An Open-Label Pilot Trial of Alpha-Lipoic Acid for Weight Loss in Patients with Schizophrenia without Diabetes

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Abstract

A possible mechanism of antipsychotic-induced weight gain is activation of hypothalamic monophosphate-dependent kinase (AMPK) mediated by histamine 1 receptors. Alpha-lipoic acid (ALA), a potent antioxidant, counteracts this effect and may be helpful in reducing weight for patients taking antipsychotics. The objective of this open-label study was to assess the efficacy of ALA (1,200 mg) on twelve non-diabetic schizophrenia patients over ten weeks. Participants lost significant weight during the intervention (-2.2 kg±2.5 kg). ALA was well tolerated and was particularly effective for individuals taking strongly antihistaminic antipsychotics (-2.9 kg±2.6 kg vs. -0.5 kg±1.0 kg). **Clinical Trial Registration: NCT01355952**.

Key Words: Schizophrenia, Obesity, Schizoaffective Disorder, Alpha-Lipoic Acid

Introduction

Antipsychotic medications appear to induce weight gain, which results in increased rates of obesity in schizophrenia (1). Schizophrenia patients have significantly shorter life expectancy than the general population (2); most of this excess mortality is attributed to diabetes and cardiovascular disease (3); weight gain is a significant contributor to the development of these diseases.

One possible mechanism of antipsychotic-induced weight gain involves the activation of adenosine monophosphate-dependent protein kinase (AMPK) in the hypothalamus (4). In the periphery, AMPK increases energy utilization; AMPK activity in the hypothalamus increases appetite. Several highly orexigenic (stimulates appetite) antipsychotics such as clozapine, olanzapine, and quetiapine are shown to activate AMPK in the hypothalamus in animal studies whereas other antipsychotic medications do not (4). Histamine (H1) receptors appear to play a role because H1-deficient mice do not exhibit the antipsychotic-induced AMPK activation (4). It is possible that AMPK activation may play a role in antipsychotic-induced weight gain in humans (5) because antipsychotic-induced weight gain seems to be correlated with potency of H1 blockade (6).

Alpha-lipoic acid (ALA) is a naturally occurring short-chain fatty acid that is an essential cofactor in mitochondrial energy metabolism (7). ALA is a powerful antioxidant that provides beneficial effects on several obesity-related conditions: insulin resistance, metabolic syndrome, and diabetic complications (7, 8). As early as the 1950s, ALA was sug-

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Clinical Implications

This pilot trial suggests alpha-lipoic acid (ALA) 1,200 mg may reduce body weight in non-diabetic individuals with antipsychotic-induced weight gain. Most of the participants reported subjective feelings of increased energy and reduced appetite, which may be particularly important for this population. ALA-mediated suppression of hypothalamic adenosine monophosphate-dependent protein kinase (AMPK) would counteract the antipsychotic-induced activation of AMPK through H1 receptor blockage, resulting in decreased appetite. This hypothesis is supported by the significant weight loss achieved by participants taking clozapine, olanzapine, or quetiapine. In the periphery, ALA activation of AMPK would increase energy expenditure without antagonistic effects by the antipsychotics.

gested to improve symptoms of schizophrenia (9), and this therapy is still of interest today (10). ALA stimulates peripheral AMPK, while also suppressing hypothalamic AMPK (7) to help regulate appetite and energy balance—which may be helpful for treating obesity associated with antipsychotic use. A previous case series of a twelve-week ALA trial in schizophrenia patients treated with atypical antipsychotic drugs resulted in a mean 3.16 kg weight loss; there was also a trend observed toward a reduction in fasting blood glucose (8). The objective of this study was to assess the efficacy of 600 mg BID of ALA on antipsychotic-induced weight gain for non-diabetic schizophrenia patients over ten weeks.

Methods

Twelve individuals (BMI ≥27) age 18 to 65 years that met *DSM-IV* criteria for schizophrenia or schizoaffective disorder based on the Structured Clinical Interview for *DSM-IV* (SCID [11]) and who were on a stable dose of antipsychotic for at least one month were recruited for the study. Individuals with diabetes mellitus or with a physical condition that would affect body weight were excluded from the study. Patients were discharged from the study if there was a change in antipsychotic medication. The protocol was approved by the Institutional Review Board of Yale University and written informed consent was obtained.

Study Design

This was an open-label, fixed-dose clinical trial. Subjects were given ALA 600 mg BID for ten weeks. Subjects did not receive any instruction about caloric intake or physical activity. Each week, subjects returned their empty pillboxes, met with study staff to have weight and blood pressure measured, and received that week's dose of ALA. Subjects were asked if they had experienced any adverse events during each study appointment.

Laboratory and Anthropometric Measurements

Weight was measured in light clothing, without shoes, to the nearest 0.1 kg and height was measured to the nearest 0.1 cm on a calibrated electronic scale, and BMI (kg/m^2) was calculated. Waist circumference was the average of two measurements of the horizontal at the iliac crest to the nearest 0.1 cm.

Fasting blood for measurement of plasma glucose levels, plasma insulin concentrations, glycosylated hemoglobin (HbA1c), and lipid profile was drawn at baseline and at study completion.

Psychiatric Measures and Cognitive Battery

The Brief Psychiatric Rating Scale (BPRS [12]) was used to monitor psychiatric symptoms. The Brief Assessment of Cognition in Schizophrenia (BACS [13]) was performed at baseline and Week 10 to assess changes in cognition.

Statistical Analyses

Intent-to-treat (ITT) analyses included all subjects who received at least one dose of study medication. Missing data for subjects in the intent-to-treat sample were imputed using the last-observation-carried-forward. To compare values with the baseline, we used Wilcoxon Signed Ranks test.

Results

Participant Characteristics

Demographic information is presented in Table 1. All twelve participants completed at least one week of study medication and nine individuals (male=5 and female=4) completed the ten-week intervention. Two women were withdrawn from the study after one week due to an increase in antipsychotic medication; one man was withdrawn at Week 7 for the same reason. Baseline values for metabolic variables are presented in Table 2. There were no significant differences in demographic variables or medications between individuals in the ITT and completer groups.

Laboratory and Anthropometric Measurements

There was a significant reduction in body weight after ten weeks of ALA 600 mg BID. The mean (SD) weight loss

Table 1 Demographic Characteristics

Variable	Baseline
Age, mean (SD), y	45 (9)
BMI, mean (SD), kg/m^2	34.1 (5.2)
Women, n (%)	6 (50)
Race, n, C/AA/H	5/4/3
Schizophrenia/schizoaffective diagnosis, n	5/7
Length of illness, mean (SD), y	18.3 (9.5)
Antipsychotic medications used	**n (%)**
Clozapine	3 (25)
Quetiapine	2 (17)
Olanzapine	2 (17)
Risperidone	2 (17)
Aripiprazole	1 (8)
Haloperidol	1 (8)
Paliperidone	1 (8)
Antidepressant medications used	**n (%)**
Bupropion	1 (8)
Citalopram	1 (8)
Mirtazapine	1 (8)
Sertraline	1 (8)
Trazadone	1 (8)
Mood stabilization medications used	**n (%)**
Valproic acid	4 (33)
Lamotrigine	2 (17)
Antianxiety medication used	**n (%)**
Clonazepam	2 (17)
Hypertension medications used	**n (%)**
Atenolol	2 (17)
Hydrochlorothiazide	1 (8)
Propranolol	1 (8)
Thiazide	1 (8)
Valsartan	1 (8)
Cholesterol medications used	**n (%)**
Atorvastatin	1 (8)
Fenofibrate	1 (8)
Rosuvastatin	1 (8)
Simvastatin	1 (8)

C=Caucasian; AA=African American; H=Hispanic.

Table 2 Changes in Metabolic Profile after 600 Mg BID for Ten Weeks in Non-Diabetic Schizophrenia Patients

Variable	Baseline	Week 10	Z	P
Weight (kg)				
ITT	101.0±24.3	99.1±24.5	-2.54	0.01*
Completers	102.0±25.0	99.8±25.0	-2.31	0.02*
BMI (kg/m^2)				
ITT	34.1±5.2	33.4±5.3	-2.41	0.02*
Completers	33.9±5.4	33.1±5.3	-2.39	0.02*
Waist (cm)				
ITT	112.7±10.7	112.5±10.9	-0.36	0.72
Completers	112.9±12.4	111.9±12.3	-1.01	0.31
Glucose (mg/dl)				
ITT	93.3±12.6	88.3±6.8	-1.84	0.06
Completers	93.7±10.9	89.7±6.7	-1.54	0.12
HbA1c (%)				
ITT	5.4±0.3	5.3±0.2	-1.80	0.07
Completers	5.4±0.4	5.2±0.2	-1.80	0.07
Insulin (uU/L)				
ITT	9.7±8.1	9.4±6.7	-0.06	0.95
Completers	10.6±8.6	10.3±7.0	-0.06	0.95
TG (mg/dl)				
ITT	138.8±52.9	135.9±84.9	-0.30	0.77
Completers	145.9±49.1	142.3±89.3	-0.30	0.77
TC (mg/dl)				
ITT	173.0±34.7	177.3±35.9	-0.18	0.86
Completers	169.3±39.0	175.1±40.9	-0.18	0.86
HDL (mg/dl)				
ITT	40.8±11.0	40.0±11.4	-0.67	0.51
Completers	41.6±11.0	39.2±12.3	-0.67	0.51
LDL (mg/dl)				
ITT	102.7±32.2	108.0±34.6	-1.84	0.07
Completers	98.8±33.8	107.4±38.7	-1.84	0.07
SBP (mmHg)				
ITT	117.9±16.0	126.9±16.8	-1.51	0.13
Completers	130.7±13.4	127.0±16.6	-0.83	0.41
DBP (mmHg)				
ITT	81.8±9.4	83.0±11.5	-0.05	0.96
Completers	83.1±9.5	82.4±10.3	-0.60	0.55

All values are reported as mean ± SD.*p≤0.05. ITT=intent-to-treat; BMI=body mass index; HbA1c=glycosylated hemoglobin; TG=triglycerides; TC=total cholesterol; HDL=high-density lipoprotein cholesterol; LDL=low-density lipoprotein cholesterol; SBP=systolic blood pressure; DBP=diastolic blood pressure.

for the ITT sample was 1.9 (2.3) kg; mean weight loss for completers was 2.2 (2.5) kg. Seven of the nine completers lost weight; four of the subjects lost at least 2.3 kg. Mean weight loss by medication was as follows: quetiapine, -6.05 kg; clozapine, -2.17 kg; paliperidone, -1.00 kg; olanzapine, -0.80 kg; haloperidol, -0.70 kg; risperidone, -0.40 kg; aripiprazole, 0 kg. For the ITT sample, participants taking clozapine, olanzapine, or quetiapine (n=7) lost significantly more weight than those receiving other antipsychotic medications (-2.9 kg±2.6 vs. -0.5 kg±1.0; z=-2.03, p=0.42).

Fasting glucose and HbA1c were decreased in all but one subject after the intervention; however, there was only a trend toward reduction for the means of these variables. Mean triglyceride, total cholesterol, HDL- and LDL-cholesterol, insulin, and blood pressure did not change significantly after the intervention.

Psychiatric Measures and Cognition

Mean BPRS did not change significantly during the study (baseline: 18.2±10.8; Week 10: 19.8±13.8; z=-0.84; p=0.40). There were no differences in mean composite z-score in the BACS after the intervention (baseline: -1.07±0.61; Week 10: -1.17±0.51; p=0.40).

Adverse Effects

One subject reported pruritus during the first week of the study; the pruritus subsided within a few days. One subject reported a hypotensive event during the first week of treatment; blood pressure returned to baseline after one day: this subject just had an increase in antipsychotic medication dosage and was withdrawn from the study in accordance with protocol. Two subjects reported a mild throat burning sensation after taking ALA, but this sensation dissipated after fifteen minutes. Both subjects were being treated for acid reflux, so this symptom may not be study related.

Discussion

This pilot trial suggests ALA 1,200 mg may reduce body weight in non-diabetic individuals with antipsychotic-induced weight gain. Most of the participants reported subjective feelings of increased energy and reduced appetite, which may be particularly important for this population. ALA-mediated suppression of hypothalamic AMPK would counteract the antipsychotic-induced activation of AMPK through H1 receptor blockage, resulting in decreased appetite. This hypothesis is supported by the significant weight loss achieved by participants taking clozapine, olanzapine, or quetiapine. In the periphery, ALA activation of AMPK would increase energy expenditure without antagonistic effects by the antipsychotics.

A previous study of ALA treatment for weight gain in patients with schizophrenia found improvements in fasting glucose and total cholesterol concentration over twelve weeks (8). We did not find significant improvements in metabolic indices in the current study, although there was a trend toward a reduction of fasting glucose and HbA1c levels. One possible reason for the discordant results may be due to the small sample sizes in both studies or differences in the sample populations. Participants in the current study were not diabetic and already had relatively healthy metabolic profiles, which would diminish the impact of ALA on these variables. Together, these results indicate that ALA may be useful for reducing antipsychotic-induced weight gain in schizophrenia patients with or without medical comorbidities.

ALA treatment has been associated with improved cognitive function in both mice (14) and dementia patients (15). To our knowledge, this is the first study to assess the effects of ALA supplementation on cognitive function in schizophrenia patients. There were no differences from baseline on mean composite z-scores using the BACS. It is possible that potential cognitive improvements may be observed with a larger sample size, longer study duration, or a higher ALA dosage.

This study has several limitations. First, this was not a randomized, placebo-controlled trial and it had a small sample size. Second, the intervention duration was only ten weeks. Finally, the ALA dose used here may not have been the optimal level. A recent study in obese Korean individuals (16) found that 1,800 mg/day of ALA resulted in significantly more weight loss than placebo, whereas 1,200 mg/day did not result in significant weight loss.

ALA 1,200 mg was effective in achieving significant weight loss in non-diabetic schizophrenia patients with minimal side effects. Results from this pilot study demonstrate that larger, placebo-controlled studies are necessary to determine the optimal dose and duration of ALA administration to provide sustained benefits for this population.

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