of post hoc sensitivity analyses that examined for the possible effect of these drugs on linear mixed-model metabolic results were qualitatively similar to those of the analyses that included all participants.

In post hoc analyses, there were no statistically significant differences between treatment groups in the number of participants who experienced an incident high metabolic value (**Table 5**), although the study may not have had sufficient statistical power to detect a difference.

Other Measures of Tolerability

Extrapyramidal Measures

The incidence of akathisia was 4.7% in the sertraline-olanzapine group and 4.8% in the sertraline-placebo group. Except for 1 participant, all were rated as mild. The incidence of tardive dyskinesia was 0% in the sertraline-olanzapine group and 3.2% in the sertraline-placebo group. Weekly changes in Simpson-Angus Scale[15] total score was significantly higher in the sertraline-olanzapine group than the sertraline-placebo group (0.022 points [95% CI, 0.009-0.036], adjusted *P* = .009); eFigure 9 in Supplement 2 shows the trajectory of this variable during the trial.

Adverse Effects

More than 5% of participants reported the following Udvalg for Kliniske Undersogelser scale[19] adverse effects at least once during the trial: 17.2% in the sertraline-olanzapine group vs 4.8% in the sertraline-placebo group reported weight gain; 7.8% vs 4.8%, weight loss; 7.8% vs 3.2%, sleepiness or sedation; 7.8% vs 3.2% orthostatic dizziness; and 3.1% vs 8.1% nausea or vomiting.

Twenty participants (31.3%) of 64 taking olanzapine and 11 (17.7%) of 62 taking placebo experienced 1 or more falls during the trial.

One or more serious adverse events occurred in 12 participants (18.8%) of 64 in the sertraline-olanzapine group and 12 (19.4%) of 62 in the sertraline-placebo group. One participant in the sertraline-olanzapine group died due to a rup-

Table 4. Secondary Outcomes: Anthropometric and Metabolic Measures at Randomized Clinical Trial (RCT) Baseline and Termination and the Unadjusted Difference in These Measures Between RCT Baseline and Termination

	Sertraline + Olanzapine (n = 64)					Sertraline + Placebo (n = 62)				
	Baseline		Termination			Baseline		Termination		
	No. of Participants	Mean (SD)	No. of Participants	Mean (SD)	Difference, Mean (95% CI)[a]	No. of Participants	Mean (SD)	No. of Participants	Mean (SD)	Difference, Mean (95% CI)[a]
Weight, lb		178.6 (39.4)	62	183.6 (40.9)	5.7 (3.3 – 8.1)	60	182.5 (39.8)	59	180.2 (42.1)	−3.1 (−5.4 to −0.8)
Waist circumference, in	63	38.1 (5.4)	59	38.5 (5.2)	0.6 (0.1 to 1.1)	58	39.4 (5.7)	55	38.4 (6.4)	−0.8 (−1.5 to −0.2)
Cholesterol, mg/dL										
Total	63	209.0 (51.3)	63	204.8 (51.3)	−4.7 (−14.9 to 5.6)		220.4 (46.8)	59	197.4 (48.2)	−22.3 (−32.7 to −11.9)
LDL	62	132.5 (42.1)	63	128.9 (42.3)	−2.8 (−12.6 to 6.9)		137.7 (38.7)	59	122.1 (44.2)	−16.0 (−25.8 to −6.2)
HDL	63	54.4 (19.6)	63	49.7 (16.1)	−5.0 (−9.1 to −0.9)		56.0 (16.0)	59	52.2 (16.0)	−3.5 (−6.2 to −0.9)
HbA_{1c}, %	63	5.9 (1.5)	62	5.7 (1.1)	−0.2 (−0.5 to 0.2)		5.9 (1.2)	58	5.9 (1.0)	0.1 (−0.1 to 0.2)
		Median (IQR)		Median (IQR)	Median (95% CI)		Median (IQR)		Median (IQR)	Median (95% CI)
Triglyceride, mg/dL	63	134 (90 to 186)	63	133 (87 to 206)	−3.9 (−18 to 12)		121 (95 to 169)	59	107 (80 to 153)	−18 (−25 to −7)
Glucose, mg/dL	63	90 (83 to 99)	63	92 (87 to 104)	1.4 (−1.8 to 5)		93 (85 to 100)	59	94 (85 to 106)	2.8 (−3.6 to 6.0)

Abbreviations: HbA_{1c}, hemoglobin A_{1c}; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein.

SI conversion factors: To convert cholesterol from mg/dL to mmol/L, multiply by 0.0259; glucose from mg/dL to mmol/L, multiply by 0.0555; triglycerides from mg/dL to mmol/L, multiply by 0.0113; lb to kg, multiply by 0.45; and in to cm, multiply by 2.54.

[a] The difference may not equal termination minus baseline because of missing data.

tured aortic aneurysm; all other serious adverse events were due to hospitalization. Of the participants who experienced a relapse, 6 (46.2%) of 13 in the olanzapine group and 11 (32.3%) of 34 in the placebo group required psychiatric hospitalization because of the relapse.

Discussion

In this RCT involving patients whose psychotic depression responded to the combination of sertraline and olanzapine, continuing the combined treatment compared with sertraline plus placebo reduced the risk of relapse over 36 weeks. However, continuing olanzapine was associated with weight gain.

As hypothesized, continuation of olanzapine was more effective than placebo in reducing relapse, with a number needed to treat of 2.8. With placebo, the majority of relapses occurred within the first 12 weeks after randomization, whereas relapses among the sertraline-olanzapine group were distributed throughout the 36-week trial. Relapses resulted in a high frequency of psychiatric hospitalization, highlighting the severity and cost of this disorder and the importance in preventing relapse.

The study's tolerability data provide information on the risks of continuing olanzapine for psychotic depression. Continuation of olanzapine was associated with weight gain, whereas discontinuation of olanzapine was associated with weight loss. Mean total cholesterol decreased in both groups, but the trajectory of decline was greater in the placebo group. There was no significant difference between groups in the trajectory of triglyceride, glucose, or HbA_{1c} values.

When this study was designed, olanzapine was the only second-generation antipsychotic with RCT evidence of efficacy in the acute treatment of psychotic depression.[3,4,6] Subsequently, Wijkstra et al[31] reported that quetiapine in combination with venlafaxine was more efficacious than venlafaxine monotherapy in the acute treatment of psychotic depression. However, their study was limited to persons aged 18 to 65 years and therefore the efficacy and tolerability of quetiapine in older persons with psychotic depression is not known. Without evidence, equivalent efficacy of other atypical antipsychotics in the treatment of psychotic depression cannot be assumed.[32] Moreover, although several other antipsychotics are associated with less weight gain than olanzapine, they can cause other adverse effects, such as akathisia, parkinsonism, and insomnia, which are potentially problematic in the treatment of psychotic depression.[32]

Limitations

This study has several limitations. First, the findings are limited to sertraline and olanzapine. Based on retrospective data[33] and a case series,[34] it is possible that the study's finding regarding risk of relapse with olanzapine discontinuation may generalize to other antipsychotic medications, but more definitive research, using alternative medication combinations, is required. Second, the study does not provide information on the optimal duration of treatment with olanzapine following remission of psychotic depression.

Table 5. Post Hoc Outcome: The Number of Participants Who Experienced an Incident High Fasting Metabolic Value in the Randomized Clinical Trial[a]

	Sertraline Plus, No. (%)		Absolute Unadjusted Difference Between Groups, % (95% CI)
	Olanzapine (n = 64)	Placebo (n = 62)	
Cholesterol			
Total (≥1 value above both participant's RCT baseline and 240 mg/dL)	9 (14.1)	6 (9.7)	4.3 (−8 to 17.2)
LDL (≥1 value above both participant's RCT baseline and 160 mg/dL)	9 (14.1)	6 (9.7)	4.3 (−8 to 17.2)
Triglycerides (≥1 value above both participant's RCT baseline and 200 mg/dL)	4 (6.3)	2 (3.2)	3.0 (−6.7 to 13.3)[b]
Glucose (≥1 value above both participant's RCT baseline and 126 mg/dL)	4 (6.3)	4 (6.5)	−0.2 (−9.9 to 9.9)[b]

Abbreviation: LDL, low-density lipoprotein; RCT, randomized clinical trial.

SI conversion factors: To convert cholesterol from mg/dL to mmol/L, multiply by 0.0259; glucose from mg/dL to mmol/L, multiply by 0.0555; triglycerides from mg/dL to mmol/L, multiply by 0.0113.

[a] An incident high-fasting metabolic value was defined as being higher than both the RCT baseline value and the threshold.[28-30]

[b] Exact confidence interval.

A sequential discontinuation design would have been more informative on how long to continue antipsychotic medication after remission, but it would have required many more participants and would have been more costly. Third, based on other data,[34] a 4-week taper of antipsychotic medication was chosen. It is possible that a slower taper would have been associated with a lower relapse rate. Fourth, patients were not assessed for the presence of comorbid personality disorders. Some personality disorders are associated with suicide attempts and risk of hospitalization,[35] which were criteria for relapse in this study. If randomized groups had differed in the frequency of personality disorders, this imbalance could have affected the primary outcome. Fifth, because of early relapse and exit from the study, 50% of the participants in the placebo group were observed for 20 weeks or less, which may have led to an underestimation of the reduction in weight and lipids associated with discontinuation of olanzapine. Sixth, there were no data on biomarkers of risk of relapse. Forty-five percent of participants switched to placebo did not relapse, and they benefited from a decline in weight and lipids. These findings suggest the need to identify clinical and biological predictors of relapse following antipsychotic discontinuation; this would allow some precision when deciding which individuals can be safely withdrawn from antipsychotic medication after remission of psychotic depression.

Conclusions

Among patients with psychotic depression in remission, continuing sertraline plus olanzapine compared with sertraline plus placebo reduced the risk of relapse over 36 weeks. This benefit needs to be balanced against potential adverse effects of olanzapine, including weight gain.

ARTICLE INFORMATION

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