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Valproate is associated with early decrease of high-density lipoprotein cholesterol levels in the psychiatric population

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ABSTRACT

Few studies have evaluated the influence of valproate on the deterioration of the lipid profile in psychiatric patients.

This observational study aimed to compare the evolution of metabolic parameters in a sample of adult patients starting valproate (n=39) with a control group (n=39) of patients starting aripiprazole, a drug associated with a low risk of metabolic deterioration.

Data were obtained from a prospective study including psychiatric patients with metabolic parameters monitored during the first year of treatment. During the first month of treatment with valproate (median: 31 days (IQR: 25-36)), mean body mass index increased significantly (from 24.8 kg/m^2 at baseline to 25.2 kg/m^2 after one month; p=0.03) and mean HDL-C levels decreased significantly (from 1.39 mmol/l to 1.27 mmol/l; p=0.02). In comparison, these metabolic variables remained stable during the first month of treatment with aripiprazole. The proportion of patients with early (i.e. during the first month of treatment) HDL-C decrease of ≥5% was significantly higher under valproate (54%) than aripiprazole (15%) treatment (p<0.001).

These findings remind the importance of a prospective metabolic monitoring in patients who initiate valproate treatment. Further research should be conducted on larger samples and should focus on finding effective interventions to prevent such metabolic adverse effects.

INTRODUCTION

Individuals with severe mental illness such as schizophrenia, bipolar and major depressive disorders have a reduced life expectancy of 10-15 years compared to subjects from the general population [1,2]. Most of this premature mortality has been attributed to cardiovascular-related diseases. Some risk factors implying complex mechanisms may explain this excess cardiovascular risk, including psychiatric disease-related factors, unhealthy lifestyle and adverse effects of treatment [3]. 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 [4].

Components of the metabolic syndrome may develop early during psychotropic treatment and may initiate a steady process leading to cardiometabolic diseases in the longer-term, underlining the importance to monitor metabolic parameters prospectively [5]. A recent longitudinal study conducted in 181 patients showed that lipid increases during the first month of treatment (i.e. for total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglycerides (TG) or non-high-density lipoprotein cholesterol (non-HDL-C)) by ≥5% and early decrease of high-density lipoprotein cholesterol (HDL-C) by ≥5% were the best predictors for subsequent important worsening of the lipid profile in the longer term of psychotropic treatment [6]. Interestingly, univariable analyses in the latter study showed that most patients taking valproate (i.e. 87.5%) had a decrease of HDL-C by ≥5% during the first month of treatment. However, due to the low number of patients receiving valproate (n=8), further analyses could not be performed. Although many studies investigated the influence of this anticonvulsant on worsening of the lipid profile in the last twenty years,

most of them were case-control studies (i.e. their design was not longitudinal) and/or did not include adult patients [7-9]. To the best of our knowledge, only two longitudinal studies in adult patients examined the influence of valproate on worsening of lipid parameters. In the first study including 34 epileptic women, valproate was associated with a worsening of lipid parameters after one year of treatment in individuals whose body mass index (BMI) was higher than 23 kg/m^2 at baseline [10], while in the second study including 73 bipolar patients, no deterioration of HDL-C levels was observed during treatment with valproate after 12 weeks of treatment [11]. Because of these discrepant results, we aimed to evaluate early deterioration of metabolic parameters (especially HDL-C levels) in a longitudinal observational psychiatric sample of adult patients taking valproate, in comparison with a control group of patients taking a psychotropic drug associated with a low risk to induce metabolic disturbances (i.e. aripiprazole [4,12,13]), an antipsychotic drug also used for the treatment of mania in bipolar disorders.

MATERIAL AND 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 known to have a potential to induce metabolic disturbances (i.e. antipsychotics, mood stabilizers and some antidepressants, as listed in **S1 Table**) were included. Monitoring of physical health risk factors during treatment includes prospective assessments of BMI, waist circumference, fasting glucose, lipid profile, blood pressure and tobacco smoking [14]. The present study included patients with informed consent from an ongoing study (PsyMetab) as described elsewhere [15]. In addition, data of patients in the clinical follow-up (PsyClin) were obtained in the hospital or in outpatients centers during medical examinations based on the departmental guideline for metabolic follow-up performed on a routine basis [5]. Both studies were approved by the ethics committee of the Lausanne University Hospital. Patients with available lipid levels at least at baseline (i.e. before starting valproate or aripiprazole) and after the first month of treatment (≥15 and ≤45 days of treatment) with no lipid-lowering treatment were included in the present study, as described in **S1 Figure**. Of note, in order to consider the best control group as possible in terms of aripiprazole influence on metabolic variables, patients with a long duration of psychiatric illness (and of psychotropic treatments including metabolic disturbances) were excluded from the control group (n=39). Low HDL-C, high LDL-C, high TG and high TC levels were defined by HDL hypocholesterolemia (≤ 1 mmol/l; ≤ 39 mg/dL), LDL hypercholesterolemia (≥3 mmol/l; ≥ 116 mg/dL), hypertriglyceridemia (≥2 mmol/l; ≥ 177 mg/dL) and hypercholesterolemia (≥ 5 mmol/l; ≥ 193 mg/dL), respectively, and/or by the prescription of a lipid-lowering drug (**S2 Table**), according to European

Society of Hypertension and of the European Society of Cardiology (ESH/ESC) guidelines [16].

Statistical analyses

Univariable analyses

For the comparison of metabolic variables between baseline and the first month of treatment, univariable analyses were conducted using McNemar tests for categorical variables. Paired t-tests were conducted for comparing continuous metabolic variables between baseline and the first month of treatment because their differences were normally distributed.

For the comparison of categorical and continuous (right-skewed distributed) metabolic variables across valproate and aripiprazole treatments, chi-squared and Wilcoxon ranksum tests were used, respectively.

Multivariable analyses

Linear models on percentage changes of metabolic outcomes during the first month of treatment with valproate or aripiprazole, adjusted for age, sex, smoking status and the baseline values of the corresponding metabolic outcome were conducted using the nlme package of R. Percentage changes of metabolic variables during the first month of valproate treatment were calculated as follow: (Metabolic variable at first month – metabolic variable at baseline)/ metabolic variable at baseline. Graphical diagnostics for fit adequacy and the gvlma package of R were used to perform validation of the linear models.

The nlme package of R was also used to fit a linear mixed effect model on HDL-C levels and BMI outcomes, adjusting for age, sex, smoking status, BMI (whenever

applicable), treatment duration and baseline value of the corresponding outcome. The fitted linear mixed effect model had a random effect at the subject level.

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

Demographic and clinical characteristics of the psychiatric sample

Demographic and clinical characteristics of the psychiatric sample are shown in **Table 1**. Thirty-nine patients receiving valproate and thirty-nine patients receiving aripiprazole (as a control group) were included. Among patients taking valproate, most patients were women (59%), median age was 42 years (interquartile range (IQR): 33-55), bipolar disorders (F30-F31.9) were the most frequent diagnosis (33%) and more than half of the patients smoked (54%). Patients included in the control group (i.e. taking aripiprazole) were less frequently suffering from bipolar disorders (8% versus 33%, p=0.005) and more frequently suffering from depressive disorders (15% versus 2.5%, p=0.048) and had a lower number of hospitalization (median (IQR): 1 (0.5-1) versus 3 (2-20); p=0.004), and a shorter duration of psychiatric illness (median (IQR): 1 (0-2) versus 9 (5.5-15.5) years; p=0.003), as compared to patients taking valproate.

Deterioration of metabolic parameters during treatment with valproate

Table 2 shows that during the first month of treatment with valproate, (35 days (IQR: 25-45)), mean BMI significantly increased (from 24.8 kg/m^2 at baseline to 25.2 kg/m^2 after one month; p=0.03) and mean levels of HDL-C significantly decreased (from 1.39 mmol/l at baseline to 1.27 mmol/l after one month; p=0.02), while no significant modification of these metabolic variables was observed during the first month of treatment with aripiprazole. Of note, no significant deterioration was observed for other metabolic variables (i.e. TC, LDL-C, non-HDL-C and fasting TG) during the first month of valproate or aripiprazole treatment. The proportion of patients with early deterioration of HDL-C levels (i.e. HDL-C decrease ≥5% after one month of treatment) was significantly higher in patients who started valproate as compared to patients who started aripiprazole (54% versus 15%, respectively, p<0.001). In addition, early

change of HDL-C (calculated as the difference of HDL-C levels during the first month divided by HDL-C levels at baseline) was significantly different across the two treatments (p=0.004). **Figure 1** illustrates the comparison of HDL-C change over the first month of aripiprazole or valproate. Among patients starting valproate, eighteen patients (46%) and 6 patients (15%) received one or two concomitant psychotropic drugs that may induce metabolic disturbances, respectively (as listed in **S1 Table**), whereas 15 patients (38%) received valproate as the only agent known to have a risk on metabolic parameters and 16 patients (41%) received at least another psychotropic drug inducing metabolic disturbances (**Table 1**). In comparison, patients starting aripiprazole started more frequently this treatment in monotherapy (72% versus 38%; p=0.003) and received less frequently one or two concomitant psychotropic drugs (26% versus 46%, p=0.02 and 2.5% versus 15%, p=0.048, respectively) or another psychotropic drug inducing lipid disturbances (13% versus 41%, p=0.005). Of note, among patients who started valproate treatment as the only agent known to have a risk on metabolic parameters (n=15), 6 (40%) had an early deterioration of HDL-C levels, which was higher (trend) than in patients taking aripiprazole (6/39=15%; p=0.051) (**Table 2**). It should be mentioned that in patients starting aripiprazole, mean BMI was significantly higher at baseline (28.1 kg/m^2) and after one month of treatment (28.1 kg/m^2) than in patients starting valproate (24.8 kg/m^2 at baseline; p=0.02 and 25.2 kg/m^2 after one month; p=0.03). This could tentatively be explained by the fact that the prescription of aripiprazole is favored in patients suffering from metabolic diseases.

Clinical moderators of metabolic worsening during treatment with valproate

Multivariable analyses allowed determining some associations between clinical factors and worsening of metabolic parameters during the first month of treatment with

valproate (**S3 Table**). Baseline HDL-C levels were negatively associated with the evolution of HDL-C (in %), with each additional unit of baseline HDL-C increasing the HDL-C decrease during the first month of treatment by 27.3% (p=0.002; **S2 Figure**). However, no other clinical variable was associated with the percentage of BMI change during the first month of treatment with valproate. Analyses considering raw values of HDL-C and of BMI during the first year of treatment were consistent with these findings (**S4 Table**; **S3 Figure**). In addition, men had lower HDL-C levels than women over the course of valproate treatment (p=0.02; **S4 Table**). **Figures 2a** and **2b** show the evolution of HDL-C levels, stratified by gender, in patients taking valproate or aripiprazole.

DISCUSSION

In the present longitudinal study, early metabolic worsening (i.e. decrease of HDL-C levels and increase in BMI) was observed during treatment with valproate, but not aripiprazole.

These findings are not fully consistent with the two previous longitudinal studies on adults treated with valproate. Thus, the first study found a worsening of lipid parameters after one year of treatment in Indian epileptic women whose BMI was higher than 23 kg/m^2 [10], whereas the second did not show any deterioration of HDL-C deterioration after 12 weeks of treatment in Asian bipolar patients [11]. These contrasting results can possibly be explained by differences in ethnicity (our study included mostly Caucasian patients (i.e. 89% of patients with available ethnicity data)). Indeed, ethnicity has been identified as a strong predictor of blood lipid levels in a recent study [17].

Multiple factors including illness characteristics and treatment-related factors influence the risk of psychotropic drugs to induce metabolic deterioration. Thus, drug naïve and/or first-episode patients are more prone to develop metabolic deterioration as compared to patients with a long treatment and/or illness history [18,19]. In the present study, early metabolic deterioration was observed in patients starting valproate even if they had a longer history of psychiatric illness and of psychotropic drugs than patients starting aripiprazole, which emphasizes the influence of valproate on the deterioration of metabolic factors (i.e. BMI and HDL-C levels).

In the present study, patients starting aripiprazole had no early metabolic worsening, which is in agreement with a previously published review [3]. Elevated values of BMI were already observed before starting aripiprazole, possibly explained by multiple causes, including personal factors. Considering that this control group included

patients with a short psychiatric illness duration with a low prevalence of co-prescription of psychotropic drugs inducing metabolic disturbances, it seems unlikely that the observed elevated BMI values at baseline exclusively resulted from past psychotropic treatments. On the other hand, the over-representation of overweight patients in this control group may be explained by the fact that having a low propensity to induce metabolic deterioration, aripiprazole is often prescribed in patients who already suffer from metabolic disturbances [13]. Of note, because a previous meta-analysis reported that the prevalence of metabolic syndrome is comparable across psychiatric diagnosis groups [20], the observed diagnosis differences between patients starting valproate and aripiprazole may not fully explain the observed difference in baseline BMI. It is noteworthy that values of lipid levels at baseline were not statistically different between patients who started valproate or aripiprazole treatment. A considerable drop-out rate was observed during the present metabolic follow-up, reducing the number of available observations by 50% and 75% after three and twelve months of treatment, respectively, possibly due to multiple factors such as the diagnosis, treatment switching, the refusal of outpatients to be followed-up and/or poor medication adherence. Because the drop-out rate in patients taking aripiprazole (43% after 3 months and 78% after one year) was comparable, we can suggest that it may result from other than side effect-related factors. The present considerable drop-out rate decreased the power to detect any metabolic difference in the longer-term of treatment. Of note, because of the observational setting of the study, no power calculation was performed. However, previous studies conducted in similar settings observed that early (i.e. during the first month) modifications of metabolic parameters (e.g. lipid levels [6] or BMI [21]) could predict important metabolic deterioration in the longer-term of treatment. Therefore, the observed considerable prevalence of patients

with early HDL-C decrease higher or equal to 5% during the first month of treatment suggests that a significant proportion of patients under valproate treatment may develop clinically important metabolic deterioration in the longer-term of valproate treatment. Further longitudinal studies including a higher number of observations would help to characterize the evolution of HDL-C levels over longer periods of valproate treatment, as well as to specifically include patients under valproate treatment as the only agent known to have a risk on metabolic parameters. Thus, alterations in metabolic parameters could result from the combination of valproate with other co-prescribed psychotropic drugs inducing metabolic disturbances (such as antipsychotics, mood stabilizers (e.g. lithium), or antidepressants (e.g. mirtazapine) [4]. In the present study, although statistical tests could not be performed because of the small number of patients starting valproate as a monotherapy, the proportion of patients with early decrease of HDL-C levels among this patients was considerable (40%, data not shown). In addition, although 61.5% (24/39) patients who started valproate received another psychotropic drug that may induce metabolic disturbance as a comedication, this comedication was in most of the cases already prescribed before starting valproate treatment. This underlines that metabolic deterioration observed during the first month of valproate treatment is relatively specific to the influence of valproate.

During the first month of treatment with valproate in monotherapy (median of 35 days; IQR: 25-45 days), levels of HDL-C decreased by 0.17 mmol/l (i.e. from 1.39 to 1.27 mmol/l, corresponding to a 9 % decrease). This HDL-C decrease associated with valproate appeared to be as important as alterations of HDL-C observed in patients being prescribed atypical antipsychotics associated with an important risk of developing dyslipidemia (e.g. olanzapine and quetiapine). Thus, previous studies on

the deterioration of metabolic parameters in patients receiving olanzapine or quetiapine in monotherapy reported HDL-C decrease of 0.07 mmol/l after 6 weeks [22] or 0.2 mmol/l after 8 weeks [23] for olanzapine and of 0.01 mmol/l after 8 weeks [24] or 0.03 mmol/l after 8 weeks [25] for quetiapine. Of note, in the present study, valproate combined with high-risk drugs for lipid level worsening (including mainly second-generation antipsychotics) did not induce a significantly stronger worsening of HDL-C during the first month of treatment as compared to valproate in monotherapy. Low levels of HDL-C have been related with increased cardiovascular disease morbidity and mortality [26], with each additional 1% decrease in HDL-C levels increasing the risk by 2-3 percent to develop cardiovascular disease [27]. Thus, the present HDL-C decrease during the first month of treatment with valproate appears clinically relevant and underlines the importance of monitoring the lipid profile when initiating this medication.

To date, even if exact mechanisms underlying metabolic side effects associated with valproate are poorly understood, possible molecular mechanisms of weight gain associated with valproate were proposed. Valproate was reported to induce an increased GABA stimulation of the hypothalamus as well as increased levels of insulin and leptin leading to insulin- and leptin-resistance [10]. Besides, the valproate-induced regulation of β-oxidation of free fatty acids would be one possible mechanism to explain the influence of this mood stabilizer on HDL-C levels [28].

The results of the present observational study should be considered with the following limitations. First, the majority of patients were not drug naïve, and the observed metabolic condition at baseline may have resulted from past treatments. However, such patients represent the majority of psychiatric populations. Second, environmental changes such as physical exercise or diet habits throughout the treatment, which

would have influenced the evolution of metabolic parameters, were not available and their effects were not taken into account. Third, the number of patients taking valproate in monotherapy was insufficient to perform multivariate analyses in this subgroup of patients. Fourth, a sample including a higher number of patients would enable to have more power. In addition, additional observations in the longer-term would allow to evaluate the evolution of lipid parameters in a longer period of treatment and to confirm the present findings. Strengths of the present study included its naturalistic and longitudinal design.

CONCLUSION

In conclusion, this study reminds the importance of monitoring metabolic parameters including the lipid profile following the introduction of valproate. Further research should be conducted on larger samples and should focus on finding effective interventions to prevent such metabolic adverse effects. In case of metabolic disturbance, if clinically possible, this mood stabilizer and/or antiepileptic drug should be replaced after a careful evaluation of the risk-benefit ratio of a drug switch. Considering the major consequences of dyslipidemia on morbidity and mortality, it is critical that healthcare professionals be aware of the risks associated with the prescription of valproate.

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ETHICS STATEMENT

This study was carried out in accordance with the Declaration of Helsinki, the good epidemiological practice written by the Swiss Society of public health, the Swiss law, and local requirements. The study protocol was approved by the Ethic committee of Vaud (CER-VD) with written informed consent from all subjects.

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AUTHOR DISCLOSURE INFORMATION

Dr CBE received honoraria for conferences or teaching CME courses from Janssen-Cilag, Lundbeck, Otsuka, Sandoz, Servier, Sunovion, Vifor-Pharma, and Zeller in the past 3 years. All authors declare no conflict of interest in relation to the content of the paper.

Table 1. Clinical characteristics of patients starting valproate or aripiprazole

Clinical characteristics	Valproate		Aripiprazole		
	N		N		p-value*
Age, median (IQR), years	39	42 (33-55)	39	36 (28-53)	0.21
Men, n(%)	39	20 (51.3)	39	17 (43.6)	0.49
Smoking, n(%)	39	21 (53.9)	39	19 (48.7)	0.21
Diagnosis, n(%)	39		39		
Psychotic disorders		3 (7.7)		9 (23.1)	0.06
Schizoaffective disorders		7 (18.0)		4 (10.3)	0.33
Bipolar disorders		13 (33.3)		3 (7.7)	**0.005**
Depressive disorders		1 (2.5)		6 (15.4)	**0.048**
Organic disorders		1 (2.5)		0 (0)	0.31
Other		3 (7.7)		4 (10.3)	0.69
Not available		11 (28.2)		13 (33.3)	0.62
Number of hospitalization, median (IQR)	9	3 (2-20)	8	1 (0.5-1)	**0.004**
Psychiatric illness duration, median (IQR), years	12	9 (5.5-15.5)	7	1 (0-2)	**0.003**
Information on psychotropic treatment					
Treatment in monotherapy, n(%)		15 (38.4)		28 (71.8)	**0.003**
Treatment combined with another psychotropic drug[1]		18 (46.1)		10 (25.6)	**0.02**
Treatment combined with two other psychotropic drugs[2]		6 (15.4)		1 (2.5)	**0.048**
Treatment combined with at least one psychotropic drug inducing lipid disturbances[3]		16 (41.0)		5 (12.8)	**0.005**

Only patients without any lipid-lowering medication are included. Values in bold are significant.

1. Includes antipsychotics, lithium or mirtazapine. In the present sample, agent co-prescribed with valproate included aripiprazole, haloperidol, mirtazapine, olanzapine or quetiapine.

2. Includes antipsychotics, lithium or mirtazapine. In the present sample, agents co-prescribed with valproate included amisulpride, asenapine, haloperidol, lithium, mirtazapine, quetiapine, risperidone and/or zuclopenthixol.

3. Includes clozapine, mirtazapine, olanzapine and/or quetiapine. In the present sample, no patient starting valproate received two co-prescribed agents inducing lipid disturbances, while 2 patients starting aripiprazole received two co-prescribed agents inducing lipid disturbances.

*P values were calculated using Wilcoxon rank-sum tests for continuous variables and chi-squared tests for categorical variables.

Table 2. Evolution of metabolic parameters in patients starting valproate or aripiprazole

	Metabolic parameters	V/A	N	Baseline	N	After 1 month [1]	p-value*	N	After 3 months [2]	p-value*	N	After 12 months [3]	p-value*
BMI	**BMI (kg/m²), mean (sd)**	V	35	24.8 (4.9)	35	25.2 (5.0)	**0.03**	22	26.75 (4.9)	**0.02**	10	26.0 (4.47)	0.7
		A	34	28.1 (5.6)	34	28.1 (5.4)	0.65	14	29.8 (5.7)	0.06	3	32.6 (2.85)	0.13
	p-value*			**0.02**		**0.03**							
	Early BMI change (%), mean (sd)	V	35			1.76 (4.50)							
		A	34			-0.01 (2.83)							
	p-value*					0.12							
	Early BMI increase (≥ 5%), n(%)	V	35			5 (14.3)							
		A	34			3 (8.8)							
	p-value*					0.48							
HDL-C	**HDL-C (mmol/l), mean (sd)**	V	39	1.39 (0.37)	39	1.27 (0.33)	**0.02**	24	1.32 (0.32)	0.53	9	1.48 (0.41)	0.79
		A	39	1.25 (0.43)	39	1.30 (0.40)	0.06	15	1.37 (0.31)	0.36	4	1.22 (0.10)	0.22
	p-value*			0.11		0.59							
	Early HDL-C change (%), mean (sd)	V	39			-5.67 (20.5)							
		A	39			6.79 (19.3)							
						0.004							
	Early HDL-C decrease (≥ 5%), n(%)	V	39			21 (53.9) **							
		A	39			6 (15.4)							
	p-value*					**<0.001**							
TC	**Total cholesterol (mmol/l), mean (sd)**	V	39	4.71 (0.94)	39	4.58 (0.94)	0.21	24	4.81 (0.90)	0.8	9	4.77 (1.04)	0.97
		A	38	4.82 (1.09)	38	4.70 (0.97)	0.25	15	5.03 (1.22)	0.56	4	5.36 (1.28)	0.58
	p-value*			0.49		0.48							
	Early TC change (%), mean (sd)	V	39			-2.01 (14.3)							
		A	38			-0.88 (13.7)							
						0.66							
	Early TC increase (≥ 5%), n(%)	V	39			12 (30.8)							
		A	38			12 (31.6)							
	p-value*					0.94							
LDL-C	**LDL-C (mmol/l), mean (sd)**	V	37	2.65 (0.82)	37	2.62 (0.77)	0.77	23	2.74 (0.74)	0.52	9	2.64 (0.89)	0.77
		A	36	2.89 (0.99)	36	2.76 (1.01)	0.22	15	3.10 (1.12)	0.51	4	3.56 (1.11)	0.27
	p-value*			0.2		0.52							
	Early LDL-C change (%), mean (sd)	V	37			1.81 (26.4)							
		A	36			-2.96 (19.8)							
						0.53							
	Early LDL-C increase (≥ 5%), n(%)	V	37			12 (32.4)							
		A	36			13 (36.1)							
	p-value*					0.74							
TG	**TG (mmol/l), mean (sd)**	V	27	1.44 (1.01)	27	1.21 (0.62)	0.24	16	1.61 (0.63)	0.93	7	1.24 (0.30)	0.78
		A	30	1.62 (0.99)	30	1.37 (0.71)	0.07	12	1.25 (0.47)	0.46	3	1.17 (0.25)	0.08
	p-value*			0.33		0.56							
	Early TG change (%), mean (sd)	V	27			1.33 (46.1)							
		A	30			-5.4 (38.7)							
						0.52							
	Early TG increase (≥ 5%), n(%)	V	27			12 (44.4)							
		A	30			10 (33.3)							
	p-value*					0.39							
Non-HDL-C	**NonHDL-C (mmol/l), mean (sd)**	V	39	3.32 (1.03)	39	3.3 (0.99)	0.82	24	3.49 (0.97)	0.98	9	3.29 (0.67)	0.92
		A	38	3.57 (1.06)	38	3.40 (1.01)	0.09	15	3.66 (1.19)	0.67	4	4.14 (1.22)	0.68
	p-value*			0.25		0.55							
	Early nonHDL-C change (%), mean (sd)	V	39			2.16 (25.1)							
		A	38			-2.89 (16.1)							
						0.45							
	Early nonHDL-C increase (≥ 5%), n(%)	V	39			15 (38.4)							
		A	38			13 (34.2)							
	p-value*					0.7							

Only patients without any lipid-lowering medication are included. Values in bold are significant. V: valproate. A: aripiprazole.
Early change of metabolic variables were calculated as (((metabolic variable after the first month of treatment-metabolic variable at baseline)/metabolic variable at baseline)*100).
1. Includes observations collected between 15 and 45 days of valproate treatment.
2. Includes observations collected between 46 and 135 days of valproate treatment.
3. Includes observations collected between 136 and 535 days of valproate treatment.

*P values were calculated using Wilcoxon rank-sum tests for continuous variables and chi-squared tests for categorical variables.

** Of note, among patients who started valproate treatment as the only agent known to have a risk on metabolic parameters (n=15), 6 (40%) had an early HDL-C decrease ≥5%, which is higher (trend) than in patients taking aripiprazole (6/39=15%; p=0.051).

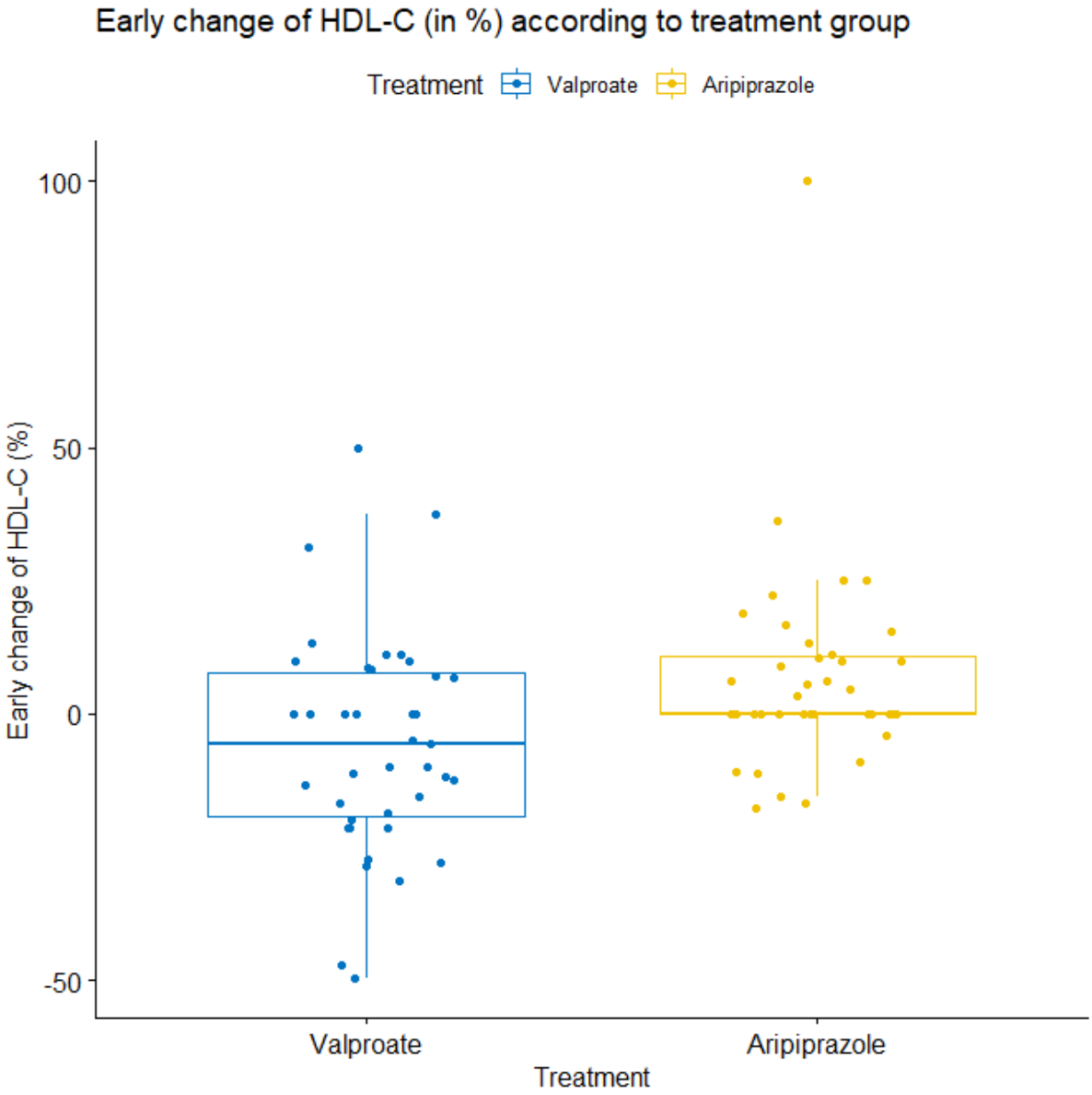

Figure 1. Early change of HDL-C (in %) according to treatment group

Boxplots indicate median and interquartile range values of early change of HDL-C levels (in %). Each point represents a single patient. Early change of HDL-C was calculated as ((HDL-C levels after the first month of treatment - HDL-C levels at baseline) / HDL-C levels at baseline)*100.

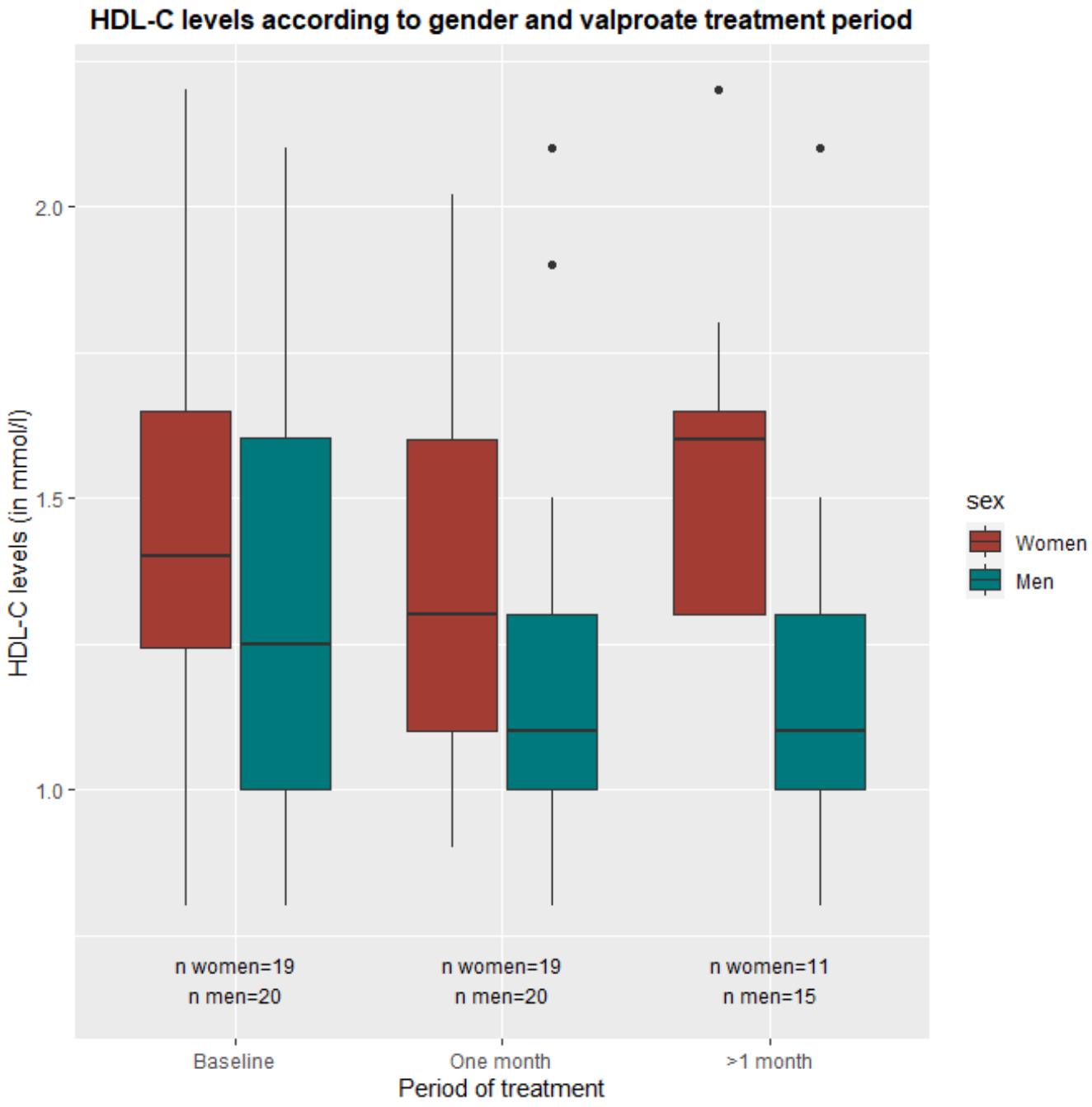
HDL-C levels according to gender and valproate treatment period
HDL-C levels (in mmol/l)
2.0
1.5
1.0
n women=19
n men=20
n women=19
n men=20
n women=11
n men=15
Baseline
One month
>1 month
Period of treatment
sex
Women
Men

Figure 2a

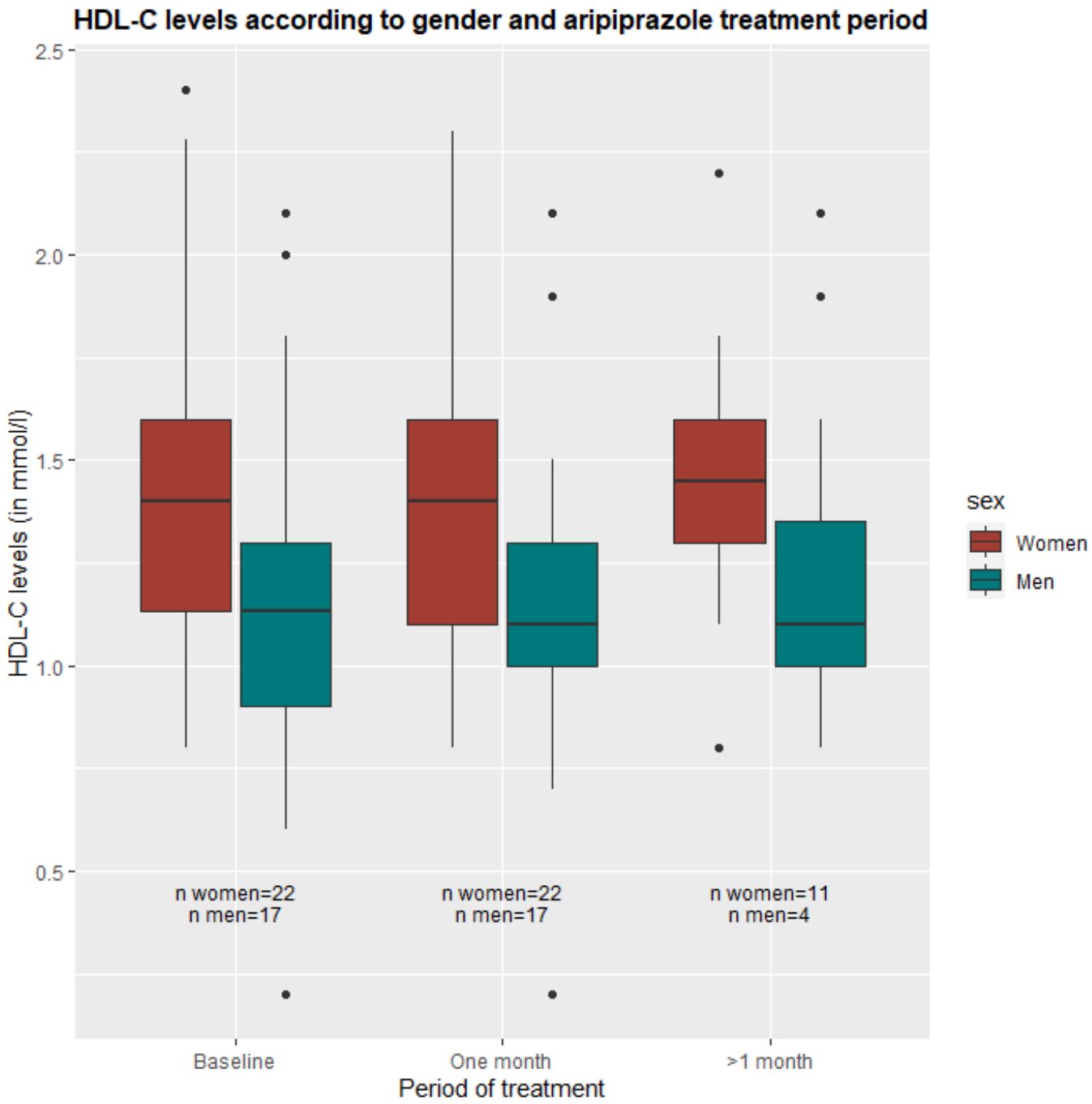
HDL-C levels according to gender and aripiprazole treatment period
HDL-C levels (in mmol/l)
2.5
2.0
1.5
1.0
0.5
n women=22
n men=17
n women=22
n men=17
n women=11
n men=4
Baseline
One month
>1 month
Period of treatment
sex
Women
Men

Figure 2b

Figure 2. HDL-C levels according to gender and the period of valproate (Figure 2a) or aripiprazole (Figure 2b) treatment.

Boxplots indicate median and interquartile range values of HDL-C levels. Number of patients are indicated in each period of valproate or aripiprazole treatment. >1 month indicates treatment duration above 1 month (i.e. from 46 days of treatment; median of treatment duration = 104 days (IQR: 88-132 days). If multiple observations were available for the same patient in the treatment period of >1 month, only one observation (i.e. the closest to the first month) was considered.

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