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Original Article

# Early changes of blood lipid levels during psychotropic drug treatment as predictors of long-term lipid changes and of new onset dyslipidemia

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**KEYWORDS:**
Early lipid changes;
Predictors;
Metabolic follow-up;
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Psychotropic drugs

**BACKGROUND:** Cardiovascular diseases and dyslipidemia represent a major health issue in psychiatry. Many psychotropic drugs can induce a rapid and substantial increase of blood lipid levels.

**OBJECTIVE:** This study aimed to determine the potential predictive power of an early change of blood lipid levels during psychotropic treatment on long-term change and on dyslipidemia development.

**METHODS:** Data were obtained from a prospective study including 181 psychiatric patients with metabolic parameters monitored during the first year of treatment and with adherence ascertained. Blood lipid levels (ie, total cholesterol [TC], low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], non–high-density lipoprotein cholesterol [non-HDL-C], and fasting triglycerides [TGs]) were measured at baseline and after 1, 3, and/or 12 months of treatment.

**RESULTS:** Receiver-operating characteristic analyses indicated that early (ie, after 1 month of psychotropic treatment) increases (≥5%) for TC, LDL-C, TG, and non-HDL-C and decrease (≥5%) for HDL-C were the best predictors for clinically relevant modifications of blood lipid levels after 3 months of

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treatment (≥30% TC, ≥40% LDL-C, ≥45% TG, ≥55% non-HDL-C increase, and ≥20% HDL-C decrease; sensitivity 70%–100%, specificity 53%–72%). Predictive powers of these models were confirmed by fitting longitudinal multivariate models in the same cohort ($P \leq .03$) as well as in a replication cohort (n = 79; $P \leq .003$). Survival models showed significantly higher incidences of new onset dyslipidemia (TC, LDL-C, and non-HDL-C hypercholesterolemia, HDL-C hypocholesterolemia, and hypertriglyceridemia) for patients with early changes of blood lipid levels compared to others ($P \leq .01$).

**CONCLUSION:** Early modifications of blood lipid levels following prescription of psychotropic drugs inducing dyslipidemia should therefore raise questions on clinical strategies to control long-term dyslipidemia.



## Introduction

Individuals with severe mental illness, in particular schizophrenia, bipolar, and major depressive disorders have a 10- to 25-year reduced life expectancy compared to subjects from the general population.[1–8] Most of this premature mortality has been attributed to cardiovascular diseases resulting from the metabolic syndrome.[9] Several risk factors implying complex mechanisms may explain this excess cardiovascular risk, including psychiatric disease–related factors, unhealthy lifestyle, poverty, and adverse effects of treatment.[10,11] Thus, the use of psychotropic medications such as antipsychotics (most atypical but also some typical), mood stabilizers (eg, lithium and valproate), and some antidepressants (eg, mirtazapine) can increase the risk of metabolic disorders including obesity, type 2 diabetes, hypertension, and dyslipidemia.[12]

Components of the metabolic syndrome may develop early during psychotropic treatment[13–15] and may initiate a steady process leading to cardiometabolic diseases in the long term, highlighting the importance to prospectively monitor metabolic parameters during treatment.[16] A threshold of 5% weight gain during the first month of psychotropic treatment was recently defined as a robust predictor for subsequent important weight gain.[13] To date, nothing is known about any other early metabolic threshold for predicting worsening of cardiometabolic parameters during treatment with psychotropic drugs. Dyslipidemia, defined as high low-density lipoprotein cholesterol (LDL-C) and/or low high-density lipoprotein cholesterol (HDL-C) and/or high triglyceride (TG) levels, constitutes an important risk factor for cardiovascular diseases as its prevalence has been shown to reach 55% in schizophrenia patients receiving psychotropic drugs.[17] This side effect induced by psychotropic drugs has long been considered as resulting from psychotropic drug–induced weight gain. However, new data revealed that these lipogenic adverse effects may occur very early during treatment and may even precede weight gain, displaying weight-independent molecular effects in addition to weight-related ones.[11,15,18–20]

To our knowledge, only 1 study investigated the predictive value of early on mid-term lipid changes.[21] This study observed that a lack of early (ie, from 6 to 12 weeks) elevation in TG concentration of 0.23 mmol/L (20 mg/dL) was predictive of later (ie, from 24 to 28 weeks) lack of substantial TG increase in patients receiving olanzapine, ziprasidone, or aripiprazole.[21] Notably, the latter study was a post hoc analysis of clinical trials examining the effects of specific drugs, with restrictions on the number of prescribed drugs, conditions that are not comparable to the usual clinical practice. Moreover, the longest treatment duration was 28 weeks, with no data on longer term.

Although no threshold of serum lipid concentration was defined as being a sign to reconsider psychotropic treatment,[22] the National Cholesterol Education Program (adult treatment panel III [ATP III]) states that increases of 50 mg/dL (0.57 mmol/L) for TG, 40 mg/dL (1.04 mmol/L) for total cholesterol (TC), and 30 mg/dL (0.77 mmol/L) for LDL-C are considered sufficient for a categorical risk change from "borderline high" to "high" and are therefore clinically significant.[23] When referring to the upper values of the clinical ranges, these increases correspond to approximately 29% of TG (0.57/2), 21% of TC (1.04/5), and 26% of LDL-C (0.77/3).

Because of the high mortality and morbidity associated with dyslipidemia, an early detection of patients who are at higher risk of developing an important change in plasma lipid levels during psychotropic treatment is of major clinical relevance. In the present study, we sought to determine, in a cohort of patients taking psychotropic medication with adherence ascertained by therapeutic drug monitoring, how plasma lipid changes during the first month of treatment could predict mid- and long-term plasma lipid changes and new onset dyslipidemia (NOD).

## Methods

### Study design

Since 2007, a longitudinal observational study is ongoing in the Department of Psychiatry of the Lausanne University Hospital. Patients starting a psychotropic treatment with amisulpride, aripiprazole, clozapine, haloperidol, lithium, mirtazapine, olanzapine, quetiapine, risperidone, and/or valproate were included, as described in the flowchart (S1