Title: Lipid Disturbances in Adolescents Treated With Second-Generation Antipsychotics: Clinical Determinants of Plasma Lipid Worsening and New-Onset Hypercholesterolemia.

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Lipid disturbances in adolescents treated with second-generation antipsychotics: clinical determinants of plasma lipid worsening and of new onset hypercholesterolemia

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ABSTRACT

Objective: Lipid disturbances following treatment with second-generation antipsychotics (SGA) represent a major health concern. A previous study determined that early changes of plasma lipid levels ≥5% during the first month of treatment with SGA predicts further lipid worsening and development of dyslipidemia. This study aimed to determine the proportion of adolescents with early lipid changes ≥5% and who develop dyslipidemia during SGA treatment. Methods: Data were obtained from a 1-year longitudinal study ongoing since 2007 including 53 adolescent psychiatric (ICD-10) patients (median 16.5 years; IQR: 14.8–17.5 years) whose metabolic parameters were monitored prospectively during treatment. Plasma lipid levels (total (TC), low-density lipoprotein (LDL-C), high-density lipoprotein (HDL-C), non-high-density lipoprotein cholesterol (non-HDL-C), and fasting triglycerides (TG)) were measured at baseline and after 1, 3 and/or 12 months of SGA treatment. Results: Half (n=26; 49%) of adolescents had early increase of TC levels by 5% or more during the first month of treatment and one third (n=8; 33%) developed new-onset hypercholesterolemia during the first year of treatment. Hypercholesterolemia developed more frequently in female patients ($p = 0.01$) and in patients with an early increase of total cholesterol ≥5% ($p = 0.02$). Finally, patients whose HDL-C levels decreased by ≥5% during the first month of treatment had a larger HDL-C worsening after three months of treatment as compared to others ($p = 0.02$). Conclusion: This study reminds the importance to monitor metabolic parameters prospectively also in adolescents after the introduction of SGAs.

INTRODUCTION

Patients suffering from severe mental illness such as schizophrenia, bipolar disorder, and major depressive disorders have a 10- to 25-year reduced life expectancy compared to individuals from the general population[1-10], which is mainly attributable to cardiovascular diseases resulting from the metabolic syndrome[11]. Multiple risk factors implying complex mechanisms may explain this excessive susceptibility for developing cardiovascular diseases, including psychiatric disease-related factors, an unhealthy lifestyle, poverty, and adverse effects of treatment[12,13]. Thus, although commonly prescribed to reduce psychotic and manic symptoms of schizophrenia and bipolar disorders, 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 and dyslipidemia[14,15]. Multiple factors have been associated with psychotropic drug-induced metabolic complications, including low baseline BMI, young age and no previous exposure to any psychotropic drug, making adolescents particularly susceptible to the development of adverse metabolic effects[13,16]. In addition, some studies, albeit controversial, suggested that women have a greater vulnerability to psychotropic drug-induced weight gain than men [12,17].

Adverse metabolic effects such as weight gain are difficult to manage and can have potential long-term cardiometabolic consequences, especially in young patients[16,18-20]. Other metabolic parameters (e.g. lipid profile) can also be worsened in young patients treated with antipsychotics,[19,21-24] which dramatically enhances the risk for long-term cardiovascular morbidity and mortality[25]. Thus, the propensity to develop dyslipidemia

(defined as high total cholesterol (TC) and/or high LDL-cholesterol (LDL-C), and/or low HDL-cholesterol (HDL-C) and/or high non-HDL cholesterol (non-HDL-C) and/or high triglyceride (TG) levels) in a young patient who receives an antipsychotic medication was estimated to be two- to threefold higher than in a patient who does not receive this type of medication[26]. In addition, this metabolic condition was shown to reach 55% in patients with first episode schizophrenia who receive antipsychotic treatment [27]. Therefore, regular monitoring for metabolic parameters in patients receiving the abovementioned drugs is an important issue. Some programs have proposed monitoring of metabolic parameters during treatment in patients receiving psychotropic drugs known to induce metabolic disturbances, including a close monitoring during the first three months of treatment [28,29]. Recent studies recognized that components of the metabolic syndrome may develop early during psychotropic treatment and may initiate a steady process leading to cardiometabolic diseases in the long term[19,20,30-32]. In particular, lipogenic adverse effects may occur very early during treatment and may even precede weight gain[13,19,33-35]. Our research group recently demonstrated the importance of early (i.e., after one month of treatment) changes of lipid levels to predict worsening of the lipid profile and development of dyslipidemia in the longer term of treatment (≥3 months of treatment)[31]. In particular, patients whose lipid levels increased by 5% or more during the first month of psychotropic treatment were more prone to have a considerable worsening of their lipid profiles after three months of treatment and to develop dyslipidemia, as compared to other patients[31]. Interestingly, these early lipid-change predictors were applicable in age-stratified samples, showing an age-independence and suggesting that they were also valid in adolescent patients. However, further characterization of lipid-profile worsening in adolescents could not be assessed due to an insufficient number of patients ≤ 18 years

(n = 16). Although some prospective studies observed that some antipsychotics (e.g., olanzapine, quetiapine, or risperidone) induced significant lipid abnormalities in children and adolescents [19,36,37], plasma lipid levels were not measured in the early period of treatment (i.e., within the first month), which would have been beneficial.

Because of the high morbidity and mortality associated with dyslipidemia, an early detection of adolescent patients at risk for developing lipid disturbances during psychotropic treatment is of major clinical concern. The aim of the present study was to determine the proportion of patients with early lipid change ≥5% and to measure the incidence of new onset dyslipidemia during treatment with psychotropic drugs. Our secondary purpose was to identify demographic and clinical risk factors associated with worsening of the lipid profile.

METHODS

Study design

A longitudinal observational study has been ongoing since 2007 in the Department of Psychiatry of the Lausanne University Hospital[38]. Patients starting a pharmacological treatment that is known to have a potential risk to induce metabolic disturbances (i.e. an antipsychotic, mood stabilizer or antidepressant listed in **Supplementary Table 1**) were included, as described in the flowchart (**Supplementary Figure 1**). The present study included patients with informed consent from an ongoing pharmacogenetic study (PsyMetab) as described elsewhere[39]. In addition, data of patients in the clinical follow-up (PsyClin) in our department were also analyzed. Due to the noninterventional post hoc analysis study design, no informed consent was requested from the patients who had clinical follow-up. Both studies were approved by the Ethics Committee of the Canton of Vaud (CER-VD).

Diagnoses were based on the International Classification of Diseases 10th (ICD-10): F10-19: psychoactive substance use; F20-29: schizophrenia; F30-39: mood disorders; F40-48: stress related disorders; F50-59: behavioral syndromes; F70-79: mental retardation; F80-89: psychological development; F90-98: behavioral and emotional disorders. Only patients treated with second-generation antipsychotics (SGA) and with available lipid levels at least at baseline and at first month (15 to 45 days of treatment; median of 29 days, IQR: 24–32) without any lipid-lowering drug (listed in **Supplementary Table 2**) were included in the sample used for descriptive statistics of early lipid changes (i.e., data 1; n = 53). Of note, 63% of patients were not drug naïve. Patients whose lipid levels were available at baseline, at first month, and later during treatment (median of 92 days, IQR: 80–101, range 56-447) and who did not meet

criteria for dyslipidemia at baseline were included in the second sample, which was used to describe the development of dyslipidemia during psychotropic treatment in function of lipid changes at first month (i.e., data 2; n ≤ 25). The majority of blood samples were drawn in the morning in fasting conditions. Non-fasting blood samples (i.e. within 6 hours following the last meal) were excluded only for triglyceride (TG) analysis (not for total (TC), HDL- (HDL-C), LDL- (LDL-C) and non-HDL- (non-HDL-C) cholesterol) [40,41]. As mentioned previously, 16 patients ≤ 18 years included in the present study were already included in a recent study designed to determine the best early thresholds for predicting further important lipid worsening[31]. However, this number was insufficient to conduct additional analyses specifically in young patients. The present study design enabled to include a greater number of participants (i.e., 37 new patients, for a total of 53).

Quantification of plasma lipids

Clinical chemistry assays from plasma samples collected before and after January 2009 were performed at the Unit of Pharmacogenetics and Clinical Psychopharmacology and at the Clinical Laboratory of the Lausanne University Hospital, respectively (both laboratories are ISO 15189 certified), using enzymatic colorimetric assays (Roche Modular P chemistry analyzer, Roche Diagnostics, Basel, Switzerland, respectively). Coefficients of variation for these assays were of ≤1.6%, ≤2% and ≤2.8% for TC, TG and HDL-C measurements, respectively. Low HDL-cholesterol level, i.e. HDL hypocholesterolemia was defined as < 1 mmol/l, high LDL-cholesterol level, i.e. LDL hypercholesterolemia was defined as ≥ 3 mmol/l, high triglyceride level, i.e. hypertriglyceridemia was defined as ≥ 2 mmol/l and high total cholesterol level, i.e.

hypercholesterolemia was defined as ≥ 5 mmol/l, according to ESH/ESC guidelines [42]. LDL-C was calculated using the Friedewald formula only when TG levels were lower than 3.5 mmol/l (310 mg/dL) [43,44]. Non-HDL-C was calculated from TC minus HDL-C.

Statistical analyses

In order to compare distribution of demographic and clinical variables across patient's groups, Wilcoxon-Mann-Whitney rank-sum tests and chi-squared tests were conducted for comparison of continuous variables and of categorical variables, respectively. For comparison of metabolic parameters between baseline and after one month of treatment, McNemar tests were performed.

Short- and long-term lipid changes

The influence of early lipid changes on long-term lipid changes was estimated by fitting linear mixed effect models on long-term lipid changes adjusting for age, gender and early weight gain groups (>4% versus ≤4%[20]) .

Short-term lipid changes and new-onset dyslipidemia

Kaplan-Meier estimates with log-rank tests were conducted to compare the incidence of new-onset dyslipidemia across patients with or without early lipid change ≥5%. For survival multivariate analyses, Cox regression tests were conducted, adjusting for age, gender, psychotropic drug category (olanzapine and quetiapine being associated with the highest risk of dyslipidemia; other drugs conferring a moderate risk [15]), and early weight gain (>4%[20]), using the survival package of R.

Statistical significance was determined by a p-value ≤0.05. Statistical analyses were performed using Stata 14 (StataCorp, College Station TX, USA) and R environment for statistical computing version 3.3.1.

RESULTS

Demographics and evolution of lipid parameters

Table 1 displays the demographic and clinical characteristics of the psychiatric sample. Fifty-three young patients monitored during treatment with SGA were included. The median age was 16.5 years (IQR: 14.8–17.5 years) and mood disorders (F30-F39) were the most frequent diagnosis (43%). Quetiapine was the most frequently prescribed psychotropic drug (62%), followed by risperidone (23%), olanzapine (13%) and amisulpride (2%). Eight out of the 53 patients (15%) received two SGAs. Seventeen percent of patients had hypercholesterolemia at baseline, i.e. TC ≥5 mmol/l (no patient received any lipid-lowering drug). Of note, in a sample including a higher number of patients (with lipid levels not systematically collected after one month of treatment (n=111), hypercholesterolemia prevalence was similar (i.e. 15.3%). In the present sample of 53 patients, 26 (49%), 23 (43%), 19 (36%), 15 (28%), and 24 patients (45%) had early changes of ≥ 5% for TC, LDL-C, TG, HDL-C, and non-HDL-C, respectively during the first month of SGA treatment. More information in Appendix 1.

A gender comparison of demographic and of clinical parameters is shown in **Supplementary Table 3**. After the first month of SGA treatment, the prevalence of hypercholesterolemia was significantly higher for females than for males (38% versus 13%; p = 0.04). Similarly, females had significantly higher levels of total cholesterol compared to males, both before and after one month of treatment (4.3 mmol/l versus 3.6 mmol/l; p = 0.02; 4.4 mmol/l versus 3.8 mmol/l; p = 0.004). Finally, quetiapine was more prescribed for females than for males (76% vs 46%; p = 0.02).

Influence of short-term lipid changes on long-term lipid changes

Linear mixed models adjusting for age, gender, early weight gain group (i.e., >4% versus ≤4%) and SGA category indicated that patients with early decrease (≥5%) of HDL-C had significantly higher decrease of HDL-C (16.2%; p=0.02) after 3 months of treatment as compared to patients without early changes of HDL-C (**Supplementary Table 4**). In addition, trends of difference for TC and non-HDL-C increase after 3 months of SGA treatment were also observed between patients with and without early increase of TC and non-HDL-C. Analyses could not be conducted for TG increase due to an insufficient number of observations. Of note, as compared to females, males had a significantly larger decrease of HDL-C levels (-13%; p = 0.04) and lower increase of TC levels (-15%; p=0.05) after 3 months of treatment (data not shown).

Influence of short-term lipid changes on new-onset dyslipidemia

Among the 53 young patients monitored during treatment with SGA, twenty-four had available data for survival analyses, which were used to characterize the development of new-onset dyslipidemia from 3 months of treatment (IQR: 80-101 days, range 56-447 days) (**Supplementary Figure 1**). Demographic and clinical characteristics of patients whose baseline lipid levels were within the normal range are indicated in **Supplementary Table 5**. The proportion of patients who met criteria for dyslipidemia at or after 3 months of SGA treatment ranged from 8% (2/24), 8% (2/25), 9% (2/21), 13% (3/24) to 33% (8/24) for LDL-C, non-HDL-C, HDL-C, TG and TC, respectively. Of note, analyses conducted in a higher number of patients (n=79) whose lipid levels at first month were not necessarily available (and whose baseline lipid levels were within

the normal range) showed similar findings, i.e. dyslipidemia incidences of 23%, 11%, 5%, 7% and 6% for TC, LDL, TG, HDL and non-HDL, respectively.

Baseline TC and LDL-C levels were significantly higher in patients who developed dyslipidemia as compared to those who did not ($p \leq 0.02$). In addition, patients developing TC hypercholesterolemia were more likely to be female ($p = 0.009$). Finally, although age range was narrow in the present psychiatric sample, patients developing TC hypercholesterolemia were significantly older as compared to those who did not ($p = 0.05$). Of note, a trend was also observed for higher age to be associated with an increased risk of LDL and non-HDL hypercholesterolemia ($p = 0.06$).

Development of new-onset dyslipidemia during treatment with SGA is displayed in **Figure 1**. As the incidence of dyslipidemia for LDL-C, TG, HDL-C, and non-HDL-C was insufficient to perform multivariate analyses, Cox regression was only conducted on TC. **Table 2** shows that females were significantly more prone to develop a TC hypercholesterolemia compared to males ($p = 0.01$). In addition, patients whose TC levels increased by ≥ 5% during the first month of treatment had a greater susceptibility to develop TC hypercholesterolemia as compared to others ($p = 0.02$). Although large confidence intervals were observed due to a small sample size, survival rate curves were significantly divided over time, depending on gender, and a trend of difference was observed for early thresholds of TC increase (**Supplementary Figure 2**).

DISCUSSION

In the present sample of adolescent patients receiving SGA, a worrisome hypercholesterolemia prevalence of 17% for total cholesterol was observed at baseline, which is comparable to baseline results from a retrospective study including first episode patients aged 23.6 years (SD = 5 years) [27]. A Spanish pediatric study observed a higher proportion of hypercholesterolemia at baseline (26%)[36], possibly attributable to less stringent criterion used to define hypercholesterolemia (i.e., ≥170 mg/dL; corresponding to 4.4 mmol/l). In adult patients included in our department, a much higher prevalence of baseline hypercholesterolemia was observed (38%[31]), which can be explained by a longer duration of illness and of lifetime exposure to psychotropic treatment.

In the present study, almost half of the adolescents had early lipid changes of ≥ 5% (i.e. 49%, 43%, 36%, 28%, and 45% for TC, LDL-C, TG, HDL-C, and non-HDL-C, respectively), which is comparable with the proportions previously observed in adults (43%, 43%, 57%, 42%, and 47%, respectively)[31]. Adolescent patients whose lipid levels changed by ≥ 5% during the first month appeared to have higher changes of lipid levels and a greater tendency to develop hypercholesterolemia during the course of a long-term treatment, as compared to patients whose early lipid levels changed by < 5%. In accordance with a previous study conducted in our department, which included mainly adult patients[31], the risk of developing hypercholesterolemia was significantly greater for females than for males. These findings are also consistent with results from a retrospective adolescent cohort[24] and with other studies, albeit controversial, suggesting that women have a greater vulnerability to develop psychotropic drug-induced metabolic disturbances than men[12,17,45].

In the present study, young females had higher levels of total cholesterol than young males, in agreement with results from a recent study on adolescent psychiatric inpatients[20]. Multivariate analyses showed that young females and patients with early increase in TC were more likely to develop new-onset hypercholesterolemia as compared to others. On the other hand, previous analyses in a sample including a higher number of patients (aged 13-89 years) showed that males were more prone than females to develop HDL hypocholesterolemia during treatment with psychotropic drugs [31]. These contrasting results suggest that further studies considering a higher number of adolescents should be performed to determine whether the present gender difference is replicated.

Considering the consequences of dyslipidemia on cardiovascular comorbidities, these worrisome findings should raise concern about the critical necessity of developing clinical strategies to monitor and control lipid levels in young patients receiving psychotropic treatments that induce metabolic side effects. According to studies conducted between 2000 and 2011 in five countries, only 22% of patients initiating a SGA had a lipid profile screen[46]. Even though local and national guideline implementations helped to significantly increase the screening rate (up to 37%), rates of testing remain insufficient[46]. Because we did not have access to information on the total cohort of adolescent patients starting a psychotropic medication in our Department, we could not calculate its screening rate. However, we observed that among 77 adolescents with available parameters collected in the context of metabolic follow-up (e.g. weight), only 60 (i.e. 78%) received a blood sample test at baseline. These observations are in accordance with another study showing an insufficient percentage of metabolic follow up in adolescent patients being prescribed psychotropic

medications inducing metabolic side effects [47]. Finally, in the present study, 13% of the patients received olanzapine, a drug without indication in Switzerland in children and adolescents, which is known to induce substantial adverse metabolic effects[48,49]. Thus, putting more effort into the dissemination of knowledge and enforcement of guidelines would tentatively help to increase the rates of metabolic follow-up and improve the quality of life and longevity of young patients [50].

The findings of the present study need to be considered with some limitations. First, although the median age was low, the majority of patients were not drug naïve, and the observed lipid levels increase may have resulted from past treatments. However, the naturalistic setting of the present study strengthens the clinical validity of the present findings. Second, information on 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, therefore, not taken into account. Third, a considerable drop-out rate was observed during the prospective study, reducing the number of available observations after three months of treatment, possibly attributable to psychiatry-related factors, such as treatment switching, poor medication adherence, and/or refusal of patients participate in follow-up. In addition, medication adherence was not guaranteed, which could lead to the inclusion of some false negatives, for example, patients who did not develop adverse lipid effects because they did not take the drug. However, exclusion of such patients might have led to even worse lipid outcomes. Finally, in the present study, no patients received other drugs than SGAs (i.e. first generation antipsychotics, mood stabilizers or antidepressants). Then, studies including adolescents receiving other drugs than SGAs should also be performed to evaluate their impact on the worsening of the lipid profile.

In conclusion, this study underlines the importance of metabolic monitoring following the introduction of SGA in young patients who are particularly susceptible to adverse metabolic effects. Further research should focus on finding effective interventions to prevent such adverse effects. In case of metabolic disturbance, if clinically possible, the causative SGA should be replaced after a careful evaluation of the risk-benefit ratio of a drug switch. Considering the major impact of dyslipidemia and its important consequences on morbidity and mortality, it is critical that healthcare professionals are aware of the risks associated with the prescription of SGA.

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Author contributions

CBE had full access to all 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, AG, CD, AL, MGR, LH, AEA, PC, and CBE were involved in data acquisition. Statistical analysis and interpretation were provided by AD. 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 were provided by PC and CBE. All authors gave their approval for the present article.

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CLINICAL POINTS

Although early changes of the lipid profile during treatment with psychotropic drugs were demonstrated in adults, this side effect has never been evaluated in adolescent patients.

Considering the major impact of dyslipidemia on morbidity and mortality, it is critical that healthcare professionals monitor and control lipid levels in young patients receiving psychotropic treatments that induce metabolic side effects.

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Table 1. Demographic parameters of patients with or without early modifications of plasma lipid levels

Demographic	All		TC < 5%	TC ≥ 5%	p-value	LDL-C < 5%	LDL-C ≥ 5 %	p-value	TG < 5%	TG ≥ 5%	p-value	HDL-C > -5%	HDL-C ≤ -5%	p-value	non-HDL-C < 5%
Number of patients	**53 (45 for TG)**		**27**	**26**		**26**	**23**		**26**	**19**		**35**	**15**		**26**
Age, median (IQR), y	**16.5 (14.8-17.5)**		15.6 (14.5-17.0)	16.9 (15.7-17.7)	**0.02**	15.6 (14.6-17.4)	16.9 (16.2-17.8)	0.05	16.8 (15.5-17.6)	16.6 (14.6-17.5)	0.6	16.6 (15.5-17.1)	15.8 (14.1-17.8)	0.86	15.8 (14.7-17.4)
Men, n(%)	**24 (44.3)**		12 (44.4)	12 (46.2)	0.9	13 (50.0)	11 (47.8)	0.88	10 (38.5)	12 (63.2)	0.1	16 (45.7)	8 (53.3)	0.62	13 (50)
Smoking, n(%)	**20 (37.0)**		11 (40.7)	9 (34.6)	0.28	11 (42.3)	8 (34.8)	0.48	11 (42.3)	7 (36.8)	0.65	12 (34.3)	8 (53.3)	0.25	10 (38.5)
Diagnosis, n(%)															
Psychoactive substance use (F10-F19)	**2 (3.8)**		1 (3.7)	1 (3.9)	0.98	1 (3.9)	1 (4.4)	0.93	2 (7.7)	0	0.22	1 (2.9)	1 (6.7)	0.53	1 (3.9)
Schizophrenia (F20-F29)	**7 (13.2)**		4 (14.8)	3 (11.5)	0.73	4 (15.4)	2 (8.7)	0.48	3 (11.5)	3 (15.8)	0.68	4 (11.4)	2 (13.3)	0.85	4 (15.4)
Mood disorders (F30-F39)	**23 (43.4)**		12 (44.4)	11 (42.3)	0.88	11 (42.3)	11 (47.8)	0.7	12 (46.2)	9 (47.4)	0.94	16 (45.7)	6 (40.0)	0.71	12 (46.2)
Stress related disorders (F40-F48)	**7 (13.2)**		2 (7.4)	5 (19.2)	0.2	3 (11.5)	3 (13.0)	0.87	3 (11.5)	3 (15.8)	0.68	4 (11.4)	3 (20.0)	0.42	2 (7.7)
Behavioral syndromes (F50-F59)	**2 (3.8)**		1 (3.7)	1 (3.9)	0.98	1 (3.9)	1 (4.4)	0.93	2 (7.7)	0	0.22	2 (5.7)	0	0.35	1 (3.9)
Mental retardation (F70-F79)	**1 (1.9)**		0	1 (3.9)	0.3	0	1 (4.4)	0.28	0	0		1 (2.9)	0	0.51	0
Psychological development disorders (F80-F89)	**2 (3.8)**		1 (3.7)	1 (3.9)	0.98	0	2 (8.7)	0.13	0	2 (10.5)	0.09	0	2 (13.3)	**0.03**	0
Behavioral and emotional disorders (F90-F98)	**6 (11.3)**		3 (11.1)	3 (11.5)	0.96	4 (15.4)	1 (4.4)	0.2	1 (3.9)	2 (10.5)	0.38	5 (14.3)	0	0.12	3 (11.5)
Not available	**3 (5.7)**		3 (11.1)	0	0.08	2 (7.7)	1 (4.4)	0.63	3 (11.5)	0	0.13	2 (5.7)	1 (6.7)	0.9	3 (11.5)
Medication, n(%)															
Amisulpride	**1 (1.9)**		1 (3.7)	0	0.32	1 (3.9)	0	0.34	1 (3.9)	0	0.39	0	1 (6.7)	0.12	1 (3.9)
Olanzapine	**7 (13.2)**		1 (3.7)	6 (23.1)	**0.04**	2 (7.7)	4 (17.4)	0.3	1 (3.9)	4 (21.0)	0.07	5 (14.3)	1 (6.7)	0.45	1 (3.9)
Quetiapine	**33 (62.3)**		18 (66.7)	15 (57.7)	0.5	18 (69.2)	13 (56.5)	0.36	17 (65.4)	12 (63.2)	0.88	23 (65.7)	9 (60.0)	0.7	18 (69.2)
Risperidone	**12 (22.6)**		7 (25.9)	5 (19.2)	0.56	5 (19.2)	6 (26.1)	0.57	7 (26.9)	3 (15.8)	0.38	7 (20.0)	4 (26.7)	0.6	6 (23.1)
Polymedication, n(%) [a]	**8/53 (15.1)**		6 (22.2)	2 (7.7)	0.14	5 (19.2)	1 (4.4)	0.11	2 (6.9)	6 (26.1)	0.06	3 (8.6)	4 (26.7)	0.09	5 (19.2)
Psychiatric illness duration, median (IQR), y	**2.5 (1.5-5.3)**		3.2 (2.0-5.1)	2.2 (1.2-10.0)	0.7	2.2 (1.8-3.5)	2.2 (1.2-8.9)	0.9	2.0 (1.1-4.7)	2.2 (1.5-3.7)	0.71	2.0 (1.2-3.3)	6.3 (2.9-10.3)	0.052	2.2 (2.0-3.3)
Early weight gain (>4%), n(%)															
1st month	**21 (40.4)**		7 (25.9)	14 (56.0)	**0.03**	6 (23.1)	12 (54.6)	**0.03**	9 (34.6)	8 (44.4)	0.51	16 (47.1)	3 (20.0)	0.07	8 (30.8)
		p-value [b]													
Total cholesterol, median (IQR), mmol/l															
Baseline	**4.1 (3.4-4.4)**		4.3 (3.7-4.5)	3.6 (3.2-4.4)	**0.04**	4.1 (3.5-5)	3.6 (3.2-4.4)	0.22	4.2 (3.5-4.4)	3.4 (3.2-4.4)	0.38	3.7 (3.2-4.3)	4.3 (3.6-5.2)	0.09	4.2 (3.6-4.5)
1st month	**4.1 (3.8-5)**	0.29	4 (3.4-4.4)	4.4 (3.8-5.2)	0.15	4 (3.4-4.4)	4.3 (3.8-5.2)	**0.05**	4.2 (3.8-5)	3.9 (3.6-4.4)	0.19	4.1 (3.8-5)	4 (3.4-4.6)	0.69	4 (3.4-4.4)
LDL cholesterol, median (IQR), mmol/l															
Baseline	**2.2 (1.8-2.6)**		2.4 (2.0-2.7)	1.8 (1.6-2.4)	**0.01**	2.3 (1.9-2.7)	1.9 (1.6-2.6)	0.08	2.3 (1.8-2.6)	1.9 (1.6-2.9)	0.63	2.2 (1.7-2.5)	2.4 (1.9-3.0)	0.12	2.3 (1.9-2.6)
1st month	**2.3 (1.8-2.8)**	0.54	2.2 (1.8-2.6)	2.4 (1.8-3.3)	0.4	2.1 (1.8-2.4)	2.6 (2.0-3.3)	0.06	2.3 (2.0-3.0)	2.1 (1.7-2.5)	0.32	2.3 (1.9-2.8)	2.1 (1.7-2.9)	0.63	2.2 (1.8-2.5)
Triglyceride, median (IQR), mmol/l															
Baseline	**1 (0.7-1.2)**		1.1 (0.6-1.3)	1 (0.7-1.2)	0.67	1.1 (0.7-1.2)	1 (0.7-1.2)	0.74	1.1 (0.8-1.3)	0.9 (0.6-1.2)	0.17	1 (0.7-1.2)	1.1 (0.8-1.2)	0.85	1.2 (0.7-1.3)
1st month	**0.9 (0.7-1.4)**	0.48	1 (0.6-1.4)	1 (0.7-1.4)	0.8	1.1 (0.7-1.4)	0.9 (0.7-1.2)	0.68	0.9 (0.6-1)	1.4 (0.8-1.6)	**0.007**	0.9 (0.4-1.4)	1.1 (0.8-1.6)	0.12	1 (0.7-1.4)
HDL cholesterol, median (IQR), mmol/l															
Baseline	**1.2 (1-1.5)**		1.2 (1.1-1.7)	1.2 (1-1.4)	0.52	1.2 (1-1.6)	1.2 (1-1.5)	0.86	1.2 (1-1.5)	1.2 (1.1-1.4)	0.98	1.2 (1-1.5)	1.2 (1.1-1.8)	0.35	1.2 (1-1.6)
1st month	**1.3 (1-1.6)**	0.66	1.2 (1-1.5)	1.4 (1.1-1.6)	0.32	1.2 (1-1.4)	1.4 (1.1-1.6)	0.11	1.4 (1.1-1.7)	1.2 (1-1.4)	0.054	1.4 (1.1-1.6)	1.1 (0.9-1.2)	**0.004**	1.1 (1-1.5)
Hypercholesterolemia (≥ 5 mmol/l), n/total (%)															
Baseline	**9/53 (17.0)**		7/27 (25.9)	2/26 (7.7)	0.07	7/26 (26.9)	2/23 (8.7)	0.1	4/26 (15.4)	4/19 (21.0)	0.62	4/35 (11.4)	5/15 (33.3)	0.07	6/26 (23.1)
1st month	**14/53 (26.4)**	0.27	3/27 (11.1)	11/26 (42.3)	**0.01**	3/26 (11.5)	9/23 (39.1)	**0.03**	8/26 (30.8)	2/19 (10.5)	0.11	10/35 (28.6)	2/15 (13.3)	0.27	2/26 (7.7)

LDL hypercholesterolemia (≥ 3 mmol/l), n/total (%)																
	Baseline	**7/49 (14.3)**		5/26 (19.2)	2/23 (8.7)	0.29	5/26 (19.2)	2/23 (8.7)	0.29	2/26 (7.7)	4/19 (21.0)	0.19	3/35 (8.6)	4/14 (28.6)	0.07	4/26 (15.4)
	1st month	**10/49 (20.4)**	0.45	3/26 (11.5)	7/23 (30.4)	0.1	3/26 (11.5)	7/23 (30.4)	0.1	6/26 (23.1)	3/19 (15.8)	0.55	7/35 (20.0)	3/14 (21.4)	0.88	2/26 (7.7)
Hypertriglyceridemia (≥ 2 mmol/l), n/total (%)																
	Baseline	**1/48 (2.1)**		0	1/22 (4.55)	0.27	0	1/23 (4.4)	0.3	1/26 (3.9)	0	0.39	1/33 (3.0)	0	0.51	0
	1st month	**4/48 (8.3)**	0.5	1/25 (4.0)	3/23 (13.0)	0.26	1/25 (4.0)	2/22 (9.1)	0.48	1/26 (3.9)	2/19 (10.5)	0.38	1/34 (2.9)	3/14 (21.4)	**0.04**	1/25 (4.0)
HDL hypocholesterolemia (≤ 1 mmol/l), n/total (%)																
	Baseline	**13/50 (26.0)**		6/26 (23.1)	7/24 (29.2)	0.62	7/26 (26.9)	6/23 (26.1)	0.95	8/26 (30.8)	4/19 (21.1)	0.47	10/35 (28.6)	3/15 (20.0)	0.53	8/26 (30.8)
	1st month	**13/50 (26.0)**	1	7/27 (25.9)	6/24 (25.0)	0.94	8/26 (30.8)	4/23 (17.4)	0.28	4/26 (15.4)	6/19 (31.6)	0.2	6/35 (17.1)	7/15 (46.7)	**0.03**	9/26 (34.6)

Only patients without any lipid-lowering medication were included. P-values were calculated using ranksum tests for continuous variables and Chi2 tests for categorical variables. Values in bold are significant.

[a]: Eight patients received an additional antipsychotic which may induce metabolic disturbances. More precisely, aripiprazole was co-prescribed once with amisulpride and once with risperidone, while amisulpride, aripiprazole, olanzapine and risperidone were co-prescribed with quetiapine in one, one, one and three patients, respectively).

[b]: p-values were calculated using McNemar tests to compare metabolic parameters between baseline and 1st month of treatment.

Abbreviations: HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; non-HDL-C: non-high-density lipoprotein cholesterol; TC: total cholesterol; TG: triglycerides.

Table 2. Risk factors for new-onset TC hypercholesterolemia during the first year of psychotropic treatment

	NODTC (n=24)	
	estimate (SE)	p-value
Age		NS
Sex	-4.40 (1.78)	0.01
Early lipid increase [a]	4.38 (1.82)	0.02
Psychotropic medication [b]		NS
Early weight gain [c]		NS

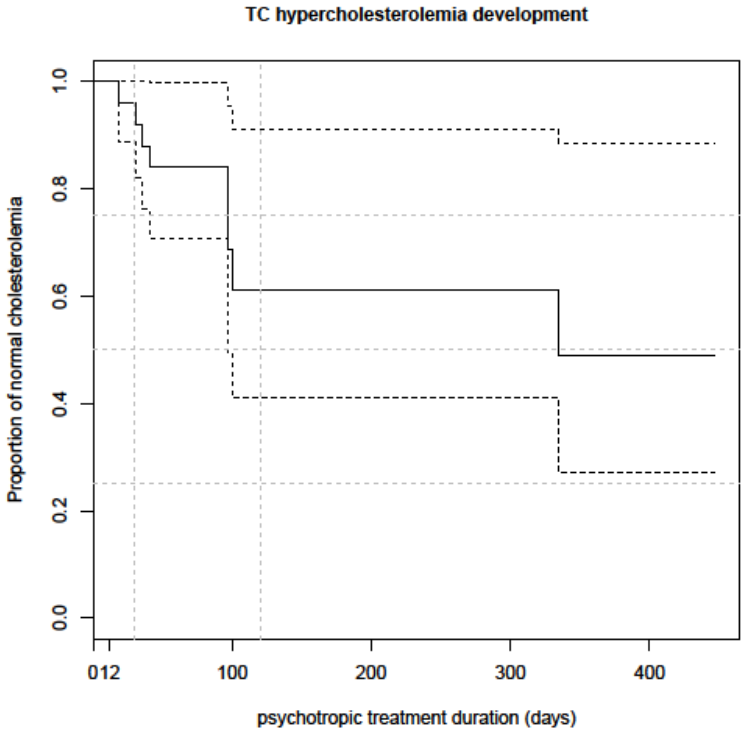
Results were obtained by fitting a Cox regression controlling for age, gender, current psychotropic drug and early weight gain >4% group. Cox regressions could not be performed on LDL hypercholesterolemia, hypertriglyceridemia and HDL hypocholesterolemia due to an insufficient number of new cases.

[a] Early lipid change groups constructed according to 5% thresholds (≥5% versus <5% of TC increase for NODTC model).

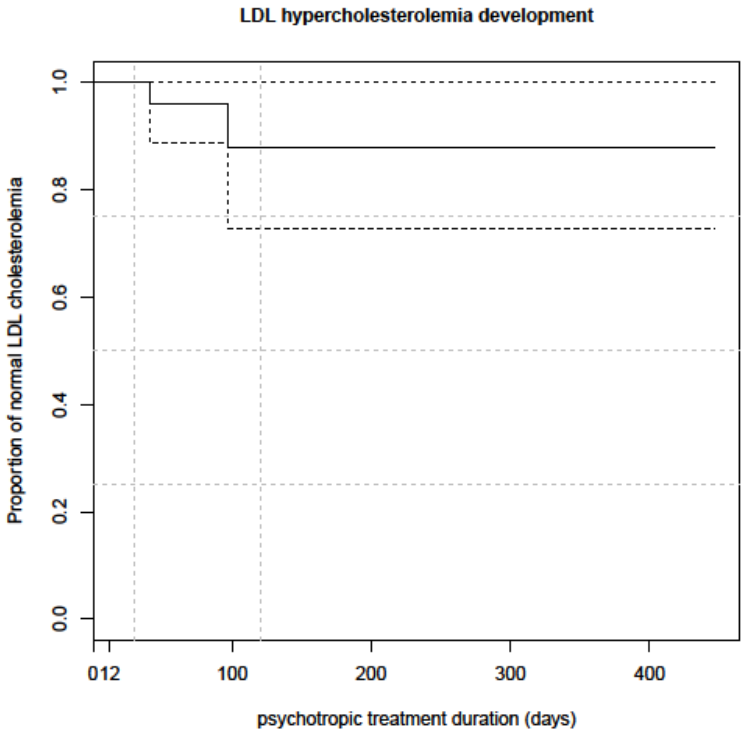
[b] Risperidone (n=4) versus Quetiapine (n=14) versus Olanzapine (n=6).

[c] Early weight gain groups were constructed according to the 4% threshold after one month of treatment [20] (>4% versus ≤4%).

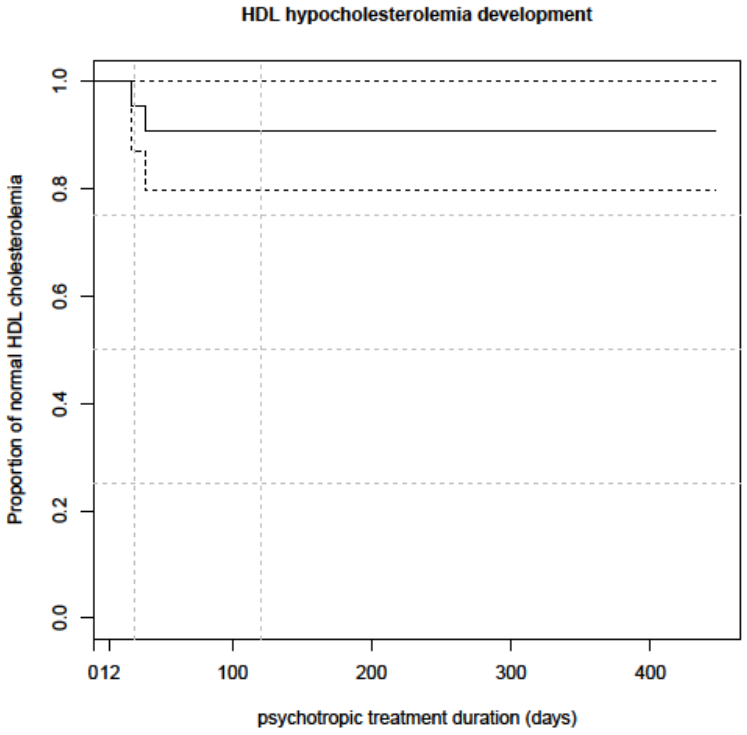
Abbreviations: NODTC: new-onset hypercholesterolemia for total cholesterol; NS: non significant; SE: standard error.


TC hypercholesterolemia development
Proportion of normal cholesterolemia
0.0
0.2
0.4
0.6
0.8
1.0
012
100
200
300
400
psychotropic treatment duration (days)

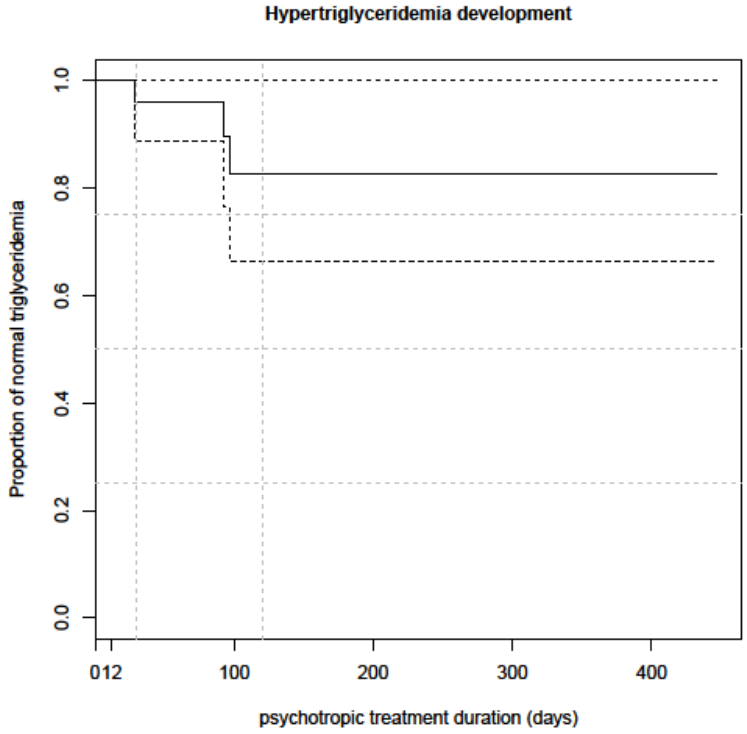
a.


LDL hypercholesterolemia development
Proportion of normal LDL cholesterolemia
0.0
0.2
0.4
0.6
0.8
1.0
012
100
200
300
400
psychotropic treatment duration (days)

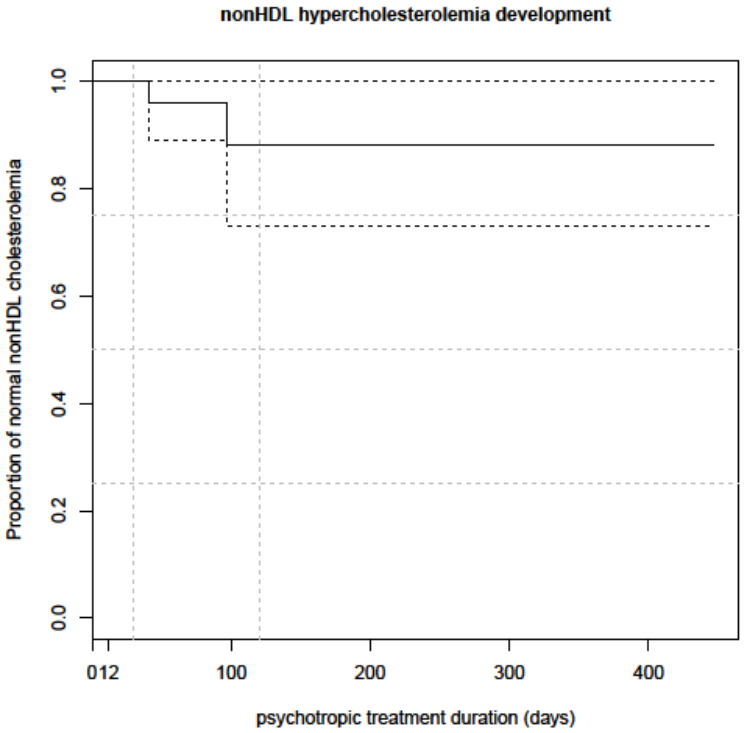
b.


HDL hypocholesterolemia development
Proportion of normal HDL cholesterolemia
0.0
0.2
0.4
0.6
0.8
1.0
012
100
200
300
400
psychotropic treatment duration (days)

c.


Hypertriglyceridemia development
Proportion of normal triglyceridemia
0.0
0.2
0.4
0.6
0.8
1.0
012
100
200
300
400
psychotropic treatment duration (days)

d.



e.

Figure 1. Survival curves for new onset dyslipidemia (NOD) by unadjusted Kaplan-Meier curves

a. Patient survival curve for NODTC (new-onset TC hypercholesterolemia) b. Patient survival curve for NODLDL (new onset LDL-C hypercholesterolemia) c. Patient survival curve for NODHDL (new onset HDL-C hypocholesterolemia) d. Patient survival curve for NODTG (new onset hypertriglyceridemia) e. Patient survival curve for NODnon-HDL (new onset non-HDL-C hypercholesterolemia). Dotted lines indicate the 95%CI of the survival curve.

Appendix 1

METHODS

Study design

Clinical data were either collected during hospitalization or in outpatient centers during a medical examination based on the department guideline for the metabolic follow-up of psychotropic drugs performed on a routine basis. Follow-up was restarted from baseline if a treatment was stopped for more than 2 weeks, if a psychotropic drug was replaced by another, or if a second psychotropic drug was added. If two or more follow-ups were available for one patient, only the longest one was included in the analysis.

RESULTS

Some demographic differences were observed between patients whose lipid levels change was <5% or ≥5% (Table 1). In particular, patients whose total cholesterol increase was ≥5% were slightly older ($p = 0.02$), were more likely to receive olanzapine (23% versus 4%; $p = 0.04$), had significantly lower levels of total cholesterol at baseline (3.6 mmol/l versus 4.3 mmol/l; $p = 0.04$), and were more likely to have early weight gain >4% (56% versus 26%; $p = 0.03$) as compared to others. Of note, within the different diagnoses, the prevalence of patients with or without early lipid worsening was similar. In addition, comparing metabolic parameters across the nine different diagnoses did not reveal any significant difference. An increased number of patients in the under-represented diagnosis categories (e.g. those with a number of patients <10) should provide an increased power and would help to perform a more accurate comparison. Finally, patients receiving two SGAs concomitantly were distributed similarly across groups of early lipid levels change (Table 1).

Supplementary Table 1. Drugs included in the metabolic follow-up recommendation

ANTIPSYCHOTICS		ANTIDEPRESSANTS		MOOD STABILIZERS
Atypical (second-generation)	**Typical (first-generation)**	**Tricyclic**	**Other**	
Amisulpride Aripiprazole Asenapine Clozapine Lurasidone Olanzapine Paliperidone Quetiapine Risperidone Sertindole	Chlorprothixene Flupentixol Haloperidol Levomepromazine Pipamperone Promazine Sulpiride Tiapride Zuclopenthixol	Amitriptyline Clomipramine Doxepine Imipramine Nortriptyline Opipramol Trimipramine	Mirtazapine	Carbamazepine Lithium Valproate

According to international recommendations, a metabolic follow-up is ongoing since 2007 in the Department of Psychiatry at the Lausanne University Hospital [1], in which inpatients and outpatients are prospectively monitored when starting a pharmacological treatment known to have a potential risk to induce metabolic disturbances (i.e. drugs listed above). The list is based on psychotropic drugs available in Switzerland).

Supplementary Table 2. Lipid-lowering drugs considered to characterize dyslipidemia

Lipid-lowering drugs
Atorvastatin
Ezetimibe
Fenofibrate
Fluvastatin
Pravastatin
Rosuvastatin
Simvastatin

The list was extracted from [2]. This list only provides lipid-lowering drugs prescribed in the present longitudinal observational study.

Supplementary Table 3. Gender comparison of demographic and clinical parameters in patients without lipid-lowering comedication

Demographic Number of patients	Men 24	Women 29	p-value
Age, median (IQR), y	16.1 (14.8-17.5)	16.9 (14.8-17.4)	0.49
Smoking, n(%)	9 (37.5)	11 (37.9)	0.46
Diagnosis, n(%)			
Psychoactive substance use (F10-F19)	1 (4.2)	1 (3.5)	0.89
Schizophrenia (F20-F29)	3 (12.5)	4 (13.8)	0.89
Mood disorders (F30-F39)	9 (37.5)	14 (48.3)	0.43
Stress related disorders (F40-F48)	3 (12.5)	4 (13.8)	0.89
Behavioral syndromes (F50-F59)	0	2 (6.9)	0.19
Mental retardation (F70-F79)	0	1 (3.5)	0.36
Psychological development (F80-F89)	2 (8.3)	0	0.11
Behavioral and emotional disorders (F90-F98)	4 (16.7)	2 (6.9)	0.26
Not available	2 (8.3)	1 (3.5)	0.44
Medication, n(%)			
Amisulpride	1 (4.2)	0	0.27
Olanzapine	4 (16.7)	3 (10.3)	0.5
Quetiapine	11 (45.8)	22 (75.9)	**0.02**
Risperidone	8 (33.3)	4 (13.8)	0.09
Polymedication, n(%) [a]	4 (16.7)	4 (13.8)	0.77
Psychiatric illness duration, median (IQR), y	3.3 (2.0-8.3)	2.2 (1.2-4.7)	0.29
Early weight gain (>4%), n(%)			
1st month	9 (39.1)	12 (41.4)	0.87
Total cholesterol, median (IQR), mmol/l			
Baseline	3.6 (3.2-4.3)	4.3 (3.7-4.6)	**0.02**
1st month	3.8 (3.3-4.2)	4.4 (4-5.2)	**0.004**
LDL cholesterol, median (IQR), mmol/l			
Baseline	2.0 (1.6-2.5)	2.4 (1.9-2.7)	0.09
1st month	2 (1.7-2.6)	2.4 (2.0-2.9)	0.1
Triglyceride, median (IQR), mmol/l			
Baseline	1 (0.6-1.2)	1 (0.7-1.2)	0.56
1st month	1 (0.8-1.4)	1 (0.7-1.4)	0.84
HDL cholesterol, median (IQR), mmol/l			
Baseline	1.2 (1-1.4)	1.2 (1.1-1.5)	0.42

1st month	1.1 (1-1.5)	1.4 (1.1-1.7)	0.08
Hypercholesterolemia (≥ 5 mmol/l), n/total (%)			
Baseline	3/24 (12.5)	6/29 (20.7)	0.43
1st month	3/24 (12.5)	11/29 (37.9)	**0.04**
LDL hypercholesterolemia (≥ 3 mmol/l), n/total (%)			
Baseline	3/24 (12.5)	4/25 (16.0)	0.73
1st month	4/24 (16.6)	6/25 (24.0)	0.52
Hypertriglyceridemia (≥ 2 mmol/l), n/total (%)			
Baseline	0	1/26 (3.9)	0.35
1st month	1/24 (4.2)	3/24 (12.5)	0.3
HDL hypocholesterolemia (≤ 1 mmol/l), n/total (%)			
Baseline	9/24 (37.5)	4/26 (15.4)	0.08
1st month	9/24 (37.5)	4/26 (15.4)	0.08

Only patients without any lipid-lowering medication were included. P-values were calculated using rank-sum tests for continuous variables and Chi2 tests for categorical variables. Values in bold are significant.

[a]: Eight patients received an additional antipsychotic which may induce metabolic disturbances. More precisely, aripiprazole was co-prescribed once with amisulpride and once with risperidone, while amisulpride, aripiprazole, olanzapine and risperidone were co-prescribed with quetiapine in one, one, one and three patients, respectively).

Abbreviations: HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; non-HDL-C: non-high-density lipoprotein cholesterol; TC: total cholesterol; TG: triglycerides.

Supplementary Table 4. Linear regressions fitted on lipid trait changes (%) over time

n	Difference of TC change (%) between <5% and ≥5% groups (95%CI)	p-value	n	Difference of LDL-C change (%) between <5% and ≥5% groups (95%CI)	p-value	n	Difference of HDL-C change (%) between <5% and ≥5% groups (95%CI)	p-value	n	Difference of non-HDL-C change (%) between <5% and ≥5% groups (95%CI)	p-value
29	11.5% (-2.2% - 25.2%)	0.10	26	17.8% (-9.2% - 44.9%)	0.19	27	-16.2% (-30.0% - (-) 2.4%)	**0.02**	27	17.6% (-2.1% - 37.3%)	0.08

Results were obtained by fitting linear regressions controlling for age, gender, early weight gain group (i.e. >4% versus ≤4%) and psychotropic treatment categories (i.e. olanzapine, clozapine, mirtazapine and quetiapine versus other drugs). P-values in bold are significant. Analyses on triglyceride could not be performed due to a too low number of observations. Abbreviations: HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; non-HDL-C: non-high-density lipoprotein cholesterol; TC: total cholesterol; TG: triglycerides.

Supplementary Table 5. Demographic parameters and comparisons between patients with and without new-onset dyslipidemia during the first year of psychotropic treatment

	Patients without NODTC (n=16)	Patients with NODTC (n=8)	p-value	Patients without NODLDL (n=22)	Patients with NODLDL (n=2)	p-value	Patients without NODTG (n=21)	Patients with NODTG (n=3)	p-value	Patients without NODHDL (n=19)	Patients with NODHDL (n=2)	p-value	Patients without NODnonHDL (n=23)
Age, median (IQR), y	15.6 (14.3-16.6)	17 (16.4-17.6)	**0.05**	16 (14.6-17)	18 (18-18)	0.06	16.4 (15.5-17.4)	17.1 (15.6-17.9)	0.36	16.3 (15.5-17.4)	15.8 (14.1-17.5)	0.81	15.8 (14.6-17.0)
Men, n(%)	11 (68.8)	1 (12.5)	**0.009**	11 (50.0)	1 (50.0)	1	12 (57.1)	1 (33.3)	0.44	9 (47.4)	1 (50.0)	0.94	12 (52.2)
Smoking, n(%)	7 (43.8)	2 (25.0)	0.59	9 (40.9)	1 (50.0)	0.85	9 (42.9)	1 (33.3)	0.67	5 (26.3)	2 (100)	0.11	9 (39.1)
Diagnosis, n(%)													
Psychotic disorders	2 (12.5)	2 (25.0)	0.44	3 (13.6)	0	0.58	4 (19.1)	0	0.41	3 (15.8)	1 (50.0)	0.24	3 (13.0)
Bipolar disorders	2 (12.5)	0	0.3	3 (13.6)	0	0.58	3 (14.3)	1 (33.3)	0.24	3 (15.8)	0	0.74	4 (17.4)
Depressive disorders	7 (43.8)	1 (12.5)	0.13	9 (40.9)	0	0.25	8 (38.1)	2 (66.7)	0.35	8 (42.1)	0	0.24	9 (39.1)
Other	4 (25.0)	3 (37.5)	0.53	5 (22.7)	1 (50.0)	0.39	5 (23.8)	0	0.34	4 (21.1)	0	0.47	5 (21.7)
Not available	1 (6.3)	2 (25.0)	0.19	2 (9.1)	1 (50.0)	0.09	1 (4.8)	0	0.7	1 (5.3)	1 (50.0)	**0.04**	2 (8.7)
Medication, n(%)													
Olanzapine	4 (25.0)	2 (25.0)	1	5 (22.7)	0	0.45	3 (14.3)	1 (33.3)	0.41	4 (21.0)	0	0.47	5 (21.7)
Quetiapine	10 (52.5)	4 (50.0)	0.56	14 (63.6)	1 (50.0)	0.7	13 (61.9)	2 (66.7)	0.9	10 (52.6)	2 (100)	0.2	14 (60.9)
Risperidone	2 (12.5)	2 (25.0)	0.44	3 (13.6)	1 (50.0)	0.19	5 (23.8)	0	0.34	5 (26.3)	0	0.41	4 (17.4)
Early weight gain (>4%), n(%)	8 (50.0)	3 (37.5)	0.56	9 (40.9)	1 (50.0)	0.8	7 (33.3)	1 (33.3)	1	5 (26.3)	1 (50.0)	0.48	9 (39.1)
Psychiatric illness duration, median (IQR) *years*	2.5 (1-7)	6 (1-10)	0.56	3 (1-5)	NA		3 (1.5-5)	6 (1-11)	0.71	2.5 (1-4)	4 (4-4)	0.42	3 (1-5)
Baseline lipid levels [a], median (IQR), *mmol/l*	3.5 (3.2-4)	4.4 (4.3-4.4)	**0.002**	2.2 (1.6-2.3)	2.8 (2.7-2.9)	**0.02**	1 (0.6-1.3)	1 (0.9-1.7)	0.33	1.4 (1.2-1.8)	1.2 (1.2-1.2)	0.27	2.5 (2.1-2.9)

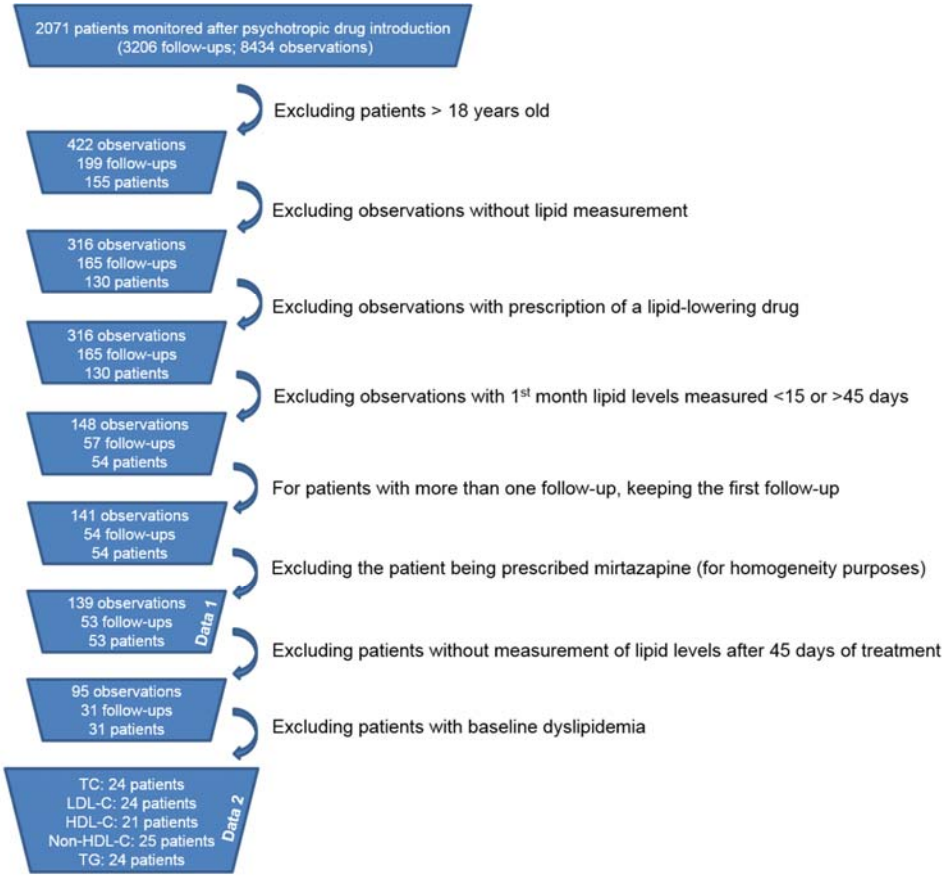
Only patients with no dyslipidemia at baseline are included. P-values were calculated using rank-sum tests (for continuous variables) and chi^2 tests (for categorical variables) between groups. Values in bold are significant.

[a] Levels of TC for NODTC groups, LDL-C for NODLDL groups, TG for NODTG groups, HDL-C for NODHDL groups and non-HDL-C for NODnonHDL groups.

Abbreviations: NA: not available; NODHDL: new-onset HDL hypocholesterolemia, defined by plasma levels of HDL cholesterol ≤1 mmol/l (39 mg/dL)*; NODLDL: new-onset LDL hypercholesterolemia, defined by plasma levels of LDL cholesterol ≥3 mmol/l (116 mg/dL)*; NODnonHDL: new-onset nonHDL hypercholesterolemia, defined by plasma levels of non-

HDL cholesterol ≥4 mmol/l (154 mg/dL)*; NODTC: new-onset hypercholesterolemia, defined by plasma levels of total cholesterol ≥5 mmol/l (193 mg/dL)*; NODTG: new-onset hypertriglyceridemia, defined by plasma levels of triglycerides ≥2 mmol/l (177 mg/dL)*.

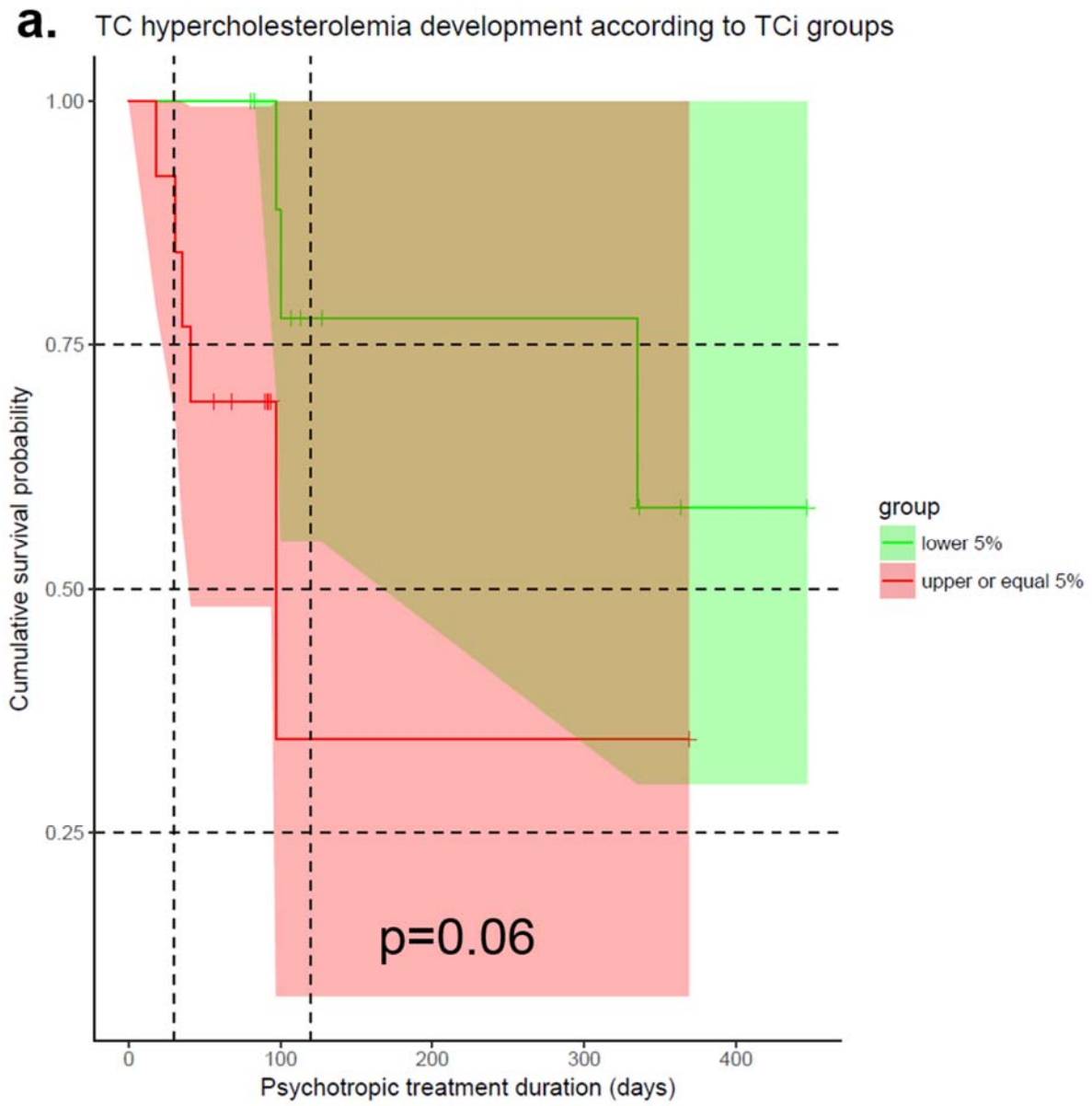
*None of the patients were prescribed lipid lowering agents.



Supplementary Figure 1. Flowchart of patient selection

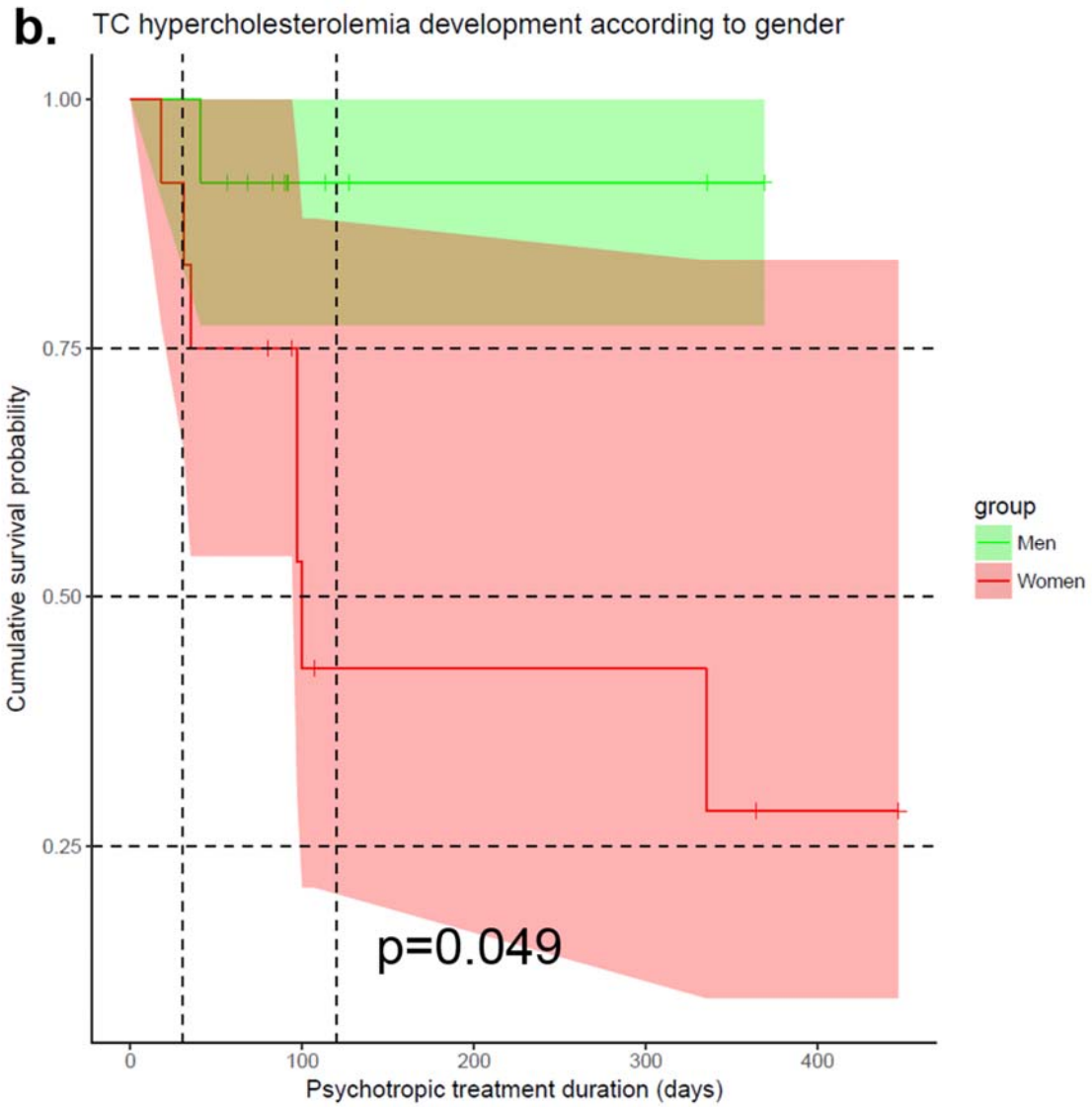
Data 1 were used for the determination of patients who developed an early increase in blood lipid levels.

Data 2 were used for the determination of risk factors associated with the development of new onset dyslipidemia.



Supplementary Figure 2. Survival curves for total cholesterol (TC) hypercholesterolemia by Kaplan-Meier curves according to clinical parameters

a. Patient survival curves for NODTC (new onset TC hypercholesterolemia) according to TCi (i.e. early 5% TC increase) threshold (n=24). Kaplan-Meier p-value=0.06; Cox p-value=0.02.



S2 Figure. Survival curves for total cholesterol (TC) hypercholesterolemia by Kaplan-Meier curves according to clinical parameters

b. Patient survival curves for NODTC (new onset TC hypercholesterolemia) according to gender (n=24). Kaplan-Meier p-value=0.049; Cox p-value=0.01.

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