Incident Users of Antipsychotic Agents and Future Use of Cholesterol-Lowering Drugs: An Observational, Pharmacoepidemiologic Study

Silje Skrede, MD, PhD; Ingunn F. Tvete, PhD; Lars Tanum, MD, PhD; Vidar M. Steen, MD, PhD; and Jørgen G. Bramness, MD, PhD

ABSTRACT

Objective: Antipsychotic agents have serious metabolic adverse effects, among them dyslipidemia, which may necessitate secondary prophylaxis with cholesterol-lowering drugs. Second-generation antipsychotics (SGAs), particularly clozapine and olanzapine, are known to confer a higher risk of metabolic adverse effects than first-generation antipsychotics (FGAs). However, little is known regarding the real-life number of antipsychotic-treated patients receiving statins.

Method: By extracting data from the Norwegian prescription database, all patients 18–69 years old that started treatment with an antipsychotic during 2004–2012 formed the basis for analysis (n = 301,713). The primary outcome measure was the proportion of FGA and SGA users prescribed with cholesterol-lowering agent during the same period. We used Cox proportional hazards regression to evaluate the risk of redeeming a cholesterol-lowering drug for formerly antipsychotic drug-naive patients (n = 147,218).

Results: Statin prescription rates in patients receiving antipsychotic agents were lower (5.3%) than comparable rates in studies covering the general population (34%) and lower than would be expected based on the recognized negative impact of antipsychotics on serum lipids. Statin prescription rates were affected by patient age, antipsychotic dose, and the number of antipsychotic agents prescribed, but rates were only 5% elevated in patients receiving SGAs compared to patients receiving FGAs ($P = .048$).

Conclusions: Our results may support the notion that patients treated with antipsychotic agents receive suboptimal care with regard to metabolic adverse effects.

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Corresponding author: *Silje Skrede, MD, PhD, Center for Medical Genetics and Molecular Medicine, Haukeland University Hospital, Bergen, 5021, Norway (silje.skrede@k2.uib.no).*

After their introduction in the 1950s, antipsychotic agents quickly became indispensable in the treatment of schizophrenia and other psychotic disorders, but they are also subject to extensive off-label use.[1–3] In spite of the available treatment, mortality in patients suffering from serious mental disorders is 2–3 times higher than in the general population.[4–6] Recent studies have demonstrated that the prevalence of somatic conditions such as cardiovascular disease, as well as mortality due to cardiovascular events, is increased 2- to 3-fold in these patients.[4,7–9] This is partly due to lifestyle issues among patients, but the contribution by metabolic adverse effects of antipsychotic treatment is significant.[4,8,10] The atypical antipsychotics, or second-generation antipsychotics (SGAs), particularly olanzapine and clozapine, are well known for their metabolic adverse effects, ie, weight gain, dyslipidemia, and diabetes.[11–15] However, some SGAs, particularly clozapine, are also recognized to have superior symptom-relieving efficacy among the antipsychotics, and are more frequently prescribed than older, first-generation antipsychotics (FGAs).[15]

The magnitude of metabolic adverse effects during treatment with antipsychotic agents is significant. In clinical studies involving young or treatment-naive patients, an increase of ≥ 7% of baseline body mass index occurred in 80% of patients treated with olanzapine for a year, while an increase of 30%–50% in serum triglycerides during olanzapine treatment has consistently been reported.[16–20] Furthermore, unfavorable alterations in cholesterol parameters, ie, increased serum total cholesterol and/or increased low-density lipoprotein cholesterol levels, have been reported during olanzapine treatment.[18,20–22] Similarly, several studies on clozapine treatment have reported increased serum triglyceride and/or cholesterol levels.[21,23,24]

Antipsychotic-induced metabolic adverse effects are to some degree preventable through both lifestyle intervention and pharmacologic treatment.[25–27] For instance, statins improved several lipid parameters that were negatively affected by antipsychotic treatment.[27–30] Still, antipsychotic-induced dyslipidemia is underdiagnosed and undertreated.[31–34] In particular, tangible data regarding coprescription of antipsychotics and lipid-lowering agents in patients treated with an antipsychotic agent are very limited. Clinical trials examining dysmetabolic effects of antipsychotic drugs often span a short period of time, and patients with somatic conditions are frequently excluded.[35,36]

AIMS OF THE STUDY

In this study, we aimed to assess the proportion of formerly treatment-naive patients being prescribed antipsychotic agents who subsequently received cholesterol-lowering agents and to examine whether the proportion of patients receiving cholesterol-lowering agents was higher in patient groups receiving SGAs, particularly clozapine or olanzapine, than in patients receiving FGAs.

Clinical Points

- Antipsychotic agents, in particular second-generation antipsychotics, have dyslipidemic adverse effects.
- Several studies have confirmed the beneficial effects of lipid-lowering drugs in patients with antipsychotic-induced dyslipidemia.
- Many patients treated with antipsychotics most likely have undetected and untreated elevation in serum lipid levels.

METHOD

Data Extraction

The data selection flow is presented in Figure 1. Data for the analysis were extracted from the Norwegian prescription database (NorPD) (http://www.norpd.no; accessed June 27, 2013; data can be obtained by applying to NorPD for data access) and initially comprised all adults who received at least 1 prescription for an antipsychotic drug during the years 2004 through 2012 (Figure 1). Adults encompass those from 18 to 69 years of age in the first redemption year. Information regarding the patients' prescriptions for cholesterol-lowering drugs was also extracted. NorPD data are anonymized for researchers and thus approval by the Regional Committees for Medical and Health Research Ethics was not required (https://helseforskning.etikkom.no; accessed June 27, 2013).

Study Population

The initial group of antipsychotic users comprised 301,713 patients and included patients as described above, omitting those who died during the study period. We then defined *drug-naive patients* as patients with no prescription fulfilments prior to January 2006 for any of the antipsychotics included in the study (Figure 1), reducing the study population to 191,603 patients. By doing this, it is reasonable to assume that the remaining patients were new antipsychotic drug users. Patients with a previous history of redeeming prescriptions for cholesterol-lowering drugs (2 years or less prior to first antipsychotic drug redemption) were also omitted. This procedure reduced the dataset for analysis to 147,218 patients, encompassing a total of 818,566 prescriptions (Figure 1).

Antipsychotics and Cholesterol-Lowering Drugs

We divided the antipsychotics into 3 groups (Table 1): a first group of FGAs/typical antipsychotics (chlorpromazine, levomepromazine, dixyrazine, fluphenazine, perphenazine, prochlorperazine, thioridazine, haloperidol, flupentixol, chlorprothixene, zuclopenthixol, pimozide, penfluridol, and tiapride), a second group of SGAs/atypical antipsychotics (melperone, droperidol, sertindole, ziprasidone, quetiapine, amisulpride, prothipendyl, risperidone, and aripiprazole), and a third group consisting of the 2 SGAs olanzapine and clozapine (the olanzapine/clozapine group). The cholesterol-lowering drugs considered were all statins (Table 1): simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, and rosuvastatin.

Patient Characteristics

Patients were characterized in terms of gender; age at first redemption; antipsychotic drug group from which they first redeemed; amount of antipsychotics redeemed, measured as numbers of defined daily doses[37]; number of different antipsychotic drug groups redeemed; and time from redemption of the first antipsychotic to the first redemption of a cholesterol-lowering drug (or throughout December 2012 if no redemption of a cholesterol-lowering drug).

Survival Analysis

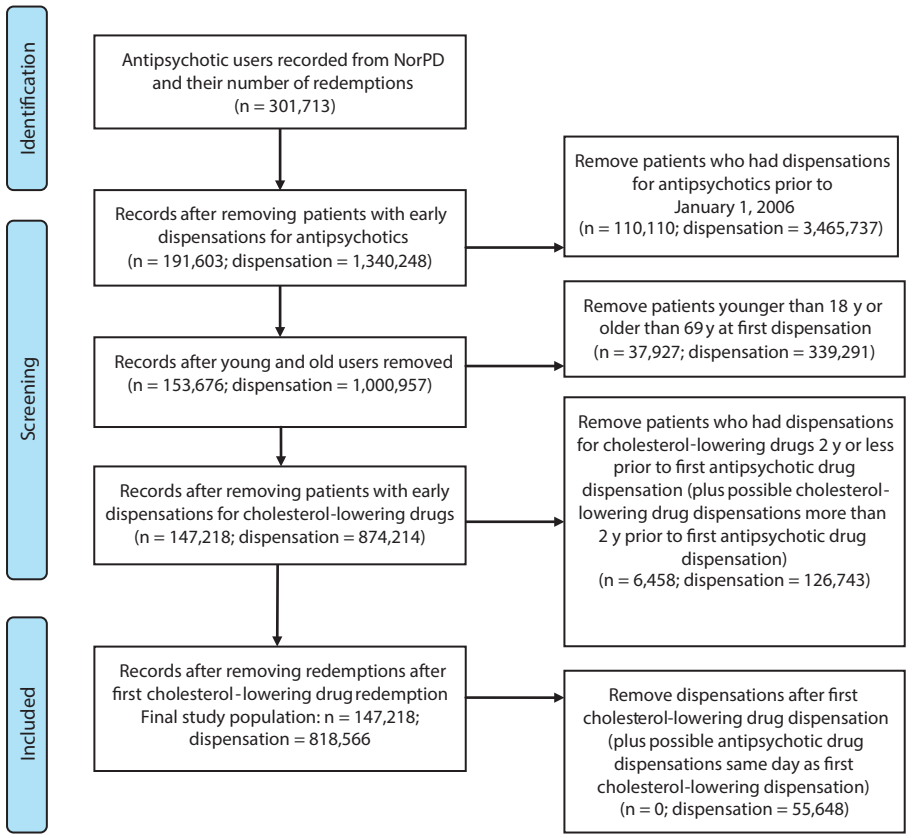
The Kaplan-Meier method was used to initially generate survival curves using the date of the first redeemed antipsychotic drug as zero time. We conducted a survival analysis by considering a Cox proportional hazards regression model with both time-independent and time-dependent explanatory variables to examine the effect of these on the time to a first redemption for a cholesterol-lowering drug after starting antipsychotic treatment. Possible explanatory time-independent variables included gender, age, and antipsychotic drug group at first redemption, and time-dependent variables included the amount of drug redeemed and the number of different antipsychotic drug groups redeemed. The outcome (survival time) was time from the first redemption of an antipsychotic drug until the time of a first redemption for a cholesterol-lowering drug. If a patient redeemed a prescription for a cholesterol-lowering drug, this was recorded as an event, while, if a patient had no such redemption, no event was recorded and the patient was censored with the censoring time December 31, 2012. We chose a step-wise model selection approach for considering the explanatory variables' relevance, and conducted partial likelihood ratio tests for the alternative models, applying a significance level of $P < .05$. Data were analyzed using R (survival package).[38]

RESULTS

Baseline characteristics of the 147,218 patients are summarized in Table 2. There were 65,973 (44.8%) male and 81,245 (55.2%) female patients, with an mean age of 42.6 years. Of these, 83,139 (56.5%) filled a prescription for an FGA, 50,131 (34.1%) for an SGA (not including olanzapine or clozapine), while 13,948 (9.5%) filled their first prescription for clozapine or olanzapine. Most patients filled prescriptions for only 1 antipsychotic (128,142; 87.0%), while 19,076 (13.0%) filled prescriptions for at least 2 different antipsychotics.

During the follow-up period, 7,832 patients (5.3%) filled a prescription for a cholesterol-lowering drug. The mean age of patients in this group was higher than that of the general study population (54.4 years). In absolute numbers, a higher share of patients that were prescribed cholesterol-lowering agents filled a prescription for an FGA (n = 5,078; 64.8%) than for SGAs (n = 2,127; 27.2%) or clozapine/olanzapine (n = 627; 8.0%). The percentage of patients receiving more than 1 antipsychotic was similar in

Figure 1. Flow Chart Demonstrating Data Selection Procedure



Abbreviation: NorPD = Norwegian prescription database.

patients prescribed a cholesterol-lowering drug (11.7%) and in patients not prescribed cholesterol-lowering medication (13.0%) (Table 2).

Kaplan-Meier Curves

The 147,218 patients represented a total of 27,036,548 weeks (mean = 184) after filling of the first prescription for an antipsychotic drug until (1) redeeming a prescription for a cholesterol-lowering drug or (2) the end of the observation period, 938,846 weeks (mean = 120) for the 7,832 who filled a prescription for a cholesterol-lowering drug, and 26,097,703 weeks (mean = 187) for the 139,386 patients who were not prescribed a cholesterol-lowering drug. Mean time until the first redemption of a cholesterol-lowering drug was 118 weeks (median = 101) for men and 121 weeks (median = 107) for women. The Kaplan-Meier curves in Figure 2 show the differences in risk for redeeming a cholesterol-lowering drug depending upon gender, age, and the antipsychotic drug first redeemed. Male patients were at a higher risk for redeeming a cholesterol-lowering drug than female patients.

Cox Proportional Hazards Regression

In a univariate analysis (Table 3, model 1), we found that patients initially receiving FGAs had a significantly higher risk of redeeming a prescription for a cholesterol-lowering drug compared to those who initially received SGAs or olanzapine/clozapine, 23.5% and 34.3%, respectively. Patients receiving FGAs, however, were older, and, when adjusting for gender and age (Table 3, model 2), we found that patients who initially received SGAs or olanzapine/clozapine had a slight but statistically significant increase in the risk of being prescribed a cholesterol-lowering drug compared to those initially receiving FGAs (hazard ratios [HRs] [95% CIs] = 1.100 [1.045–1.158], $P < .001$, and 1.136 [1.045–1.235], $P = .003$, for the 2 groups, respectively) (Table 3).

Using model 3, ie, adjusting for age, gender, initial antipsychotic drug group, number of different antipsychotic drug groups, amount of drug prescribed, and the interaction of age with number of different antipsychotic drug groups (model obtained after a stepwise model selection approach), a slight increase (HR = 1.0538; ie, 5.4%; $P = .048$) in the risk for statin redemption was maintained in patients initially redeeming SGAs other than olanzapine/clozapine compared to those initially redeeming FGAs (Table 3). There was no longer any significant difference between risk in patients receiving FGAs and clozapine/olanzapine. Notably, patients with redemptions within all 3 antipsychotic drug groups were 4.1 times more likely to have a redemption for a cholesterol-lowering drug than a patient with redemption(s) within just 1 antipsychotic drug group.

DISCUSSION

It is well known that SGAs, particularly clozapine and olanzapine, are associated with a higher risk of metabolic adverse effects than FGAs.[15,33] In this observational study, we determined the proportion and characteristics of antipsychotic-naive patients starting treatment with antipsychotics who also received prescriptions for a statin during a median follow-up period of 3.5 years. During the follow-up period, 5.3% of the patients filled a prescription for a statin. In comparison, a prospective study on a Norwegian cohort showed that among individuals with low risk of cardiovascular disorder, 8% of individuals were prescribed statins during a 2-year follow-up period.[39] In individuals with a high risk of cardiovascular disorder, likely comparable to that of patients treated with antipsychotics, the statin prescription rate was 34%.[39] It is, however, challenging to answer the question of how many patients receiving antipsychotics "should" be treated with lipid-lowering agents. The prevalence of dyslipidemia in our study population is unknown, but it has been reported at 20%–30% in patients receiving antipsychotics in general, and within the 30%–40% range in olanzapine-/clozapine-treated patients.[40,41] In light of these reports, it seems fair to claim that more patients than

Table 1. Overview of Pharmacologic Agents Included in the Study

Group	Generic Name	ATC Number
First-generation antipsychotics	Chlorpromazine	N05A A01
	Levomepromazine	N05A A02
	Dixyrazine	N05A B01
	Fluphenazine	N05A B02
	Perphenazine	N05A B03
	Prochlorperazine	N05A B04
	Thioridazine	N05A C02
	Haloperidol	N05A D01
	Flupentixol	N05A F01
	Chlorprothixene	N05A F03
	Zuclopenthixol	N05A F05
	Pimozide	N05A G02
	Penfluridol	N05A G03
	Tiapride	N05A L03
Second-generation antipsychotics, except clozapine and olanzapine	Melperone	N05A D03
	Droperidol	N05A D08
	Sertindole	N05A E03
	Ziprasidone	N05A E04
	Quetiapine	N05A H04
	Amisulpride	N05A L05
	Prothipendyl	N05A X07
	Risperidone	N05A X08
	Aripiprazole	N05A X12
Clozapine and olanzapine	Clozapine	N05A H02
	Olanzapine	N05A H03
Statins	Simvastatin	C10A A01
	Lovastatin	C10A A02
	Pravastatin	C10A A03
	Fluvastatin	C10A A04
	Atorvastatin	C10A A05
	Rosuvastatin	C10A A07

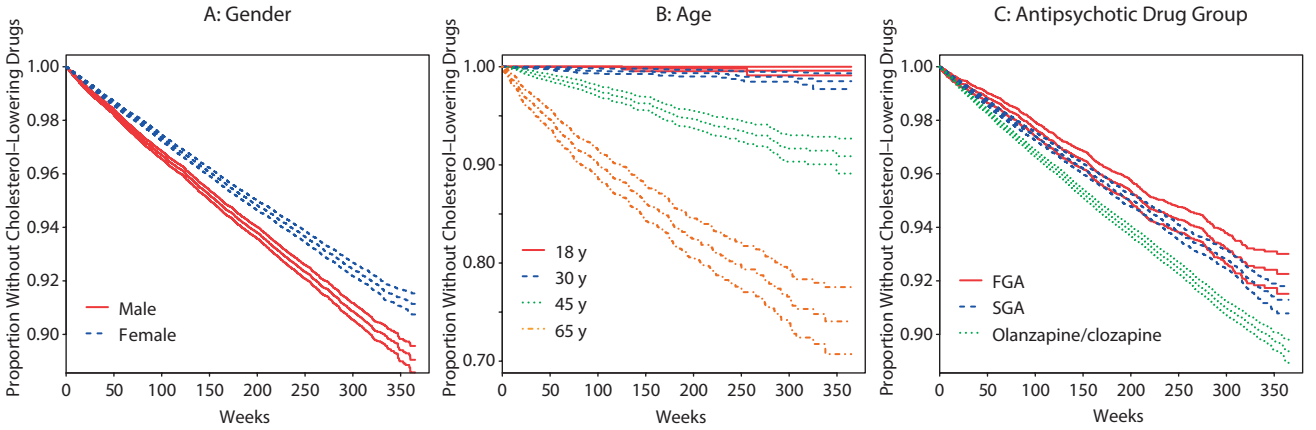
Abbreviation: ATC = Anatomical Therapeutic Chemical.

Table 2. Baseline Characteristics of Incident Antipsychotic Users (n = 147,218) Who Did or Did Not Fill a Prescription for a Cholesterol-Lowering Drug in the Follow-Up Period

	Patients Not Filling a Prescription for a Cholesterol-Lowering Drug (n = 139,386)		Patients Filling a Prescription for a Cholesterol-Lowering Drug (n = 7,832)	
Variable	n	%	n	%
Gender				
Male	62,119	44.6	3,854	49.2
Female	77,267	55.4	3,978	50.8
First prescription				
Typical antipsychotic	78,061	56.0	5,078	64.8
Atypical antipsychotic	48,004	34.4	2,127	27.2
Olanzapine or clozapine	13,321	9.6	627	8.0
No. of antipsychotic drug groups				
1	121,224	87.0	6,918	88.3
2	15,710	11.3	802	10.3
3	2,452	1.7	112	1.4
Amount in defined daily dose[a]				
< 10	79,538	57.1	4,356	55.6
10–100	38,588	27.7	2,336	29.8
100–1,000	17,352	12.4	984	12.6
> 1,000	3,908	2.8	156	2.0

[a]Defined daily dose, as defined by the World Health Organization, is "the assumed average maintenance dose per day for a drug used for its main indication in adults."[37]

Figure 2. Kaplan-Meier Plots of the Explanatory Variables Gender, Age, and First Antipsychotic Drug Group



Abbreviations: FGA = first-generation antipsychotic, SGA = second-generation antipsychotic.

Table 3. Survival Analysis: Cox Proportional Hazards Regression Models for the Risk of Redeeming a Prescription for a Cholesterol-Lowering Drug

Model	Explanatory Variables[a]	Cox Model Hazard Ratio (95% CI)	*P* Value
1	First drug group		
	Atypical	0.8093 (0.7693–0.8513)	<.001
	Olanzapine or clozapine	0.7447 (0.6855–0.8092)	<.001
2	Gender	0.762 (0.7289–0.7967)	<.001
	First drug group		
	Atypical	1.100 (1.0451–1.1577)	<.001
	Olanzapine or clozapine	1.136 (1.0451–1.2354)	.003
	Age	1.080 (1.0775–1.0819)	<.001
3	Gender	0.7652 (0.7319–0.8001)	<.001
	First drug group		
	Atypical	1.0538 (1.0005–1.1100)	.048
	Olanzapine or clozapine	0.9540 (0.8724–1.0433)	.303
	Defined daily dose[b]	1.0001 (1.0001–1.0002)	<.001
	No. of antipsychotic drug groups		
	2	3.6580 (2.7086–4.9403)	<.001
	3	4.1278 (2.0637–8.2563)	<.001
	Age	1.0835 (1.0811–1.0859)	<.001
	Age: no. of antipsychotic drug groups		
	2	0.9825 (0.9768–0.9883)	<.001
	3	0.9818 (0.9679–0.9959)	.011

[a]Reference levels: first drug typical antipsychotic, gender male, only redeemed within 1 of the drug groups. Age and defined daily dose are continuous variables, defined daily dose and the number of antipsychotic drug groups are time-varying variables.
[b]Defined daily dose, as defined by the World Health Organization, is "the assumed average maintenance dose per day for a drug used for its main indication in adults."[37]

5.3% in a cohort receiving antipsychotic agents could benefit from treatment with statins.

We used 3 different approaches to estimate the effect of the antipsychotic group first prescribed on the risk of being prescribed a statin, revealing that the impact of antipsychotic class was low. In order to examine whether the slight increase in incidence of cholesterol-lowering prescriptions in the SGA and clozapine/olanzapine groups was dose-related, we adjusted for the amount of prescribed drug (defined daily dose) in addition to gender and age. Indeed, high doses of antipsychotic seemed to increase the likelihood of statin prescription. Furthermore, we found that the likelihood of being prescribed a statin was increased 4-fold in patients redeeming antipsychotic agents from all 3 antipsychotic groups included. A former, relatively small study[42] examining prescription redemptions and biochemical diagnosis also failed to demonstrate differential influence of antipsychotic class on redemption of lipid-lowering drugs, but we are not aware of former studies on the impact of the number or dose of different antipsychotics on statin prescription rates.

In light of the recognized propensity for SGAs, in particular clozapine and olanzapine, to induce dyslipidemia, the small differences between antipsychotic groups may seem surprising. One important reason may be the low overall prescription rate of clozapine and olanzapine in the study population (9.5%). In addition, antipsychotics with intermediate risk for metabolic adverse effects (such as risperidone and quetiapine) included in the SGA group may have masked clozapine/olanzapine effects in our multivariate model. Possibly, overadjustment for antipsychotic dose could also contribute to masked differences in statin prescription among the different antipsychotic groups.

Several limitations to the study deserve mentioning. First, the a priori grouping of atypical agents into FGAs, SGAs, and clozapine/olanzapine most likely influenced our results. Several authors have argued against the conventional FGA/SGA grouping.[15,43] However, as well as facilitating comparison with other studies, our grouping largely follows risk profile, with the FGA group consisting mostly of low-risk agents, the SGA group containing mostly intermediate-risk agents, and the clozapine and olanzapine group containing the most metabolically potent agents.[33] Second, selecting statin prescription as an outcome will fail to identify patients receiving other lipid-lowering agents, such as fibrates and drug combinations, ie, ezetimib + simvastatin (Anatomical Therapeutic Chemical classification code C10B A02). According to the NorPD database, however, general prescription rates of such drugs were very low in Norway during the study period. A third weakness of the study is the lack of access to data regarding serum lipid levels and lifestyle issues of patients. The actual prevalence of dyslipidemia in the patients would provide a more refined indicator of statin requirement than the prevalence data mentioned above.

In summary, our findings indicate that differences in prescription rates for adjuvant cholesterol-lowering agents in patients treated with SGAs, including clozapine and olanzapine, and FGAs, are not as large as would be expected based on the high prevalence of dyslipidemia described in patients treated with SGAs. Importantly, our data support previous reports that, in spite of published recommendations for systematic monitoring for dyslipidemic and diabetogenic effects of antipsychotic agents, such adverse effects are frequently undertreated.[31,32,44–46] Issues such as patient compliance and prejudice and lack of awareness among health care providers, in addition to separation of somatic and mental health care systems, most likely contribute to neglect of somatic health in patients diagnosed with serious mental disorders.[7,9,32,47,48] Future studies should combine data regarding prescription rates and the prevalence of dyslipidemia in naturalistic settings. Such data could contribute to improved general care for a vulnerable patient group.

Drug names: aripiprazole (Abilify), atorvastatin (Lipitor and others), clozapine (Clozaril, FazaClo, and others), droperidol (Inapsine and others), fluvastatin (Lescol and others), ezetimib (Liptruzet, Zetia), haloperidol (Haldol and others), lovastatin (Altoprev and others), olanzapine (Zyprexa and others), pimozide (Orap), pravastatin (Pravachol and others), prochlorperazine (Compro and others), quetiapine (Seroquel and others), risperidone (Risperdal and others), rosuvastatin (Crestor), simvastatin (Simcor, and others), ziprasidone (Geodon and others).

Author affiliations: Dr Einar Martens Research Group for Biological Psychiatry, Center for Medical Genetics and Molecular Medicine, Haukeland University Hospital, Bergen; The Norwegian Centre for Mental Disorders Research (NORMENT) and the K.G. Jebsen Centre for Psychosis Research, Department of Clinical Science, University of Bergen (Drs Skrede and Steen); The Norwegian Computing Center (Dr Tvete); Norwegian Center for Addiction Research, University of Oslo (Drs Tanum and Bramness); Diakonhjemmet Hospital, Centre for Psychopharmacology (Dr Bramness),

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Role of the sponsors: The sponsors did not influence collection, interpretation, or reporting of the results.
Additional information: Access to the Norwegian prescription database (NorPD) can be obtained by applying to the NorPD at http://www.norpd.no.

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