

# N-3 Fatty Acids for Hypertriglyceridemia in Patients Taking Second-Generation Antipsychotics

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## Abstract

**Objective:** Cardiovascular disease is a frequent cause of early disability and death in patients with severe mental illness (SMI). Second-generation antipsychotic medications may cause increased risk of cardiovascular disease in some patients by elevating serum triglyceride levels. Idiopathic hypertriglyceridemia can be effectively treated with N-3 fatty acid (N-3 FA) supplementation, but little research has evaluated this treatment for hypertriglyceridemia that can occur in patients using second-generation antipsychotics. **Methods:** A six-week, open-label pilot study of N-3 FA, two grams twice daily, was performed to assess efficacy of this supplement in patients with SMI who were being treated with second-generation antipsychotics. Serum triglyceride levels (the main endpoint) were assessed at baseline and six weeks. Levels of C-reactive protein (CRP), cholesterol (total, high density lipoprotein [HDL] and low density lipoprotein [LDL]), fasting glucose, and fasting insulin (to calculate the Homeostatic Model Assessment for Insulin Resistance [HOMA-IR]), as well as weight and blood pressure, were also assessed. **Results:** Mean triglyceride levels decreased by  $70.4 \pm 50.4$  mg/dL ( $p=0.001$ ). Among secondary endpoints, mean HDL increased by  $2.6 \pm 3.5$  ( $p=0.03$ ). However, LDL and total cholesterol, blood pressure, HOMA-IR and CRP did not significantly change. **Conclusions:** In this pilot study, treatment with N-3 FA was associated with improvements in triglyceride and HDL levels. Further study is warranted to assess more completely whether this prescription dietary supplement can reduce triglycerides in patients taking second-generation antipsychotics.

**Key Words:** Triglyceride, Antipsychotic, Schizophrenia, Omega-3 Fatty Acid, Metabolic Syndrome, Cardiometabolic Risk

## Background and Significance

Research suggests that people with severe mental illness (SMI; schizophrenia and severe mood disorders) die 20 to 30 years earlier than age-matched controls (1). Accidents and suicide are elevated in this group, but the leading cause of excess mortality is cardiovascular disease (2, 3). Treatment with antipsychotics is necessary for many patients with SMI, but treatment with these agents, especially second-

generation antipsychotics, often worsens the risk of cardiovascular disease by causing lipid abnormalities (1, 4-7), as well as other cardiovascular risk factors, including weight gain (8, 9), insulin resistance and diabetes (5-7, 10-15), as well as hypertension (16). High triglyceride (TG) levels increase risk for myocardial infarction directly (17) and can lead to insulin resistance and type 2 diabetes (18), which is itself a cardiovascular disease risk factor (5). Clozapine, olanzapine, quetiapine, and risperidone are the second-generation antipsychotic medications (SGAs) most likely to cause these abnormalities (15, 19).

Consensus guidelines (20) recommend that psychiatrists assess for, monitor, and mitigate antipsychotic medication-induced cardiometabolic side effects. Clinicians and patients often use various strategies to mitigate these side effects, but each has drawbacks. Statins (21, 22) and fibrate medications (22) can be effective, but they can cause

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### Clinical Implications

Psychiatrists who adhere to monitoring guidelines are likely to detect hyperlipidemia and diabetes in a substantial number of patients who are taking SGAs. In order to prevent cardiometabolic side effects from leading to serious morbidity and mortality, psychiatrists must intervene, but they may have difficulty linking patients with primary care providers for treatment of these conditions and they may be uncomfortable with treating these conditions themselves. Thus, a perceived lack of therapeutic options may deter effective monitoring. N-3 FAs may become an attractive option for the treatment of antipsychotic medication-induced hypertriglyceridemia by psychiatrists. N-3 FAs may be used alone or in addition to lifestyle interventions (30-32), other medication augmentation strategies (33-42), or switching from a high-risk antipsychotic to an agent with a lower cardiometabolic risk profile (43-45).

Beyond the effect on hypertriglyceridemia described in this study, N-3 FA may have other protective effects. Three randomized, prospective studies including 32,000 patients demonstrated that people taking N-3 FAs experienced 19–45% fewer cardiovascular events than patients taking placebo (46-48). Pre-clinical data also suggest that N-3 FA supplementation may decrease insulin resistance or delay progression to frank diabetes (49), perhaps by stimulating muscle glycogen synthesis (50). Additionally, recent data suggest that N-3 FA supplementation may delay progression of psychotic disorders (51). This study provides preliminary evidence for the efficacy of N-3 FA for antipsychotic medication-induced hypertriglyceridemia among patients in typical psychiatric treatment settings. N-3 FA may mitigate cardiometabolic side effects in patients who need to remain on SGAs for their severe mental illness. Further investigation is needed to confirm these findings.

significant side effects that necessitate laboratory monitoring. Exercise and diet programs require intensive effort and have demonstrated poor sustainability in the general population (23). Switching to an antipsychotic with a lower risk profile when a patient is psychiatrically stable may pose unacceptable risks for psychiatric relapse among many patients, particularly those taking clozapine (24).

N-3 fatty acid (N-3 FA) supplementation (25, 26) reduces triglyceride levels (TG) with minimal side effects, making it an excellent candidate for use in psychiatric patients. Interestingly, N-3 FAs have been used by some investigators to augment various treatments for mental illness (27) and improve tardive dyskinesia (28) without serious side effects. Only one study, however, has assessed N-3 FAs for hypertriglyceridemia associated with antipsychotic treatment. In an open-label trial among twenty-eight clozapine-treated patients with hypertriglyceridemia, Canniati and colleagues assessed the impact of a high dose of 10 grams of N-3 FAs per day for 4 weeks (29). They reported a 22% reduction of serum TG levels among these patients. The purpose of the present study was to evaluate whether six weeks of treatment with N-3 FAs at the FDA-recommended dose of 2 grams daily would reduce hypertriglyceridemia associated with use of any SGA in patients with SMI.

### Methods

#### **Participant Inclusion and Exclusion Criteria**

Patients with SMI were eligible if they were receiving services at one of the three study sites, were age 18 or greater, were currently taking an SGA, were medically stable, were

able to give informed consent, and had a fasting TG level between 200 and 499 mg/dL within 2 weeks of N-3 FA initiation. The TG lower limit of 200 mg/dL is the lowest value which typically will trigger clinician-initiated pharmacological therapy. The upper limit of 499 mg/dL was chosen because patients with levels above 500 mg/dL are at risk for medical complications such as pancreatitis and may benefit from non-experimental intervention.

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Patients were excluded if they were pregnant, had a known adverse reaction to fish oil, had taken N-3 FA supplements or other medication for hyperlipidemia during the past month, had a known bleeding disorder, or were receiving current treatment with coumadin or heparin.

### Procedures

The study was reviewed and approved by the New Hampshire Department of Health and Human Services Institutional Review Board, as well as the Dartmouth College Committee for the Protection of Human Subjects. Patients with SMI were recruited from one inpatient site and two outpatient community mental health treatment sites by clinician referral and study flyers. After providing written informed consent, patients were assessed for eligibility with medical record review, laboratory exam, and physical exam.

Ineligible patients were discharged without receiving any study medication. Eligible patients were prescribed Lovaza, an oral supplement that contains ethyl esters of N-3 FA derived from fish oil. Each capsule contains 465 mg of eicosapentaenoic acid and 375 mg of docosahexaenoic acid. Patients took Lovaza two grams twice per day for three weeks (25). Patients were assessed in the clinic at weeks 3 and 6, and by phone on weeks 1, 2, 4 and 5. At baseline, study staff provided brief diet and exercise recommendations to all participants. Subjective compliance with self-determined diet and exercise goals was assessed weekly using a 10-point Likert scale, and medication adherence was assessed by weekly pill count. Patients were assessed for concomitant medications, side effects, and outcomes at baseline and again at weeks 3 and 6.

## Assessments

Psychiatric and medical diagnoses were obtained from clinical records. Weight, height, vital signs, and waist circumference were obtained at baseline, 3, and 6 weeks. Fasting serum lipids, insulin, glucose, and high sensitivity C-reactive protein (CRP) were obtained at baseline and week 6. The primary endpoint was change in fasting TG from baseline to week 6. Secondary endpoints included changes in glucose and insulin (which were used to calculate homeostasis model assessment-insulin resistance [HOMA-IR], an estimate of insulin resistance), systolic and diastolic blood pressures, body mass index, and CRP, as well as self-assessed compliance with diet and exercise goals.

## Statistical Methods

Analyses were performed using SPSS 17.0. Descriptive statistics were calculated. Two-tailed paired t-tests were used to assess primary and secondary outcomes.

Two secondary analyses assessed whether the main analysis outcome persisted within subgroups. First, all endpoints were analyzed separately in patients with and without diabetes. Secondly, to assess the impact of adherence to diet and exercise recommendations on TG levels during the study, the change in TG levels for patients with diet and exercise adherence scores above the sample mean were analyzed separately from those scoring below the mean adherence score.

## Results

A total of 20 patients taking SGAs with TG levels >200 mg/dL were screened. Eleven eligible patients initiated study medication. The most frequent reasons for ineligibility were normalization of TG levels (likely due to starting a low-fat inpatient diet) and withdrawal of consent before treatment initiation. All patients who began the study medication completed the six-week study treatment and assessments.

Among the 11 patients (see Table 1), the average age was  $41 \pm 13.2$  years, and six (55%) were women. Patients were taking quetiapine (n=6), aripiprazole (n=2), clozapine (n=5), ziprasidone (n=1), olanzapine (n=1), and risperidone (n=2). Four patients were prescribed more than one SGA.

Three patients each were diagnosed with schizophrenia, schizoaffective disorder and bipolar disorder. One was diag-

**Table 1**

Patient #	Sex	Age	Antipsychotic	Diagnosis	Diabetes	BMI	Pre TG	Post TG
1	M	50	QUE	Bipolar	No	45.3	326	278
2	F	42	QUE, ARI	Borderline PD	No	45.1	359	293
3	M	56	CLOZ	Dementia	No	31.63	391	245
4	F	19	QUE, RISP	Bipolar	No	38	271	121
5	F	45	ZIP	Schizoaffective	Yes	22.4	231	209
6	M	31	OLZ, RISP	Schizoaffective	No	41	375	256
7	F	24	CLOZ	Schizophrenia	No	44.3	241	175
8	F	55	CLOZ, ARI	Schizophrenia	No	42.3	207	119
9	M	38	QUE	Schizophrenia	No	34.3	261	264
10	F	54	CLOZ, QUE	Schizoaffective	Yes	34.8	232	202
11	M	55	CLOZ, OLZ	Bipolar	Yes	19.5	271	229

ARI=aripiprazole, CLOZ=clozapine, OLZ=olanzapine, QUE=quetiapine, RISP=risperidone, ZIP=ziprasidone, TG=triglycerides, BMI=body mass index, in kg/m<sup>2</sup>.

nosed with dementia and another with borderline personality disorder. All patients met criteria for severe mental illness based on New Hampshire state criteria. Three patients had been diagnosed with diabetes, another three with gastroesophageal reflux disease, one with congestive heart failure, one with hypertension, and one had a history of myocardial infarction.

The mean serum TG level decreased from  $288\pm 64.1$  mg/dL at baseline to  $217\pm 59.2$  mg/dL at week 6 (mean difference of  $70.3\pm 50.4$  mg/dL;  $t=4.6$ ,  $p=0.001$ ). Three patients' TG levels entered the normal range. Only one patient experienced no change in TG levels. Outcomes were assessed separately in patients with and without diabetes. Reductions in TG levels were seen in both diabetic patients ( $n=3$ , mean difference  $31.3\pm 10.1$ ) and non-diabetic patients ( $n=8$ , mean difference  $80.0\pm 52.0$ ).

Analysis of secondary endpoints revealed that HDL values decreased by  $2.6\pm 3.5$  mg/dL ( $t=2.5$ ,  $p=0.03$ ). Other secondary measures did not significantly change. LDL decreased by  $4.52\pm 29.4$  ( $p=0.61$ ), total cholesterol increased by  $11.7\pm 30.4$  ( $p=0.23$ ), HOMA-IR decreased by  $0.05\pm 0.66$  ( $p=0.837$ ) and CRP decreased by  $1.78\pm 3.69$  ( $p=0.21$ ). In patients without diabetes, TG/HDL ratio decreased significantly, with a mean change of  $1.7\pm 2.03$  ( $t=2.4$ ,  $df=7$ ,  $p=0.05$ ). In contrast, among patients with diabetes, only diastolic blood pressure showed a significant decrease of  $9.7\pm 2.5$  mmHg ( $t=6.7$ ,  $df=2$ ,  $p=0.02$ ). Other outcome measures did not differ significantly between the two groups.

Side effects were minimal. A few patients reported fishy taste ( $n=2$ ), gas ( $n=2$ ), or upset stomach ( $n=1$ ). No patients discontinued study medication due to side effects.

Adherence to medication treatment was excellent. Two patients each missed two doses of study medication. Adherence to diet and exercise goals was only fair, however. Of eight patients able to report on the 10-point Likert scale, mean subjective exercise goal adherence was 6.3 and mean diet adherence was 6.6. The main outcome was assessed among participants with high or low adherence (excluding the three patients who were unable to answer the lifestyle questionnaire). Mean TG levels decreased by  $89\pm 34.6$  mg/dL in the five patients with high adherence to diet and exercise recommendations, and by  $50.4\pm 20.7$  mg/dL in the three patients with low adherence.

## Discussion

In this small, open-label study of patients with SMI currently taking SGAs, use of N-3 FA for six weeks resulted in decreased triglycerides. This improvement occurred in participants with both high and low quality of diet and exercise. The study design used here differs from previous work (30) in that patients taking any SGA antipsychotic were included (rather than only patients taking clozapine), and

participants took the FDA-approved dose of N-3 FA (4 g daily), rather than a higher dose (10 g daily). This study suggests that FDA-approved doses of N-3 FA may be tolerable and effective in psychiatric patients. Further research is needed to confirm the results of this small, uncontrolled study.

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If further research confirms the findings here, N-3 FAs may become an attractive option for the treatment of antipsychotic medication-induced hypertriglyceridemia by psychiatrists. N-3 FAs may be used alone or in addition to lifestyle interventions (30-32), other medication augmentation strategies (33-42), or switching from a high-risk antipsychotic to an agent with a lower cardiometabolic risk profile (43-45).

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The main advantage of N-3 FA supplementation over lifestyle interventions is the high safety and tolerability, which may contribute to high compliance, as opposed to the low rate of sustained compliance with such lifestyle programs (23). Unlike lifestyle interventions, however, the efficacy of N-3 FA has not been established for reducing weight, blood pressure, and risk of diabetes in high cardiovascular risk populations (52-54). One randomized trial assessed

the efficacy of rosuvastatin therapy versus placebo in 100 patients with schizophrenia and high coronary risk (55). Participants who took rosuvastatin experienced a 41% decrease in TG, as well as decreased LDL cholesterol, but no increase in HDL cholesterol. One patient taking rosuvastatin stopped therapy due to elevated liver enzymes and creatine kinase levels. In contrast, N-3 FA treatment does not require laboratory monitoring for liver toxicity or elevated creatine kinase (25).

Total cholesterol increased 5.7% over this six-week study, which was not statistically significant ( $p=0.23$ ). With the low magnitude of this change, a concurrent rise in HDL cholesterol, and without a rise in LDL cholesterol, the clinical significance of this trend is low.

The obvious limitations of the current study are its small size, open-label design, and lack of control group. We did not have the power to detect change in any of the secondary endpoints. We did not control for multiple statistical tests. Furthermore, the small convenience sample may be different from other groups of patients treated with antipsychotic medications.

Nevertheless, this study provides preliminary evidence for the efficacy of N-3 FA for antipsychotic medication-induced hypertriglyceridemia among patients in typical psychiatric treatment settings. N-3 FA may mitigate cardiometabolic side effects in patients who need to remain on SGAs for their severe mental illness. Further investigation is needed to confirm these findings.

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