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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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ABSTRACT

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 (i.e. total- (TC), low-density lipoprotein- (LDL-C), high-density lipoprotein- (HDL-C), non-high-density lipoprotein- (non-HDL-C) cholesterol and fasting triglycerides (TG)) were measured at baseline and after 1, 3 and/or 12 months of treatment. *Results*: Receiver operating characteristic analyses indicated that early (i.e. after one 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 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 ($p \leq 0.03$) as well as in a replication cohort ($n=79$; $p \leq 0.003$). 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 ($p \leq 0.01$). *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 (e.g. lithium and valproate) and some antidepressants (e.g. 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 LDL-cholesterol (LDL-C) and/or low HDL-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 19, 20].

To our knowledge, only one study investigated the predictive value of early on mid-term lipid changes [21]. This study observed that a lack of early (i.e. from 6 to 12 weeks) elevation in triglyceride concentration of 0.23 mmol/l (20 mg/dL) was predictive of later (i.e. from 24 to 28 weeks) lack of substantial triglyceride 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 of 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 (ATPIII) states that increases of 50 mg/dL (0.57 mmol/l) for TG, of 40 mg/dL (1.04 mmol/l) for total cholesterol (TC) and of 30 mg/dL (0.77 mmol/l) for low-density lipoprotein cholesterol are considered as 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 Figure**). The present study included patients with informed consent from an ongoing pharmacogenetic study (PsyMetab) as described elsewhere [24]. In addition, data of patients in the clinical follow-up (PsyClin) were obtained in the hospital or in outpatients centers during a medical examination based on the department guideline for metabolic follow-up performed on a routine basis [16]. Monitoring for physical health risk factors include prospective assessments of body mass index (BMI), waist circumference, fasting glucose, lipid profile, blood pressure and tobacco smoking during treatment [25]. When a treatment was stopped for more than 2 weeks, or if a drug was replaced by another drug on the list, the follow-up was restarted from baseline. In case of the introduction of a second studied drug, the follow-up was restarted and the last introduced drug considered as the main treatment. Because of the noninterventional post hoc analysis study design, no informed consent was requested from the clinical follow-up patients. Both studies were approved by the ethics committee of the Lausanne University Hospital.

Only patients with available lipid levels at least at baseline, first month (15 to 45 days of treatment; median of 32 days (interquartile range (IQR): 28-36)) and another month, i.e. either month 3 (45 to 135 days of treatment; median of 94 days (IQR: 88-106)) or month

12 (136 to 535 days of treatment; median of 365 days (IQR: 277-392)) without any lipid-lowering drug (**S1 Table**) were included for the determination of early thresholds. For analyses of NOD incidence, only patients without dyslipidemia at baseline were included (**S1 Figure**; see Supplementary Material (paragraph 1.2)).

Statistical analyses

Marginal analyses were conducted using Wilcoxon-Mann-Whitney rank-sum tests to compare continuous variables across groups and Chi-squared and Fisher's exact tests to assess associations among categorical variables.

Short-term lipid changes as predictors of long-term lipid changes in the discovery sample

To assess the predictive value of an early change of blood lipid levels (i.e. during the first month of treatment) on long-term lipid change (3 and 12 months), sensitivity, specificity, positive predictive value and negative predictive value were calculated using the pROC R package [26]. Sensitivity was defined as the percentage of patients predicted as high-risk patients among all truly high-risk patients. Specificity was defined as the percentage of patients predicted as low-risk patients among all truly low-risk patients.

Thresholds for early lipid changes were examined in 5% increments (from 5 up to 35, whenever the number of observations was sufficient) to find the best predictors for long-term increases of TC, LDL-C, TG and non-HDL-C increase and HDL-C decrease (increments of 5% from 5 up to 55, whenever the number of observations was sufficient). These analyses allowed assessing the best relation between sensitivity and specificity to find acceptable thresholds for short and long term blood lipid changes. More details in Supplementary Material (paragraph 1.4.1).

Confirmatory analyses in discovery and replication samples

The nlme package of R was used to fit a linear mixed effect model on long-term lipid changes adjusted for age, gender, baseline BMI, treatment duration, smoking status, current psychotropic drug and early weight gain (≥5%) groups. More details in Supplementary Material (paragraph 1.4.2).

Short-term lipid changes and new onset dyslipidemia

Kaplan-Meier estimates with log-rank tests, logistic mixed regression and Cox regression tests adjusting for variables mentioned below were used to compare the incidence of dyslipidemia development between early and non-early lipid change groups, i.e. TC ≥5% vs TC <5%, LDL-C ≥5% vs LDL-C <5%, TG ≥5% vs TG <5%, HDL-C ≤-5% vs HDL-C >-5% and non-HDL-C ≥5% vs non-HDL-C <5%, using the survival package of R. More details in Supplementary Material (paragraph 1.4.3). Statistical significance was determined by a p-value ≤0.05. Statistical analyses were performed using Stata 12 (StataCorp, College Station TX, USA) and R environment for statistical computing version 3.3.1.

RESULTS

Demographics and evolution of metabolic parameters

One hundred and eighty one patients who did not receive any lipid lowering agent during psychotropic treatment were included (**Table 1**, **S2 Table**). More details in Supplementary data (paragraph 2.1).

Short-term lipid changes as predictors of long-term lipid changes in a discovery cohort

For the selection of predictors, thresholds with the highest sensitivity combined with high area under the curve (AUC) values were chosen to maximize the detection of patients at high risk for important lipid profile worsening in the long-term.

Early (i.e. after one month of psychotropic treatment) increase (≥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 treatment (≥30% TC, ≥40% LDL-C, ≥45% TG, ≥55% non-HDL-C increase and ≥20% HDL-C decrease; sensitivity 70-100%, specificity 53-72%) (**S3 Table**) and one of best predictors after 12 months of treatment (**S4 Table**). More details in Supplementary data (paragraph 2.2).

Demographic and clinical characteristics of the psychiatric discovery sample according to defined thresholds are shown in **Table 1** (more details in Supplementary data (paragraph 2.3)).

Confirmation of early lipid changes as predictors of long-term lipid changes

The above-mentioned thresholds of 5% for TC, LDL-C, TG, non-HDL-C increase and 5% for HDL-C decrease were confirmed as being significant predictors for subsequent increase of TC, LDL-C, TG and non-HDL-C, and of HDL-C decrease after 3 months of

psychotropic treatment in linear mixed models (**S5 Table**). Patients exceeding early thresholds had 25% ($p<0.0001$) higher TC increase (TCi), 34% ($p=0.0001$) higher LDL-C increase (LDLi), 40% ($p=0.03$) higher TG increase (TGi), 36% ($p<0.0001$) higher non-HDL-C increase (non-HDLi) and 14% ($p<0.0001$) higher HDL-C decrease (HDLd) after 3 months compared to patients who did not outreach such thresholds. Of note, some clinical variables were associated with these lipid changes as well (more details in Supplementary data (paragraph 2.4)).

These early thresholds of lipid change were replicated in an independent psychiatric sample (**S6 Table**). In the replication sample, patients outreaching early thresholds had 22%, 29%, 57%, 31% and 21% higher TCi, LDLi, TGi, non-HDLi and HDLd after 3 and/or 12 months of psychotropic treatment compared to patients who did not ($p\leq0.003$).

Of note, patients exceeding early thresholds for TC, LDL-C, non-HDL-C and TG had a 3% higher weight increase compared to patients who did not outreach such thresholds ($p\leq0.004$; data not shown).

Influence of early lipid thresholds on new onset dyslipidemia

Demographic and clinical data of patients with no dyslipidemia at baseline, namely in patients who did not receive any lipid-lowering drugs at baseline and for whom baseline lipid levels were within normal range, are reported in **S7 Table**. An important proportion of patients developed NOD during the first year of psychotropic treatment (more information in Supplementary data).

Incidence of NOD during treatment is displayed in **Figure 1**. It is noteworthy that survival rate curves sharply divided over time according to early threshold groups (**Figure 2**). Thus, the incidence of NOD was significantly higher in patients with TCi≥5%, LDLi≥5%, HDLd≥5%, TGi≥5% and non-HDLi≥5% compared to patients without early lipid changes ($p=1*10^{-6}$; $p=3*10^{-7}$; $p=2*10^{-7}$; p=0.01 and $p=1*10^{-3}$, respectively). These results were confirmed by Cox and logistic regressions and were replicated in an independent psychiatric sample for TCi≥5%, LDLi≥5% and non-HDLi ≥5% threshold groups (data not shown). **S8 Table** shows clinical risk factors associated with NODs. Apart from early lipid increase thresholds, some factors such as sex, early weight gain group and medication group were also associated with dyslipidemia incidence (**S2 Figure)**.

Influence of the number of early lipid thresholds on new onset dyslipidemia

S9 Table and **Figure 3** display dyslipidemia incidence according to the number of early exceeded thresholds (EET) after the first month of treatment, namely according to the number of outreached lipid phenotype (either TCi≥5%, LDLi≥5%, TGi≥5% and/or HDLd≥5%). When developing one or more EET during the first month of treatment, the risk of developing dyslipidemia at a later stage in any of the four lipid variables was increased 14.4 fold, independently of the nature of EET.

DISCUSSION

The present study aimed to explore whether early lipid increase during the first month of psychotropic treatment may predict further important lipid increase and/or dyslipidemia development in patients receiving psychotropic drugs. In the present psychiatric sample, dyslipidemia prevalence of 37% for TC, 32% for LDL-C, 17% for HDL-C and 11% for TG were observed at baseline. These values are higher than those reported in the RAISE study (Recovery After an Initial Schizophrenia Episode) [17], possibly because of the shorter lifetime exposition to psychotropic treatment in the later (less than 6 months) than in the present psychiatric sample (around 8 years) and/or to the less stringent criterion used to define dyslipidemia in RAISE study. Nonetheless, in the present study a worsening of lipid parameters was observed during treatment despite of the high prevalence already observed at baseline, in parallel with a deterioration of other metabolic parameters. It is unlikely that the increase of dyslipidemia observed over time was due to a loss of follow-up of patients with no metabolic disturbances. Indeed, follow-up was required whatever the metabolic status of patients. In addition, an increase of dyslipidemia was observed after one month despite the same numbers of patients at both periods. This emphasizes the importance to prospectively monitor metabolic (including lipid) parameters during psychotropic treatment in all patients starting a psychotropic medication [16]. Thus, the potential for psychotropic drugs to cause or to exacerbate metabolic syndrome in patients is not restricted to at-risk patients (e.g. drug naive, first episode disease, non-obese or young patients) [11]. Because clinicians have been found to have a poor adherence to guidelines for metabolic monitoring worldwide [27-29], there is a need for programs to help educate

providers and to facilitate monitoring of these cardiometabolic risk factors. Beside, a poor quality of management of potential physical health problems in psychiatric patients has also been recognized [28]. For instance, a study investigating cardiometabolic risks in first-episode schizophrenic patients showed that only a small proportion of patients with dyslipidemia were treated with lipid-lowering agent, underlining an under-recognition of lipid abnormalities [17], which is consistent with other studies from Mitchell and collaborators [27, 30, 31] and with the low proportion (i.e. less than 10%) of patients with hyperlipidemia who receive lipid-lowering drugs in the present psychiatric sample. To date, no consensus has been established among clinicians with regard to thresholds of lipid increase that would need a reconsideration of the psychotropic treatment. Nevertheless, recent guidelines from the European Society of Cardiology and European Atherosclerosis Society were proposed for the management of dyslipidemia in patients receiving antipsychotics [32]. These recommendations emphasize the importance of starting primary prevention earlier rather than later in psychiatric patients receiving psychotropic medication associated with metabolic disturbances [33]. According to the National Institute for Health and Care Excellence (NICE) [34] and to the Joint British Societies [35] guidelines on the management of cardiovascular risk, all people with dyslipidemia should receive advice about diet, exercise, weight management and smoking cessation. If lifestyle advice is ineffective in normalizing the lipid profile, a statin should be considered after screening for the risk of cardiovascular disease [25].

The present study showed that an early lipid increase of 5% or more for TC, LDL-C, TG and non-HDL-C and an early decrease of 5% or more for HDL-C were the best predictors for subsequent important lipid changes after 3 and 12 months of psychotropic

treatment. These predictors displayed high sensitivities, meaning that among all truly at-risk patients at 3 and 12 months, high percentages of patients were classified as being at risk during the first month of treatment. Additionally, these predictive models had high negative predictive values for the five lipid traits after 3 and 12 months, implying that most patients who did not reach early lipid threshold did not have substantial increase of lipid levels after 3 and 12 months of psychotropic treatment. Since a 1% reduction in LDL-C on average was shown to reduce risks for hard coronary heart disease events by approximately 1% in short-term controlled trials [23], our clinical predictive thresholds to prevent important lipid level increases appear clinically relevant. As from a clinical point of view, it is better to misclassify a patient in the high-risk group rather than to miss a truly high-risk patient, the present study aimed at maximizing sensitivity, with a lesser focus on specificity. Such as misclassification may result in possible unnecessary preemptive advices about diet, exercise, weight management and smoking cessation for low-risk patients identified as high risk, which can be considered beneficial whatever the metabolic status of the patient.

The present findings are in agreement and expand those from a previous study in our Department, underlining the importance of a 5% weight increase during the first month of treatment to predict further important weight gain during longer-term treatment [13]. Additionally, the present TG negative predictive value is in accordance with the results of a previous post-hoc randomized clinical trial reporting that a lack of early (i.e. from 6 to 12 weeks) elevation in triglyceride concentration was predictive of later (i.e. from 24 to 28 weeks) lack of substantial triglyceride increase in patients receiving olanzapine, ziprasidone or aripiprazole [21]. Notably, predictors of a 5% increase in lipid levels were

also significant in age-stratified, gender-stratified and medication-stratified subgroups of patients. These findings emphasize the robustness of these clinical predictors and should motivate clinicians to systematically monitor early lipid changes for each patient subgroups and not only in patients with known risk factors (e.g. young patients, women). Additional multivariate analyses showed that an early increase of weight (5% or more) [13] was not associated with longer-term lipid increases for TC, LDL-C, non-HDL-C and TG, meaning that both lipids and weight should be monitored during treatment. These results are in accordance with a study that observed a lack of early predictive value of BMI to explain dyslipidemia on the long-term in patients receiving olanzapine and risperidone [36].

In line with the expected metabolic effects, i.e. olanzapine, clozapine and valproate being associated with the highest risk of dyslipidemia, risperidone and quetiapine conferring an intermediate risk, and aripiprazole and amisulpride being at lower risk [37], the incidence of LDL-C dyslipidemia was significantly associated with risk-categorized drugs. Psychotropic drug categories were not associated with significant difference of dyslipidemia incidence for the remaining lipid phenotypes. This does not mean that the prescribed drugs did not have risk differences but rather underlines the relevance of the 5% predictor independently of the drug prescribed. Of note, some studies have documented significant reductions in TC and LDL-C in patients treated with valproate [38, 39]. Additional analyses considering valproate as conferring a low risk for TC and LDL-C hyperlipidemia did not modify the present results (data not shown). Finally, the present study showed that patients who outreached one or more early lipid thresholds of 5% during the first month of treatment had a 14 fold risk of developing subsequent

dyslipidemia, regardless of the nature of lipid phenotype, highlighting the need to implement clinical strategies to control long-term dyslipidemia.

Of note, according to NICE guidelines [34], the consideration of non-HDL-C instead of LDL-C is regarded as more appropriate, because this gives a measure of all of the lipids that may promote arterial plaque production. In addition, LDL-C is not directly measured but requires a calculation using a fasting sample and for triglyceride levels to be less than 4.5 mmol/l, whereas the measurement of non-HDL-C does not. In the present study, non-HDL-C and LDL-C analyses provided consistent results, which strengthen the clinical predictive value of LDL-C.

Several limitations of the present study need to be mentioned. Firstly, the majority of patients were not drug naive, and the observed lipid level increase may have resulted from past treatments. However, such patients constitute the majority of psychiatric populations, which therefore may even strengthen the clinical validity of the present findings. Secondly, the follow-up period lasted a median period of time of 378 days and even if most lipid trait worsening occurred within the period covered by the present study, it would be interesting to investigate the validity of these findings in longer-term treatment durations. Thirdly, environmental changes such as physical exercise or diet habits throughout the treatment, which could have influenced the evolution of lipid levels, were not available and their effects were not taken into account. Finally, although 10 psychotropic drugs known as potentially leading to weight gain and/or worsening of other metabolic parameters were analyzed in the present study, the results cannot be extrapolated to other drugs. The major strength of this study is its longitudinal design with prospective monitoring of plasma lipid levels. In addition, the use of therapeutic

drug monitoring allowed assessing patient adherence at each time of treatment, which is a critical issue to exclude false negatives (i.e. patients not taking the drug with no lipid increase).

In conclusion, this study underlines the importance of metabolic monitoring following the introduction of antipsychotic drugs, mood stabilizers or some antidepressants for all patients, regardless of gender, age, baseline BMI and previous treatment history. Lipid level increases and a decrease of HDL-C by 5% or more during the first month of treatment should be used by clinicians as an early warning sign to consider such patients as being at higher risk for further important lipid level increases and/or dyslipidemia development during longer term treatment. Of note, we also previously demonstrated that a threshold of >5% weight gain could be used as the best predictor of important long-term weight gain. Clinical strategies such as preemptive lifestyle interventions should be implemented to prevent these adverse effects. The causative psychotropic drug should be replaced if clinically possible, after a careful evaluation of the risk-benefit ratio of a drug switch, considering the major impact of obesity and/or metabolic symptoms including dyslipidemia and their major consequences on morbidity and mortality.

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Author contributions

CBE had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design was provided by CBE. AD, FV, NSM, AG, JT, AST, SK, SF, PB, SB, SVZ, JA, RH, KE, AvG and PC were involved in data acquisition. Statistical analysis and interpretation was provided by AD and MGR. Drafting of the manuscript was provided by AD. Critical revision of the manuscript for important intellectual content was provided by all authors. CBE and PC obtained funding for the study. Administrative, technical or material support was provided by AvG, PC and CBE. All authors gave their approval for the present article.

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