Associations of Valproate Doses With Weight Gain in Adult Psychiatric Patients:

A 1-Year Prospective Cohort Study

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Abstract

Objective: The aim of this study was to evaluate valproate dose association with weight change, blood glucose, lipid levels, and blood pressure in a psychiatric population.

Methods: Data from 215 patients taking valproate for up to 1 year were collected from 2 longitudinal studies that monitored metabolic variables between 2007 and 2022. Linear mixed-effect models and logistic regressions were used to analyze the associations between valproate doses and metabolic outcomes.

Results: An increase in valproate dose of 500 mg was associated with a weight change of +0.52% per month over a year ($P<.001$). The association between valproate dose and weight change was evident both before and after 3 months of treatment. Weight increase was greater for treatment durations of <3 months compared to ≥3 months (+0.56%, $P<.001$ and +0.12%, $P=.02$ per month, respectively). Using piecewise regression, a significant association between dose and weight gain was observed in patients receiving doses equal to or above the median dose (1,300 mg/d), with a +0.50% increase in weight for each dose increment of 500 mg ($P=.004$). Among men, each 500 mg dose increment was associated with weight increases of +0.59% per month ($P=.004$), whereas a trend was observed for women (+0.40%, $P=.09$). No associations were found between valproate doses and blood glucose, lipid levels, or blood pressure over a 6-month treatment period.

Conclusions: This study provides evidence that valproate dose, mainly for doses at or above 1,300 mg/d, is associated with weight gain in psychiatric patients, suggesting that the lowest effective doses should be prescribed to minimize weight gain.

J Clin Psychiatry 2024;85(2):23m15008

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Valproate (VPA) is an antiepileptic agent prescribed for seizures, migraines, bipolar disorder characterized by mixed episodes, maintenance treatment following a response of manic episodes to this molecule, insufficient clinical response to lithium, or contraindications for lithium due to its renal side effects.[1] When used to treat seizures, VPA is introduced gradually, starting with daily doses of 10 to 15 mg/kg and increasing every 2 to 3 days until the optimal dose is reached, typically within a week.[2] In adults, the target dose often reaches 20 mg/kg.[2] For bipolar disorders, the initial recommended dose is 20 mg/kg/d. Increasing the dose quickly until it reaches the minimum therapeutic dose is necessary to achieve the desired clinical effect.[2] The recommended maintenance dose ranges from 1,000 to 2,000 mg per day.[2] It is important to note that VPA is not usually prescribed to women of childbearing age due to its teratogenic effect.[3,4]

Weight gain is a well-known side effect of VPA treatment,[5] which can lead to obesity and/or other metabolic disorders such as hypertension, type II diabetes, and coronary heart disease in the long term,[6] eventually leading to treatment discontinuation.[7] Clinical study findings suggest that some risk factors, such as young age, female gender, and a low baseline body mass index (BMI), may contribute to weight gain induced by VPA.[8] Weight gain associated with VPA is commonly observed within the first 2–3 months of administration.[7,9,10]

Mixed results were found in pediatric or young patients with epilepsy regarding the association between VPA doses and metabolic outcomes such as weight gain and changes in blood metabolic variables.[7,11–17] In addition, epileptic women appear to be more susceptible than men to weight gain during VPA therapy, reporting a higher percentage of body fat and lower waist-to-hip ratio than men.[18–20]

Clinical Points

- While valproate treatment is known to be associated with weight gain and potential metabolic alterations in blood lipids and glucose, it remained unclear whether these metabolic adverse effects are dose-dependent.
- Early monitoring is crucial when initiating valproate treatment as substantial weight gain can occur within the first months, especially at higher doses. In clinical practice, prioritizing the use of minimum effective doses is strongly recommended to mitigate the potential metabolic consequences associated with valproate treatment.

A study in psychiatric patients showed increased weight gain for high serum VPA levels.[21] In contrast, a cross-sectional study found no significant association between high doses of VPA and weight gain in patients taking VPA in association with antipsychotics (APs).[22] To date, no studies have investigated the influence of VPA doses on weight gain specifically in men and women in psychiatric populations.

In addition to causing weight gain, VPA treatment has been associated with increased plasma insulin and triglyceride levels and lower fasting glucose and/or high-density lipoprotein (HDL) levels in psychiatric patients,[23] with a reduction of HDL levels in men compared to women.[24] Furthermore, in VPA-treated epileptic patients, several clinical studies have reported lower blood glucose levels when compared to controls, which could potentially lead to weight gain by stimulating appetite.[25–28] Importantly, metabolic effects are challenging to reverse with dietary restrictions, and results are limited on whether lowering the dose of VPA is an effective strategy.

Despite the well-known association between VPA treatment and weight gain,[5] the association between VPA doses and metabolic variables in psychiatric populations is still unclear.

Due to the limited studies available on the influences of VPA doses on metabolic variables in adults with psychiatric disorders, and the conflicting findings in studies of epileptic patients, the objective of the present study was to evaluate the association between VPA doses and weight gain and changes in blood metabolic variables in a cohort of psychiatric patients with longitudinal follow-up in Switzerland.

METHODS

Study Design

Data were collected from patients who started VPA treatment in 2 cohort studies, PsyClin and PsyMetab. PsyMetab is an ongoing non-interventional longitudinal study that started in 2007 at the Department of Psychiatry of the University Hospital of Lausanne in collaboration with a private mental health care center (Les Toises; Lausanne, Switzerland). This cohort was established with the primary aim of investigating the clinical and genetic factors associated with psychotropic treatments known to induce metabolic alterations, such as weight gain and changes in blood metabolic variables. Patients who seek psychiatric treatment and are receiving or planned to receive psychotropic medications at risk to induce weight gain, including VPA, are included.[29] Specific inclusion and exclusion criteria are described elsewhere.[29] Informed consents are obtained from each participant before their inclusion, and PsyMetab received approval from the Ethics Committee of the Canton de Vaud (last approval number: 2017-01301).

PsyClin included patients hospitalized at the Department of Psychiatry of the University Hospital of Lausanne from 2007 to 2015. Because data were collected for clinical purposes, no specific informed consent from patients was collected and the Ethics Committee of the Canton of Vaud granted access to patients' data due to the non-interventional, post hoc analysis design (2016-00281).

Both PsyMetab and PsyClin studies were conducted in accordance with the ethical guidelines outlined in the Declaration of Helsinki. Patients starting VPA treatment from both PsyMetab and PsyClin cohorts and who had at least 2 weight observations and a minimum of 3 weeks of clinical follow-up data available were included (see Supplementary Figure 1).

For more information regarding the cohort: https://www.chuv.ch/en/psychiatrie/dp-home/recherche/research-centres-and-units-of-the-department-of-psychiatry/center-for-psychiatric-neurosciences/unit-of-pharmacogenetics-and-clinical-psychopharmacology-uppc/psymetab.

Measurements

Sociodemographic data (age, sex), smoking status, and psychiatric diagnosis were assessed using the *ICD-10* classification system, including diagnoses such as bipolar disorder, schizoaffective disorder, and schizophrenia, among others. Anthropometric measurements (height, weight, waist circumference) and cardiometabolic characteristics (blood pressure, lipids, and blood glucose) were collected from patient medical records at the initiation of VPA treatment and after 1, 3, and 12 months. Systolic blood pressure (SBP), diastolic blood pressure (DBP), and weight were also measured over a 6-month treatment period. Information on daily dose, concomitant psychotropic, and somatic comedications such as lipid-lowering, antidiabetic, and antihypertensive treatments were also obtained (see Supplementary Table 1 for the comedication list).

Statistical Analyses

Descriptive statistics were used to characterize the study sample. Continuous variables were reported as means

with interquartile ranges, and categorical variables were presented as counts and percentages. These characteristics were compared between patients taking VPA at doses above or equal to the median of the sample (1,300 mg/d) and those below this cutoff. Categorical variables were analyzed using the Pearson χ^2 test, while continuous variables were assessed using the Wilcoxon test.

Considering the repeated measures on most patients, linear mixed-effects models were employed to analyze weight change and metabolic variables. The models were adjusted for covariates including age, sex, duration of treatment, baseline BMI, smoking status, psychiatric diagnoses, and categories of comedication according to the risk of potential metabolic side effects[30–32] (low risk: amisulpride, aripiprazole, chlorprothixene, flupentixol, haloperidol, lurasidone, pipamperone, sertindole; medium risk: asenapine, amitriptyline, levomepromazine, lithium, mirtazapine, paliperidone, quetiapine, risperidone, zuclopenthixol; and high risk: olanzapine, clozapine). Medical environment was first included as a variable in our linear mixed-effect model to assess its potential influence on weight change. However, upon careful analysis, no significant association was observed ($P = .79$, data not shown). Consequently, medical environment variable was removed from the model.

Piecewise regression analysis was conducted to evaluate the association between weight gain and dose increases above or equal to the median dose (1,300 mg/d) and below this threshold. Across retrospective or prospective studies in children and adults with various seizure disorders, initiation of VPA therapy consistently resulted in weight increase, typically observed within the first 3 months.[7,9,10] To account for this, a piecewise function with a knot at 3 months was applied to the treatment duration variable, allowing the analysis of the dose's effect before and after this knot. Linear mixed-effects models

Table 1.

Clinical Variables Comparison Between Patients Receiving < 1,300 or ≥ 1,300 mg/d of Valproate

	Total[a] (N = 215)	< 1,300 mg/d (N = 112)	≥ 1,300 mg/d (N = 103)	*P*[b]
Dose (mg/d)[c]	1,300 (930–1,600)	940 (750–1,100)	1,600 (1,400–1,800)	**<.001**
Age (y)	48 (33–60)	48 (32–60)	48 (35–60)	.85
Sex (female)	108 (50%)	67 (60%)	41 (40%)	**.005**
Smoking status (smokers)	120 (56%)	57 (51%)	63 (61%)	.19
Diagnoses[d]				**.015**
Bipolar disorder	81 (38%)	38 (34%)	43 (42%)	
Others	35 (16%)	27 (24%)	8 (8%)	
Schizoaffective disorders	57 (26%)	26 (23%)	31 (30%)	
Schizophrenia	36 (17%)	17 (15%)	19 (18%)	
Missing	6 (3%)	4 (4%)	2 (2%)	
Follow-up duration (days)	110 (44–320)	120 (43–300)	98 (48–340)	.76
Baseline weight (kg)[e]	72 (63–85)	67 (59–80)	80 (67–93)	**<.001**
Baseline BMI (kg/m^2)[e]	25 (22–29)	24 (22–27)	27 (23–30)	**.001**
Missing	13 (6%)	6 (5%)	7 (7%)	
Medical environment (inpatients)	131 (61%)	58 (52%)	73 (71%)	**.006**
Psychotropic comedication with risk of metabolic adverse effect (yes)				.08
No comedication	42 (19%)	28 (25%)	14 (14%)	
Comedication at low risk of inducing metabolic adverse effect	36 (17%)	20 (18%)	16 (15%)	
Comedication at medium risk of inducing metabolic adverse effect	107 (50%)	53 (47%)	54 (52%)	
Comedication at high risk of inducing metabolic adverse effect	30 (14%)	11 (10%)	19 (18%)	
Benzodiazepine comedication (yes)	179 (83%)	85 (76%)	93 (90%)	**.009**
Antidepressant comedication (yes)	58 (27%)	39 (35%)	19 (18%)	**.01**
Antidiabetic comedication (yes)	9 (4%)	4 (4%)	5 (5%)	.90
Antihypertensive comedication (yes)	37 (17%)	16 (14%)	21 (20%)	.32
Lipid lowering comedication (yes)	20 (9%)	9 (8%)	11 (11%)	.67

[a]Continuous variables are reported as median (Q1–Q3) and categorical variables as number (%).
[b]Wilcoxon test.
[c]Median value of the dose was 1,300 mg/d.
[d]First available observation.
[e]*ICD-10* classification: depression, organic disorders, anxiety, personality disorder, intellectual disability, dementia, and substance use disorder were classified together as "other."
Abbreviations: BMI = body mass index, N = number.

were fitted for other metabolic outcomes over a 6-month period of VPA treatment since the majority of patients had observations only up to this duration (eg, less than 19% of patients had cholesterol observations after 6 months).

In psychiatry, weight gain exceeding 5% of the initial weight after 1 month of treatment with a psychotropic drug has been established as a predictor for further long-term weight increases.[29] Additionally, gaining more than 7% of weight during the follow-up period is considered a threshold indicative of substantial weight gain.[33] Considering documented sex differences in metabolic effects,[18–20,24] the associations between VPA dose or treatment duration and weight gain, as well as other metabolic variables, were assessed separately for women and men.

Logistic regression analysis was used to examine the potential association between VPA dose and significant weight gain (defined as ≥ 5% after 1 month and ≥ 7% during the follow-up). Furthermore, logistic regression was used to determine whether the dose increased the odds of developing hyperglycemia (fasting glucose ≥ 5.6 mmol/L), hypercholesterolemia (total cholesterol ≥ 5.2 mmol/L and LDL cholesterol ≥ 4.1 mmol/L), hypocholesterolemia (HDL ≤ 1.03 mmol/L for men and ≤ 1.29 mmol/L for women), hypertriglyceridemia (fasting triglycerides ≥ 1.7 mmol/L), and hypertension (SBP ≥ 140 mm Hg and DBP ≥ 90 mm Hg). All analyses were performed using the R environment for statistical computing version 4.1.0 (Team R Core, 2018). The R codes are available on request to the corresponding author. The level of statistical significance was set at $P \leq .05$.

RESULTS

The sample description is provided in Table 1. Prescribed doses of VPA ranged from 250 mg/d to 3,000 mg/d. Patients were categorized into those with a dose lower than the median dose of 1,300 mg/d (N = 112, 52%) and those with a dose ≥ 1,300 mg/d (N = 103, 48%). Patients receiving higher doses were more likely to be men, to have bipolar disorder or schizoaffective disorder, to be hospitalized, to have a higher baseline weight, or to have a higher baseline BMI. Correlation between weight gain (%) and VPA doses (mg/d) is depicted in Supplementary Figure 2. The correlation, while statistically significant, exhibits a very weak positive linear relationship with an R-value of 0.15 ($R^2 = 0.025$), indicating that this relationship is minimal, particularly when not accounting for covariates. It is noteworthy that the majority of patients received VPA doses up to 2,000 mg/d, with only a small minority (N = 22, 10% of the cohort) receiving doses exceeding 2,000 mg/d. When these patients are excluded, the relationship remains similar ($R = 0.13$; $R^2 = 0.017$), as demonstrated in Supplementary Figure 3.

In multivariate analysis, treatment duration was significantly associated with weight change over 1 year (Table 2), with a +0.16% increase in weight for each additional month ($P < .001$). Concerning the dose, significant associations were found (Table 2), with weight increases of +0.52% for each additional 500 mg ($P < .001$). The models revealed associations of weight change with patients taking psychotropic comedication at medium risk for metabolic disorders (+1.04%, $P = .001$).

After applying the piecewise function at a dose of 1,300 mg/d, the weight gain for each additional 500 mg was +0.50% ($P = .004$) for doses ≥ 1,300 mg/d. On the other hand, the dose was not associated with weight change for dose values < 1,300 mg/d (Model 1, Table 3).

The piecewise function was also applied to the treatment duration covariate at 3 months, and the dose effects were evaluated before and after this cutoff (Model 2, Table 3). For each additional month, the dose was associated with weight change for treatment duration values before and up to 3 months (+0.34%, $P = .04$ and +0.62%, $P < .001$, respectively). The estimated weight increase per additional month was greater for treatment durations < 3 vs ≥ 3 months (+0.56% and +0.12% per month, respectively, with $P < .001$ and $P = .02$, respectively).

No significant interaction of the dose with sex category was found (data not shown). However, as previous studies have suggested that women may be more susceptible to weight gain with VPA compared to

Table 2.

Linear Mixed-Effect Model on Weight Change Over 1 Year

	Weight change over 1 year (%)[a,b]		
Variables	Estimates	95% CI	*P*
(Intercept)	6.87	3.34 to 10.41	**<.001**
Treatment duration (month)	0.16	0.10 to 0.23	**<.001**
Dose mg/d (500 mg/d)	0.52	0.22 to 0.83	**.001**
Sex (female)	1.29	0.12 to 2.46	**.031**
Age (years)	−0.03	−0.06 to 0.01	.14
Baseline BMI (kg/m^2)	−0.26	−0.37 to −0.15	**<.001**
Smoking status (smokers)	−0.23	−1.45 to 0.98	.71
Schizoaffective disorders[c] (yes)	−0.46	−1.91 to 0.99	.53
Schizophrenia[c] (yes)	0.35	−1.32 to 2.03	.68
Other diagnoses[c] (yes)	−0.42	−2.10 to 1.26	.62
Low metabolic side effect comedication (yes)	−0.25	−0.87 to 0.37	.43
Medium metabolic side effect comedication (yes)	1.04	0.50 to 1.58	**.001**
High metabolic side effect comedication (yes)	0.24	−0.55 to 1.03	.54
N patients		196[d]	
N observations		1,840	

[a]Weight gain was established as the percentage change from the baseline (((value-initial value)/initial value) × 100).
[b]The weight of a 60-kg fictional patient at 3 months and with a dose increment up to 2,000 mg/d would increase by 2.56% [ie, (3 × 0.16%) + (4 × 0.52)] with a final weight of 61.53 kg.
[c]Diagnoses were compared to bipolar disorder.
[d]13 missing values for BMI and 6 missing diagnoses (215 – 13 – 6 = 196).
Abbreviations: BMI = body mass index, CI = confidence interval, N = number.

men,[18–20] sex subgroup analyses were also performed (Table 4). Treatment duration and dose were positively associated with weight gain in men (+0.28%, $P < .001$ and +0.59%, $P = .004$, respectively). On the other hand, the duration of treatment and dose were not associated with weight change in women, although a trend was observed for the dose (+0.40%, $P = .09$).

Table 3.

Piecewise Functions Applied to Valproate Daily Dose Intake and Treatment Duration

Variables	Weight change over 1 year (%)[a] Estimates	95% CI	P
Model 1[b]			
Treatment duration (month)	0.16	0.10 to 0.23	**<.001**
Dose (500 mg/d) in patients with dose < 1,300 mg/d	0.45	−0.06 to 0.97	.08
Dose (500 mg/d) in patients with dose ≥ 1,300 mg/d	0.50	0.16 to 0.84	**.004**
Model 2[c]			
Treatment duration < 3 months (month)	0.56	0.31 to 0.81	**<.001**
Treatment duration ≥ 3 months (month)	0.12	0.02 to 0.21	**.02**
Dose if treatment duration < 3 months (500 mg/d)	0.34	0.02 to 0.67	**.04**
Dose if treatment duration ≥ 3 months (500 mg/d)	0.62	0.29 to 0.95	**<.001**
N patients		196[d]	
N observations		1,840	

[a]The two models were adjusted for sex, age, baseline BMI, smoking status, diagnostic and psychotropic comedication risks.
[b]After 3 months, the weight of a 60-kg fictional patient with a dose increment up to 500 mg/d from 1,500 to 2,000 mg/d would be increased by 0.98% (3 × 0.16% + 0.50%)).
[c]When passing from the first to the second month of treatment, the weight of a 60-kg fictional patient would increase by 0.56%, with a final weight of 60.33 kg. Moreover, if the patient's dose was also increased from 500 to 1,000 mg/d, the patient's weight would be 60.54 kg [ie, 0.34% + 0.56%]. On the other hand, when passing from the fourth to the fifth month of treatment, the weight of a 60-kg fictional patient would be 60.07 kg (ie, +0.12%), and with a supplementary dose increase from 500 to 1,500 it would be 60.82 kg [ie, (0.62% × 2) + 0.12%].
[d]13 missing values for BMI and 6 missing diagnoses (215 – 13 – 6 = 196).
Abbreviations: BMI = body mass index, CI = confidence interval, N = number.

Table 4.

Linear Mixed-Effect Models on Weight Gain According to Sex Categories[a]

Variables	Weight change over 1 year (%) Women Estimates	95% CI	P	Men[b] Estimates	95% CI	P
Treatment duration (month)	0.06	−0.04 to 0.16	.25	0.28	0.19 to 0.38	**<.001**
Dose mg/d (500 mg/d)	0.40	−0.06 to 0.86	.09	0.59	0.19 to 0.99	**.004**
N patients		98			98	
N observations		960			880	

[a]The model was adjusted for age, baseline BMI, smoking status, diagnostics, and psychotropic comedication risks.
[b]For an 80-kg man, with a dose increment up to 500 mg/d his weight after 3 months would be 61.14 kg (+1.43%, ie, 0.28% × 3 + 0.59%).
Abbreviations: BMI = body mass index, CI = confidence interval, N = number.

Duration of treatment had a negative association with SBP, with decreases of −0.84 mm Hg for each additional month ($P = .014$) and no significant association with the dose. No associations between treatment duration or dose were found with DBP; blood glucose; total-, HDL-, or LDL-cholesterol; or triglyceride levels over 6 months of treatment (Table 5). Sensitivity analysis, including only observations over 6 months, was therefore performed to ascertain the dose and treatment duration effect on weight changes over this time-lapse, which confirmed our results showing a +0.31% weight increase for each additional month and a +0.57% weight increase for each 500 mg increment in the dose ($P < .001$, respectively; data not shown).

The maximum dose values during the first month were found to increase the odds of developing ≥ 5% weight gain (OR = 1.62, $P = .015$; Supplementary Table 2). On the other hand, although a trend was observed, the mean dose prescribed did not show a significant increase in these odds (OR = 1.49, $P = .06$). Neither the mean nor the maximum dose values increased the odds of developing ≥ 7% weight gain for 1 year (OR = 1.21, $P = .30$; OR = 1.31, $P = .12$, respectively).

In relation to other potential adverse effects, an association was observed between the duration of treatment and an increased odds of developing hypertriglyceridemia (OR = 1.16, $P = .025$). In addition, no association was found between the dose or duration of treatment and increased odds of developing hyperglycemia, hypercholesterolemia, hypocholesterolemia, or hypertension (data not shown).

DISCUSSION

The present 1-year longitudinal study showed a positive association between VPA doses and weight gain in psychiatric patients. Our study, with a sample size comparable to previous investigations exploring the impact of VPA doses on metabolic disturbances, stands out as the first longitudinal study involving a substantial number of psychiatric patients.

When the piecewise function was applied to the dose, an association between dose and weight gain was observed in patients with doses ≥ 1,300 mg/d. In contrast, no association between dose and weight gain was detected for patients with doses lower than 1,300 mg/d, indicating that higher doses may contribute to greater weight gain. Additionally, our analyses revealed that a substantial weight increase can occur at the beginning of VPA treatment, and there appears to be a dose effect both before and after 3 months of treatment, with a more pronounced weight gain observed after this period. These findings suggest that the impact of VPA dose on weight gain may become more significant following

Table 5.

Linear Mixed-Effect Models Over 6 Months on Metabolic Outcomes

Variables	Estimates	95% CI	*P*
Glucose, mmol/L[a,b]			
Treatment duration (month)	−0.04	−0.12 to 0.04	.29
Dose (500 mg/d)	0.06	−0.05 to 0.18	.26
N patients		135	
N observations		233	
Total cholesterol, mmol/L[c,d]			
Treatment duration (month)	0.04	−0.01 to 0.09	.09
Dose (500 mg/d)	−0.02	−0.12 to 0.07	.66
N patients		162	
N observations		328	
Cholesterol LDL, mmol/L[c,d]			
Treatment duration (month)	0.01	−0.04 to 0.05	.70
Dose (500 mg/d)	0.01	−0.09 to 0.08	.87
N patients		158	
N observations		308	
Cholesterol HDL, mmol/L[c,d]			
Treatment duration (month)	0.01	−0.01 to 0.03	.31
Dose (500 mg/d)	0.00	−0.04 to 0.04	.97
N patients		158	
N observations		308	
Triglycerides, mmol/L[c,d]			
Treatment duration (month)	0.04	−0.01 to 0.09	.15
Dose (500 mg/d)	0.01	−0.08 to 0.10	.78
N patients		157	
N observations		308	
Systolic blood pressure, mm Hg[e]			
Treatment duration (month)	−0.84	−1.50 to −0.17	**.014**
Dose (500 mg/d)	−0.59	−2.02 to 0.84	.42
N patients		157	
N observations		837	
Diastolic blood pressure, mm Hg[e]			
Treatment duration (month)	−0.48	−0.97 to 0.01	.056
Dose (500 mg/d)	−0.26	−1.24 to 0.72	.60
N patients		157	
N observations		837	

[a]Non-fasting observations were excluded.
[b]Patients taking antidiabetic drugs were excluded.
[c]Model adjusted also for fasting status.
[d]Patients taking lipid-lowering drugs were excluded.
[e]Patients taking antihypertensive drugs were excluded.
Abbreviations: CI = confidence interval, N = number.

treatment adaptation, typically occurring after 3 months of therapy. Furthermore, the maximal VPA doses increased the odds of reaching clinically relevant weight gain within a short period (≥ 5% in 1 month). This finding suggests that higher doses of VPA are associated with a rapid onset of weight gain. It is worth noting that weight gain could be attributed to the effect of hospitalization.[34] During the first 3 months of the study, a total of 132 patients, representing 61% of the population considered, were hospitalized. However, when looking at the multivariate analyses, the medical environment did not appear to have a significant influence on the results of the study.

The association between dose of VPA and weight gain contradicts a previous cross-sectional study in psychiatric patients that found no significant association between higher doses of VPA (2,000–4,000 mg) and metabolic side effects, including weight gain in patients taking concomitant atypical and typical APs with VPA (N = 200) when compared to APs only (N = 426).[22] Of note, the cross-sectional design of the above-mentioned study did not account for changes in medication doses over time or transient factors that may affect outcomes. In addition, the mean weight of the VPA plus AP patients was higher than that of the AP-only patients, which, as suggested by the authors, may indicate that weight gain had already occurred before the study began.

On the other hand, in a 1-year study with 372 patients who met recovery criteria within 3 months of onset, researchers randomized participants to receive VPA (N = 187), lithium (N = 94), or placebo (N = 94) for maintenance treatment.[21] The study demonstrated that patients with higher serum levels of VPA (levels above 125 µg/mL) experienced weight gain,[21] thus suggesting an effect of high doses on weight gain. Some studies with small sample sizes (ie, 15, 63, and 48) found no significant association between doses of VPA and weight gain in epileptic patients.[14–16] Another study with 36 obese epileptic Chinese patients found a low positive association between metabolic syndrome and high VPA doses ($R = 0.323$).[17]

The present study also suggests that patients taking VPA in combination with a medium-risk AP (N = 107) gained more weight than patients taking VPA only, indicating a potential aggravating effect of the combination. However, no significant associations were found between weight gain and the combination of low-risk or high-risk APs, possibly because of the low sample sizes of these subgroups (N = 36 and N = 30; respectively). Interestingly, a previous cross-sectional study reported no significant difference in weight gain or metabolic effects between patients taking an AP alone (N = 426) and those taking VPA plus an AP (N = 200).[22] Because the latter study did not differentiate the risk categories of weight gain among the APs, additional research is warranted to investigate weight gain and other metabolic changes in patients concurrently using VPA and an AP.

The association between dose and weight gain was also investigated separately in men and women. The study found a dose association among men with no association in women. However, a trend toward dose association was observed for the dose among women. These observations differ from previous studies in epileptic patients, where females were found to be more susceptible to weight gain.[14,19] The observed difference could potentially be explained by the inclusion of children with epilepsy in the later studies. Additionally, since VPA

can potentially cause congenital disabilities when taken during pregnancy, women of reproductive age who are prescribed VPA may be given lower doses or are more often monitored compared to men as a precautionary measure to minimize the risk to a developing fetus. It is important to note that caution should be exercised, and VPA usage should be avoided in women.

Duration of treatment had a significant negative association with SBP, with no association found for the dose. Of note, in a study with a rat model of epilepsy, VPA was found to reduce blood pressure.[35] A previous study showed that VPA could decrease the transmission of the neurotransmitter glutamate while increasing levels of GABA at corresponding synapses by inhibiting GABA transaminase.[36] GABA has been found to have a protective effect in hypertensive mice, significantly reducing blood pressure.[37] In addition, a clinical study demonstrated that high levels of glutamate increased blood pressure.[38] Hence, the potential modulation of glutamate levels by VPA might account for the blood pressure changes observed, although further replication of these findings is necessary in psychiatric patients.

Neither the duration of treatment nor the dose had an influence on levels of glucose, triglycerides, HDL- and LDL-cholesterol, total cholesterol, or DBP. These findings contradict prior studies that demonstrated an association between VPA and a reduction in fasting glucose levels in adult[25] and young[26–28] epileptic patients, as well as bipolar patients.[23] Additionally, several studies in adult patients have examined the association between VPA and lipid variables.[23,39] Among them, one study found that patients taking VPA have deterioration in HDL-cholesterol, triglyceride, and total cholesterol levels,[40] and another group found decreased HDL levels and higher triglyceride levels in remitted bipolar patients compared to drug-free bipolar patients and healthy controls.[23] These discrepancies may be attributed to a selection bias, where patients with elevated glucose, cholesterol, and/or blood pressure levels stopped taking VPA or received drugs to treat these conditions. However, VPA duration was associated with an increased risk of developing hypertriglyceridemia, regardless of the dose, which aligns with earlier studies reporting elevated triglyceride levels.[23,39]

Several limitations to the present study should be mentioned. First, the present study examined only associations and did not claim any causality. Second, the study was unable to ascertain compliance with treatment. However, the actual daily dose administered to hospitalized patients was available, increasing the accuracy of these data. Information regarding lifestyle, such as dietary habits, physical activity, and substance use, such as alcohol consumption, which could affect weight gain and blood metabolic variables, was unavailable. Another limitation of this study is the lack of available data regarding the duration of illness of the included patients.

Moreover, data on plasma VPA concentration were lacking. While serum levels of VPA provide a more direct measure of drug exposure in the body, using VPA doses as a proxy can still offer valuable insights as they are more readily available in medical records. The majority of patients were taking APs, which could induce weight gain, with varying levels of risk and through multiple mechanisms, including alterations in appetite and metabolism.[41–45] The specific types and doses of APs prescribed to our patients varied, which could introduce additional complexity into our results, although statistical methods were used to control for their effects. It should also be acknowledged that the present study lacked information on the patients' history of previous psychotropic use, which might play a role in weight changes when treated with VPA. Of note, due to the limitations of our data sources, we were unable to ascertain the complete drug history, including previous psychotropic medication usage. Additionally, patients with a previous follow-up on VPA could not be excluded from our analysis. One of the study's strengths is its longitudinal design, incorporating multiple time points for each patient after VPA initiation. This design enabled a more comprehensive examination of the effects of VPA dose on metabolic adverse effects in a real-world setting.

CONCLUSION

In summary, the present study demonstrated a positive association of VPA dose with weight changes but not with other metabolic variables. These findings underscore the need for clinicians to closely monitor patients on VPA for weight gain and to prescribe the lowest effective doses.

Article Information

Published Online: March 27, 2024. https://doi.org/10.4088/JCP.23m15008

Submitted: July 10, 2023; accepted November 14, 2023.

To Cite: Grosu C, Hatoum W, Piras M, et al. Associations of valproate doses with weight gain in adult psychiatric patients: a 1-year prospective cohort study. *J Clin Psychiatry.* 2024;85(2):23m15008.

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Relevant Financial Relationships: Dr Eap received honoraria for conferences from Forum pour la formation médicale, Janssen-Cilag, Lundbeck, Otsuka, Sandoz, Servier, Sunovion, Sysmex Suisse AG, Takeda, Vifor-Pharma, and Zeller in the past 3 years. The

other authors report no relevant financial relationships. All authors declare that they have no conflict of interest in relation to the content of this work.

Funding/Support: This work was funded by the Swiss National Research Foundation (Drs Eap and Conus: 320030-120686, 324730- 144064, and 320030-173211; Drs Eap, Conus, and Plessen: 320030-200602). The funding source had no role in the writing of the manuscript or in the decision to submit it for publication.

Acknowledgments: The authors thank L. Maw, MA (University of Kentucky) for editorial assistance. L. Maw declares no conflict of interest.

Supplementary Material: Available at Psychiatrist.com.

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The Journal of Clinical Psychiatry

Supplementary Material

Article Title: Associations of Valproate Doses With Weight Gain in Adult Psychiatric Patients: A 1-Year Prospective Cohort Study

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DOI Number: 10.4088/JCP.23m15008

LIST OF SUPPLEMENTARY MATERIAL FOR THE ARTICLE

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Supplementary Table 1: Comedications taken by the participants

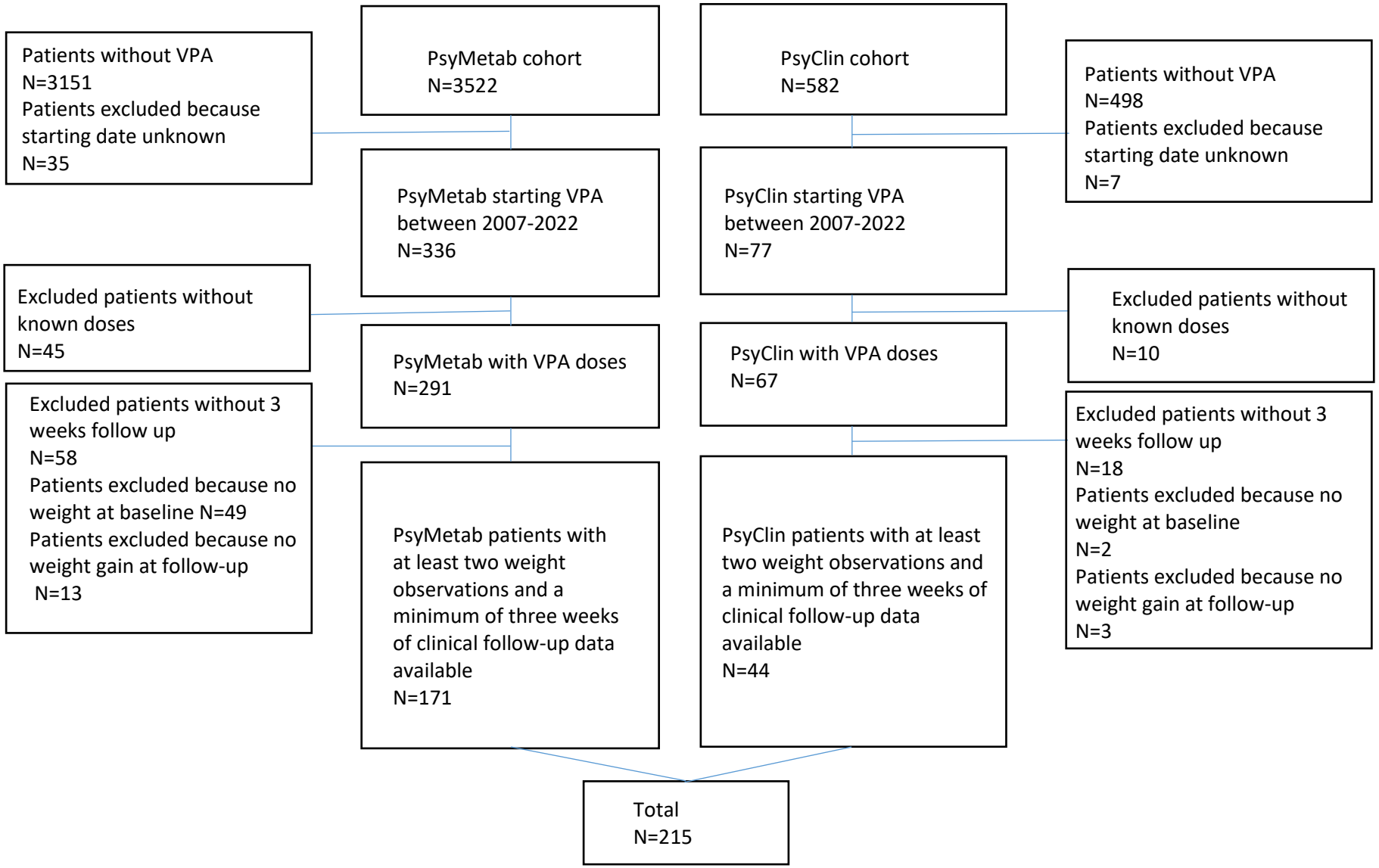
Antidepressants	Benzodiazepines	Lipid-lowering drugs	Antidiabetics	Antihypertensives	Weight-inducing psychotropic drugs
Citalopram Duloxetine Escitalopram Fluoxetine Fluvoxamine Moclobemide Paroxetine Reboxetine Sertraline Trazodone Venlafaxine	Alprazolam Bromazepam Clobazam Clorazepate Diazepam Flurazepam Lorazepam Lormetazepam Midazolam Oxazepam Triazolam	Atorvastatin Rosuvastatin Simvastatin	Gliclazide Insulin Insulin aspart Insulin degludec Insulin glargine Insulin lispro Liraglutide Metformin Repaglinide Sitagliptin	Amlodipine Bisoprolol Candesartan Diltiazem Enalapril Furosemide Glyceryl trinitrate Hydrochlorothiazide Indapamide Irbesartan Lercanidipine Lisinopril Losartan Metoprolol Modamide Nifedipine Perindopril Spironolactone Torasemide Verapamil	Amisulpride Amitriptyline Aripiprazole Asenapine Chlorprothixene Clozapine Flupentixol Haloperidol Levomepromazine Lithium Lurasidone Mirtazapine Olanzapine Paliperidone Pipamperone Quetiapine Risperidone Sertindole Zuclopenthixol

Supplementary Table 2. Logistic regression[a]

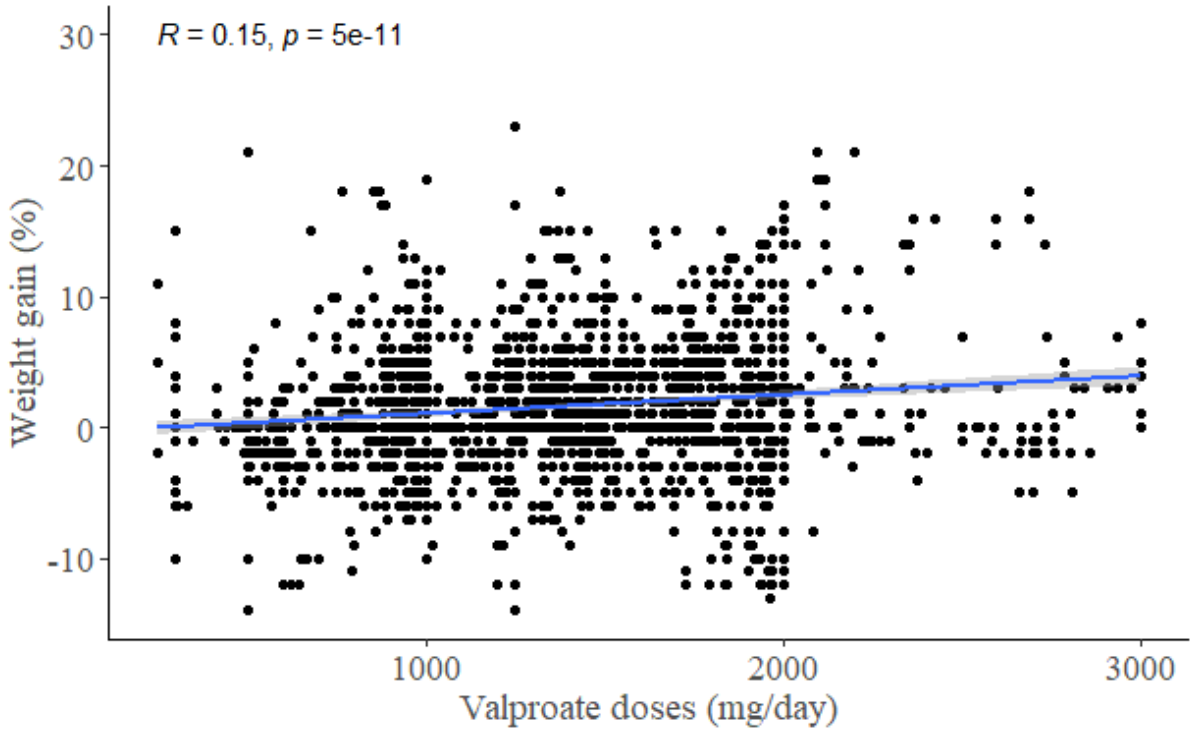
	Weight gain ≥ 5% in 1 month			*Weight gain ≥ 7% in 1 year*		
Variables	*Odds ratio*	*95%CI*	*P*	*Odds ratio*	*95%CI*	*P*
Mean dose[b]	1.49	0.99 to 2.27	0.06	1.21	0.84 to 1.76	0.30
Max dose[b]	1.62	1.11 to 2.41	**0.015**	1.31	0.94 to 1.83	0.12
N patients	196					

[a]*Logistic regression on the occurrence of ≥5%* weight gain *within the first month of treatment and on the development of ≥7% weight gain within the following year. The models were adjusted for age, sex, baseline BMI, smoking status, diagnostic and psychotropic comedication risks.*
[b]*Mean dose (mg/day) reflects the average value of dose received during the first month of treatment (weight gain ≥5%) and within 12 months (weight gain ≥7%), and max dose (mg/day) represents the maximum value.*
Abbreviations: CI: confidence interval, N: number.

Supplementary Figure 1. Flowchart of the selection of patients



Supplementary Figure 2. Scatter plot of the correlation between valproate doses (mg/day) and weight gain (%)



Supplementary Figure 3. Scatter plot of the correlation between valproate doses (mg/day) and weight gain (%), excluding patients who received doses greater than 2000mg/day (N=22, 10% of the cohort)