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Is Clozapine-induced Weight Gain Dose-dependent? Results From a Prospective Cohort Study

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***Background*: Antipsychotic-induced metabolic adverse effects are risk factors for cardiometabolic comorbidities. Whether dose lowering could mitigate such effects remains unclear. The present study aims to investigate the associations between clozapine doses and modifications of weight, blood pressure, blood glucose, and lipid levels. *Study Design*: Linear mixed-effects models of weight changes over 1 year and of variations of other metabolic parameters over 4 months were applied to a prospective cohort of 115 patients. Age- and sex-stratified analyses of weight changes were also performed. *Study Results*: Each 100 mg dose increment of clozapine was associated on average with a +0.48% weight increase ($P = .004$) over 1 year of treatment. Weight increase was greater for treatment duration ≤3 vs >3 months (+0.84% and +0.47% per month, respectively, $P < .001$), with a significant association with the dose for durations >3 months (+0.54%, $P = .004$) and a trend for durations ≤3 months (+0.33%, $P = .075$). Dose increments of 100 mg were also associated with weight increases of +0.71% among adults ($P = .001$), +1.91% among the elderly ($P < .001$) and +1.32% among men ($P < .001$) with no associations among women ($P = .62$). Among young adults, weight change was positively associated with doses ≤300 mg/day (+2.19% per 100 mg, $P = .001$), whereas no association was found with doses >300 mg/day ($P = .60$). No significant effect of clozapine dose on other metabolic parameters was found. *Conclusions*: This study reports a modest effect of clozapine dose increases on weight gain over 1 year with differences among age categories and sexes and no dose effect on other metabolic parameters over 4 months.**

Key words: metabolic adverse effects/psychotropic drugs/dose dependency

Introduction

Antipsychotic treatments are risk factors for cardiometabolic comorbidities among the psychiatric population.[1] Indeed, weight gain is an adverse effect occurring generally from the first month of treatment, which can then lead to obesity and/or generate other metabolic complications such as hypertension, type II diabetes, and cardiovascular diseases in the long term.[2] Several risk factors for antipsychotic-induced weight gain such as young age, female sex, and low baseline body mass index have been described[2] with non-pharmacological (ie, diet and physical activity) and pharmacological strategies such as adjuvant treatments (eg, metformin) or antipsychotic switching often being used to induce weight loss.[3] Dose lowering has also been suggested as an alternative pharmacological strategy to reverse antipsychotic-induced weight gain.[3] However, its efficacy remains uncertain with mixed evidence in the literature suggesting specific dose effects on weight depending on the antipsychotic drug.[4–7]

Clozapine, the first atypical antipsychotic is widely used for treating treatment-resistant schizophrenia, psychoses induced by dopaminergic agents used to treat

Parkinson's disease, for reducing the risk of suicide,[8,9] and for treating other off-label diseases, such as bipolar disorder and depression.[10] Nevertheless, its prescription is limited due to several adverse effects, especially agranulocytosis requiring constant blood cell monitoring.[8] Clozapine is also one of the antipsychotics most associated with weight gain, blood lipids, and glucose alterations.[11] However, whether these metabolic adverse effects are dose-dependent remains unclear.[4]

Thus, weight gain was associated with clozapine dose in a case-series report, in which a gain of 4.5 kg was reported in 4 out of 5 patients within the first month of treatment after a dose increase from 50 to 600 mg/day.[12] Additionally, a 16-week double-blind randomized study including 50 patients starting clozapine reported greater weight gain of +2 kg among patients receiving 600 mg/day vs patients receiving 300 mg/day.[13] On the other hand, a 21-month open-label study of 15 patients starting clozapine reported +5 kg and +12.5 kg gain among patients receiving high (ie, 600 mg/day) and low doses (ie, 200 mg/day), respectively,[14] while a retrospective study showed no significant association between weight gain and clozapine dose after 3 and 6 months of treatment among 117 patients (mean doses 300 and 316 mg, respectively).[15] Glucose fasting concentrations and clozapine dose were negatively correlated in a cross-sectional study including 24 patients taking clozapine for at least 2 months,[16] and no association between hyperglycemia severity and the dose was found among 384 patients in an 11-year retrospective study, although improvement in fasting glucose levels was observed in 4/5 participants after dose lowering.[17] Moreover, neither glucose nor triglyceride levels were associated with clozapine dose among 96 patients starting clozapine in a 5-year naturalistic study.[18] On the other hand, a positive association between total cholesterol levels and serum clozapine concentrations was found in a cross-sectional study including 38 patients treated with clozapine for at least 4 months.[19]

Contradictory results call for further investigations on whether clozapine-induced metabolic adverse effects are dose-dependent. The present study aims to analyze the effect of clozapine dose on weight changes, blood pressure, glucose, and lipid levels in a prospective cohort study of psychiatric patients based in Switzerland.

Methods

Study Design

PsyMetab and PsyClin cohort studies provided data for the present study and both were approved by the ethics committee of the canton of Vaud. Through a signed informed consent, PsyMetab (started in 2007 and still ongoing) collects clinical and genetic data from patients followed at the Department of Psychiatry of the University Hospital of Lausanne.[20] PsyClin (2007–2015) collects clinical data of patients hospitalized at the University Hospital of Lausanne, which access was granted by the ethics committee of the canton of Vaud because of the non-interventional post hoc analysis design. Patients starting clozapine from both cohorts (included from 2007 to 2020), with at least 2 weight observations and at least 3 weeks of clinical follow-up, were included. Previous psychotropic medication could not be ascertained, and patients with a previous follow-up on clozapine could not be excluded.

Variables and Measurements

PsyMetab and PsyClin collect metabolic (ie, weight, height, waist circumference, blood pressure, blood glucose, triglycerides, and total, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol) and clinical (ie, diagnosis, age, sex, and smoking status) data from patients' medical records at the beginning of weight-inducing psychotropic treatments, and at 3 and 12 months. Weight measures are also available at 2 and 6 months of treatment. Daily dose intake, concomitant psychotropic, and medical (ie, lipid-lowering, antidiabetic, and antihypertensive treatments) comedications were also obtained (see Supplementary table 1 for the comedication list). Additional metabolic observations were obtained for inpatients (eg, weight observations collected during the hospital stay) in the present study.

Statistical Analyses

Clinical variables were compared between patients taking a total average dose above or below the median value (ie, ≥200 vs <200 mg/day, which was determined considering every dose observation of each patient), using the χ^2 or Fisher tests for categorical variables as appropriate, and the Wilcoxon test for continuous variables. The dose effect on weight change was evaluated using linear mixed-effects models, adjusted for treatment duration, age, sex, baseline weight, treatment setting (ie, in- vs out-patients), and the intake of medical (ie, lipid-lowering, antidiabetic, and antihypertensive drugs) and psychotropic comedications (ie, antidepressants, benzodiazepines, and weight-inducing psychotropic drugs). As the clozapine prescribed dose depends on the diagnoses and serum clozapine levels are affected by smoking status, models were also adjusted for both diagnoses and smoking status.[8] Weight changes were expressed as a percentage of baseline weight. Since greater weight gain can be detected in the first 3 months of treatment,[21,22] the piecewise function was applied with a knot at 3 months to the treatment duration variable, and the effect of the dose was also analyzed before and after this knot. The piecewise function was also applied to the dose variable to evaluate its effect on weight change for dose increases above (eg, 250–350 or 400–500 mg) and below (20–120 or 50–150 mg) the median dose (ie, 200 mg). Since the

Table 1. Comparison of Clinical Variables Among Patients Receiving an Average of <200 or ≥200 mg/day

	<200 mg (N = 61)	≥200 mg (N = 54)	P-value	Total[a] (N = 115)
Dose (mg/day)[b]	100 (64–140)	300 (270–410)	**<.001**	180 (98–290)
Age (years)	70 (45–77)	36 (27–51)	**<.001**	51 (31–73)
Sex			1	
Female	31 (50.8%)	27 (50.0%)		58 (50.4%)
Age categories[c]			**<.001**	
Young adults	5 (8.2%)	12 (22.2%)		17 (14.8%)
Adults	19 (31.1%)	35 (64.8%)		54 (47.0%)
Elderly	37 (60.7%)	7 (13.0%)		44 (38.3%)
Smoking status			**.001**	
Smokers	13 (21.3%)	28 (51.9%)		41 (35.7%)
Diagnoses[d]			**<.001**	
Schizophrenia	20 (32.8%)	34 (63.0%)		54 (47.0%)
Schizoaffective disorders	7 (11.5%)	12 (22.2%)		19 (16.5%)
Others	34 (55.7%)	8 (14.8%)		42 (36.5%)
Follow-up duration (days)	100 (49–270)	140 (64–360)	.13	120 (56–290)
Baseline weight (kg)[e]	64 (57–80)	75 (65–88)	**.02**	70 (59–81)
Baseline BMI (kg/m^2)[e]	23 (21–26)	24 (21–27)	.21	24 (21–27)
Missing	5 (8.2%)	4 (7.4%)		9 (7.8%)
Treatment setting			.98	
Inpatients	43 (70.5%)	37 (68.5%)		80 (69.6%)
Psychotropic co-medication[f]			.93	
Yes	23 (37.7%)	19 (35.2%)		42 (36.5%)
Benzodiazepine co-medication[g]			**.005**	
Yes	18 (29.5%)	31 (57.4%)		49 (42.6%)
Antidepressant co-medication[g]			**.03**	
Yes	28 (45.9%)	13 (24.1%)		41 (35.7%)
Antidiabetic co-medication[g]			.14	
Yes	8 (13.1%)	2 (3.7%)		10 (8.7%)
Antihypertensive co-medication[g]			**.03**	
Yes	24 (39.3%)	10 (18.5%)		34 (29.6%)
Lipid-lowering co-medication[g]			.67	
Yes	7 (11.5%)	4 (7.4%)		11 (9.6%)

Note: [a]Continuous variables are reported as median (Q1–Q3) and categorical variables as number (%).
[b]Median value of the dose was 200 mg/day.
[c]Young adults: Age ≤25 years; adults: Age >25 and <65 years; elderly: Age ≥65 years.
[d]ICD-10 classification: Organic disorders, anxiety, personality disorder, intellectual disability, dementia, substance use disorder, depression, and bipolar disorder were classified together as "others."
[e]First available observation.
[f]Weight-inducing psychotropic comedications (see Supplementary table 1).
[g]See Supplementary table 1. Bold values under the P column indicate statistically significant results.

majority of included patients had glucose and/or cholesterol and/or blood pressure observations only in the first 4 months of treatment, linear mixed-effects models were performed over this time frame adjusting for treatment duration, age, sex, baseline body mass index, smoking status, and diagnoses. Patients taking medical drugs related to our outcomes were excluded (ie, patients taking antihypertensive, antidiabetic, and lipid-lowering medications were excluded from models evaluating blood pressure, glucose, and lipid values, respectively). Finally, logistic regression was also applied to detect whether the dose was associated with a substantial weight gain (≥ 5% for 1 month[23] and ≥ 7% during follow-up[22]). Statistical significance was set at a P-value ≤ .05 and the analyses were performed using Stata 16.1 (StataCorp; College Station, Texas) and the statistical software package R-4.0.2.

Results

Table 1 compares clinical variables between patients whose total average dose during the follow-up was < 200 or ≥ 200 mg/day. Patients receiving high doses were more likely to be smokers (P = .001), diagnosed with schizophrenia or schizoaffective disorder (P < .001), had higher weight at baseline (P = .02) and were younger (P < .001), most of the adults (64.8%) taking doses ≥200 mg/day in contrast with old-age patients mainly taking doses <200 mg/day (60.7%).

Treatment duration and dose were significantly associated with weight change over 1 year (table 2), with a 0.50% increase in weight for each additional month (P < .001), and a 0.48% increase in weight for each 100 mg dose increase (P = .004). Applying the piecewise function

Table 2. Linear Mixed-effect Models of Weight Change Over 1 Year

	Weight change over one year[a]		
Variables	Estimates	CI	*P*
Model 1[b]			
Treatment duration (month)	0.50	0.40–0.61	**<.001**
Dose (100 mg/day)	0.48	0.15–0.81	**.004**
Model 2[c]			
Time (month)	0.49	0.38–0.60	**<.001**
Dose ≥ 200 mg/day (100 mg/day)	0.59	0.24–0.94	**.001**
Dose < 200 mg/day (100 mg/day)	1.12	0.37–1.87	**.003**
Model 3[d]			
Treatment duration ≤3 months (month)	0.84	0.47–1.21	**<.001**
Treatment duration >3 months (month)	0.47	0.34–0.61	**<.001**
Dose if treatment duration ≤3 months (100 mg/day)	0.33	−0.03 to 0.69	.075
Dose if treatment duration >3 months (100 mg/day)	0.54	0.18–0.90	**.004**
N patients	115		
N observations	1261		

Note: CI, confidence interval; *N*, number.
[a]The 3 models included the same number of patients and observations until follow-up day 365 and were also adjusted for sex, age, baseline weight, smoking status, diagnoses, treatment setting, medical (ie, lipid-lowering, antidiabetic, and antihypertensive drugs), and psychotropic comedications (ie, antidepressants, benzodiazepines, and weight-inducing psychotropic drugs).
[b]The weight of a 60 kg fictional patient after 3 months and with a dose increment up to 500 mg/day would increase by 3.9% [ie, (3*0.5%) + (5*0.48%)], with a final weight of 62.34 kg. To lose 2 kg of weight (ie, −2.94%), a 68 kg fictional patient would need a dose decrease of 600 mg (ie, −2.94%/0.48%, ie, the dose-effect for each 100 mg increase as reported in model 1).
[c]The weight of a 60 kg fictional patient after 3 months and with a dose increment from 80 to 180 mg/day would increase by 2.59% [ie, (3*0.49%) + 1.12%], with a final weight of 61.55 kg. On the other hand, if the dose increased from 400 to 500 mg/day, the weight increase would be 2.06% [ie, (3*0.49%) + 0.59%], with a final weight of 61.24 kg.
[d]When passing from the first to the second month of treatment, the weight of a 60 kg fictional patient would increase by 0.84%, with a final weight of 60.50 kg. Moreover, if the patient's dose was also increased from 200 to 600 mg/day, the patient's weight would be 61.29 kg [ie, (0.33%*4) + 0.84%] (even though only a trend for an effect of dose increase during the first 3 months is observed). 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 60.28 kg (ie, +0.47%), and with a supplementary dose increase from 200 to 600 it would be 61.58 kg [ie, (0.54%*4) + 0.47%]. Bold values under the *P* column indicate statistically significant results.

at a dose value of 200 mg/day, the weight increase for each additional 100 mg was +0.59% for doses ≥ 200 mg/day (eg, for dose increases from 300 to 400 mg/day, $P = .001$), and +1.12% for doses <200 mg/day (eg, for dose increases from 20 to 120 mg/day, $P = .003$). Since weight gain can occur rapidly in the first 3 months of treatment,[21] 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. The estimated weight increase for each additional month was +0.47% for treatment duration values greater than 3 months and +0.84% for treatment duration values up to 3 months ($P < .001$). The dose was significantly associated with weight change for treatment duration values greater than 3 months, with a +0.54% weight increase estimated for each additional 100 mg increment ($P = .004$). On the other hand, the dose was not associated with weight change for treatment duration values up to 3 months, although a trend was observed (+0.33%, $P = .075$). The 3 models revealed no further associations between weight change and another clinical covariate (eg, age, sex, baseline weight, see Supplementary table 2). However, patients taking antihypertensive drugs gained a mean of 2.77% more weight than patients not taking these comedications ($P = .03$).

Since a significant interaction between the dose and both age and sex covariates was found (data not shown), stratified analyses were performed (table 3). Treatment duration was positively associated with weight change among young adults (ie, study available age range 17–24 years), adults (ie, study available age range 26–63 years), and the elderly population (ie, study available age range 65–87 years), with +0.77%, +0.30, and +0.46% in weight increase predicted for each additional month, respectively ($P < .001$). The dose was negatively associated with weight change among young adults, with −1.19% for each 100 mg increase. However, since among young adults different weight change patterns were found for doses ≤300 and >300 mg/day using data visualization (see Supplementary figure 1), the piecewise function was applied, showing a +2.19% weight increase for each 100 mg dose increment for doses ≤300 mg/day ($P = .001$), and no effects with doses >300 mg/day ($P = .61$). Among adults and the elderly, the dose was positively associated with weight change, with +0.71% and +1.91% weight increases for each additional 100 mg increase in dose, respectively ($P =$

Table 3. Linear Mixed-effect Models of Weight Change Over 1 Year According to Age and Sex Categories

	Weight change over 1 year		
Variables	Estimates	CI	*P*
Young adults[a,b]			
Treatment duration (month)	0.77	0.47–1.06	**<.001**
Dose (100 mg/day)	−1.19	−2.10 to −0.28	**.01**
N patients	17		
N observations	142		
Adults[a]			
Treatment duration (month)	0.30	0.15–0.46	**<.001**
Dose (100 mg/day)	0.71	0.30–1.13	**.001**
N patients	54		
N observations	561		
Elderly[a]			
Treatment duration (month)	0.46	0.30–0.63	**<.001**
Dose (100 mg/day)	1.91	1.12–2.71	**<.001**
N patients	44		
N observations	558		
Men[c,d]			
Treatment duration (month)	0.16	−0.01 to 0.33	.073
Dose (100 mg/day)	1.32	0.88–1.77	**<.001**
N patients	57		
N observations	496		
Women[c]			
Treatment duration (month)	0.65	0.52–0.78	**<.001**
Dose (100 mg/day)	−0.12	−0.58 to 0.35	.62
N patients	58		
N observations	765		

Note: CI, confidence interval; *N*, number.
[a]Models adjusted for treatment duration, dose, sex, baseline weight, diagnoses, smoking status, treatment setting, medical (ie, lipid-lowering, antidiabetic, and antihypertensive drugs), and psychotropic comedications (ie, antidepressants, benzodiazepines, and weight-inducing psychotropic drugs).
[b]None of the included patients were taking medical comedications.
[c]Models adjusted for treatment duration, dose, age, baseline weight, diagnoses, smoking status, treatment setting, medical (ie, lipid-lowering, antidiabetic, and antihypertensive drugs), and psychotropic comedications (ie, antidepressants, benzodiazepines, and weight-inducing psychotropic drugs).
[d]A 60 kg fictional man's weight after a dose increase up to 500 mg/day would be 63.96 kg [ie, + 6.6% (5*1.32%)]. Bold values under the *P* column indicate statistically significant results.

.001 and $P < .001$, respectively); data visualization did not imply different patterns for weight change vs dose (data not shown). Treatment duration was positively associated with weight change among women, with a +0.65% weight increase for each additional month ($P < .001$), while only a trend was found among men ($P = .073$). On the other hand, the dose was associated with weight change only among men, with a +1.32% weight increase predicted for each additional 100 mg of dose increment ($P < .001$).

Since serum clozapine levels are influenced by smoking with polycyclic aromatic hydrocarbons (PAHs) present in tobacco smoke being a strong inducer of the clozapine metabolizer cytochrome P4501A,[8] a sensitivity analysis considering smokers ($N = 41$, median dose 280 mg) and nonsmokers ($N = 74$, median dose 130 mg) separately was applied, indicating a trend ($E = 0.81$, $P = .090$) and a slightly significant ($E = 0.94$, $P = .047$) effect of the dose on weight change, respectively, probably due to the low sample size. Moreover, since dose prescription can vary between both ages and diagnoses (as shown in table 1), a sensitivity analysis including only schizophrenic and schizoaffective patients was performed for the models reported in table 3 (see Supplementary table 3), reporting similar results. However, a non-significant effect of the dose was found for adults, probably due to the low sample size.

No associations between treatment duration or dose were found with systolic or diastolic blood pressure, blood glucose, total, HDL, LDL cholesterol, or triglyceride levels during a time range of 4 months (table 4). A sensitivity analysis including only observations over 4 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 +0.90% weight increase for each additional month, and a +0.37% weight increase for each 100 mg increment in the dose ($P < .001$ and $P = .02$).

Neither the mean nor the maximum dose values increased the odds to develop a +5% weight increase in 1 month or a +7% weight increase during follow-up (Supplementary table

Table 4. Linear Mixed-effect Models Over 4 Months of the Other Metabolic Parameters

Variables	Estimates	CI	*P*
Glucose[a,b,c]			
Treatment duration (month)	−0.06	−0.22 to 0.09	.41
Dose (100 mg/day)	−0.03	−0.14 to 0.08	.59
N patients	69		
N observations	115		
Cholesterol[a,d,e]			
Treatment duration (month)	0.03	−0.08 to 0.15	.56
Dose (100 mg/day)	0.04	−0.06 to 0.14	.42
N patients	83		
N observations	164		
Cholesterol LDL[a,d,e]			
Treatment duration (month)	0.06	−0.03 to 0.15	.22
Dose (100 mg/day)	0.06	−0.02 to 0.13	.13
N patients	80		
N observations	144		
Cholesterol HDL[a,d,e]			
Treatment duration (month)	−0.03	−0.07 to 0.01	.16
Dose (100 mg/day)	0.01	−0.03 to 0.04	.71
N patients	81		
N observations	151		
Triglycerides[a,b,e]			
Treatment duration (month)	−0.04	−0.14 to 0.07	.48
Dose (100 mg/day)	−0.03	−0.11 to 0.05	.47
N patients	82		
N observations	142		
Systolic blood pressure[f]			
Treatment duration (month)	−0.48	−1.70 to 0.74	.44
Dose (100 mg/day)	−0.13	−1.32 to .06	.83
N patients	53		
N observations	405		
Diastolic blood pressure[f]			
Treatment duration (month)	−0.30	−1.19 to 0.58	.50
Dose (100 mg/day)	0.60	−0.24 to 1.44	.16
N patients	53		
N observations	405		

Note: CI, confidence interval; *N*, number.
[a]Expressed in mmol/l.
[b]Non-fasting observations were excluded.
[c]Patients taking antidiabetic drugs were excluded.
[d]Model adjusted also for fasting status.
[e]Patients taking lipid-lowering drugs were excluded.
[f]Patients taking antihypertensive drugs were excluded. Expressed in mmHg.

4). Logistic models of the development of obesity (ie, body mass index ≥30 kg/m^2), hyperglycemia (ie, fasting glucose ≥5.6 mmol/l), hypercholesterolemia (ie, total cholesterol ≥5.2 mmol/l and LDL cholesterol ≥4.1 mmol/l), hypocholesterolemia (ie, HDL ≤1.03 mmol/l for men and ≤1.29 mmol/l for women), hypertriglyceridemia (ie, fasting triglycerides ≥1.7 mmol/l) and hypertension (ie, systolic blood pressure ≥140 mmHg and diastolic blood pressure ≥90 mmHg) over time could not be performed given the limited sample size (eg, only data for <50 patients with a cholesterol disturbance was available).

Discussion

With a 1-year naturalistic study design, a positive association between clozapine dose and weight change was observed. This result is in accordance with a previous 16-week double-blind randomized study reporting a 2 kg greater weight gain among patients receiving 600 mg/day vs those receiving 300 mg/day.[13] However, in the present observational study patients were not randomized into receiving fixed doses, but prescribed doses could change over time (ie, increase and/or decrease) depending on the clinical needs (ie, adverse effects and/or symptom severity) and/or on clozapine blood levels checked through therapeutic drug monitoring, which is often used by psychiatrists in our department to check for the therapeutic window in case of non-response and/or side-effects, and also for adherence. In addition, the percentage of weight increase after each 100 mg increment of the dose could be predicted, such results being more informative than

an absolute estimation of weight gain after a given time. Moreover, the influence of covariables such as sex, age, baseline weight, smoking status, treatment setting, medical, and psychotropic comedications could be integrated with the model. Interestingly, in contrast with previous findings[24] of our models did not show an association between baseline weight and weight change, possibly because of the difference in baseline weight among patients taking doses above or below the median dose value as reported in table 1.

A positive dose-weight gain association was not found in a 21-month open-label study reporting +5 kg or +12.5 kg gains among patients receiving 600 or 300 mg/day, respectively; the discrepancy with the present results is probably due to a low sample size in the mentioned study (ie, 15 patients).[14] Similarly, the absence of the association between weight gain and clozapine doses found in a 6-week observational study[25] was probably due to a short study duration (ie, 6 weeks) and/or a smaller sample size as compared to the present study (ie, 81 vs 115 patients). A 12-month retrospective study of 117 patients also failed to associate weight changes between 3 and 12 months of treatment with clozapine dose.[15] However, in the latter study the dose averages (ie, 300 vs 316 mg/day, respectively) at the 2-time points were only slightly different, which was not the case in the present study (ie, 270 and 480 mg/day at 3 and 12 months).

In the present study, dose increases up to 200 mg/day were also associated with greater weight changes than dose increases from 200 mg/day, suggesting a plateau effect. Nevertheless, patients increasing their doses up to 200 mg/day were older, and, unlike schizophrenic and schizoaffective patients who receive other antipsychotics before clozapine treatment, elderly patients could have been diagnosed with psychoses induced by dopaminergic agents used for treating Parkinson's disease, which does not require previous antipsychotic trials.[9] Therefore, such antipsychotic-naïve patients were possibly more vulnerable to antipsychotic-induced weight gain.[26]

Our analyses also confirmed that greater weight increase can occur at the beginning of the antipsychotic treatment,[21,22] and suggested a different dose effect in the first 3 months of treatment vs thereafter. Indeed, the dose was positively associated with weight change for durations after 3 months, whereas only a trend for a dose effect was found for durations up to 3 months. This result suggests that early weight increase could be due mainly to treatment onset itself, whereas the dose effect on weight increase could be more important after an adaptation to the treatment (eg, after 3 months).

Among the various age categories, young adults reported the highest weight increase per month, this result being in line with previous studies indicating young age as a risk factor for antipsychotic-induced weight gain.[22,24] A negative association between the dose and weight change was also reported for young adults. This result is probably due to a possible inclusion bias (ie, doses increased over 300 mg/day only in patients reporting lower weight increases). This was supported by weight increases found for dose increments up to ≤300 mg/day and no dose effect for doses >300 mg/day. A higher dose effect on weight change was reported for the elderly vs the adult population, possibly because of the reduced clearance of clozapine among elderly patients, and/or the presence among the elderly population of antipsychotic-naïve patients, as previously discussed. Whereas among men the dose and not the treatment duration affected weight changes, dose-unrelated weight increases were predicted among women. These results were probably due to the low sample sizes and/or to the different ages between men and women (ie, median 37 and 61.5 years, respectively, Wilcoxon test $P = .005$).

Neither the treatment duration nor the dose had an impact on glucose; total, LDL, or HDL cholesterol; triglyceride, and blood pressure values over a 4-month period. This could be explained by the lower sample size (eg, 115 vs 69 patients with weight change and glucose observations, respectively), a short period of follow-up, as well as a selection bias, with patients with high glucose, cholesterol, and/or blood pressure levels stopping clozapine and/or receiving drugs to treat those conditions (ie, lipid-lowering, antidiabetic, and antihypertensive drugs). Finally, neither the mean nor the maximum doses per patient were associated with increased odds of gaining more than 5% of the initial weight after 1 month (ie, a predictor of further weight increases in the long term[23]) or more than 7% of weight along the follow-up (considered a threshold for substantial weight gain).

One of the main limitations of the present study was the limited sample size; followed by the lack of information on food, alcohol intake, and/or physical activity; which could have influenced the weight change. History of previous antipsychotic use was also unavailable, and it probably also influenced the weight change, as patients previously taking high-risk drugs for inducing weight gain might have gained weight differently than patients previously taking low-risk drugs or no psychotropic drug (eg, after a wash-out period). However, since clozapine prescription is limited to non-responders to other antipsychotic drugs (ie, except for patients affected by dopaminergic agent-induced psychoses),[8,9] we are confident that most of the included patients were not antipsychotic naïve, with the exception of elderly patients. Additionally, the homogeneous previous exposure to antipsychotics may explain the discrete, albeit statistically significant, effect size of weight gain per month and/or per clozapine dose unit in this study, since weight gain probably occurred already during the previous treatments, and clozapine was prescribed in a stage where more weight gain is less likely. Therefore, the clinical trend suggesting that clozapine should be used in the early stages of psychosis[27,28] may reveal that clozapine as

a first-choice treatment can induce greater weight gain per month and/or per 100 mg. Adherence to treatment through clozapine plasma concentrations could also not be ascertained, but the administered doses for inpatients were available. Moreover, it would also have been of interest to analyze weight change and plasma concentration correlation, since there is interindividual variability in the metabolism of clozapine based on environmental (ie, smoking status with PAHs present in tobacco smoke being a strong inducer of the clozapine metabolizer cytochrome P4501A2) and genetic factors (ie, cytochrome P4501A2 and other gene polymorphisms).[8] Finally, concerning glucose, lipid levels, and/or blood pressure, a 12-month analysis could not have been done due to the limited number of observations after the first 4 months of treatment. On the other hand, the present naturalistic study allowed examination of the effect of clozapine dose on metabolic adverse effects in a real-world setting, giving further indications about weight consequences following clozapine dose lowering and/or increasing. Altogether, additional studies need to be performed to better define the dose effect on weight change in larger age- and sex-stratified cohorts, and also on glucose; total, LDL, and HDL cholesterol; triglyceride and blood pressure values, taking into account additional confounders unavailable in the present study (eg, physical activities), and interventional controlled studies randomized for age, diagnosis, and other weight-related clinical variables (eg, physical activity and diet) should be considered to confirm our results.

Conclusions

The present study reports a modest effect of clozapine dose increment on weight increase over 1 year, with differences among age categories and sexes, and no dose effect on other metabolic parameters over 4 months.

Supplementary Material

Supplementary material is available at https://academic.oup.com/schizophreniabulletin/.

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Conflict of Interest

All authors declare that they have no conflict of interest in relation to the content of this work.

Author Contributions

CBE had full access to the data in the study and takes responsibility for its integrity and accuracy. Study concepts and designs were provided by CBE. Acquisition of data were provided by MP, NL, CG, and by KJP, AvG, and PC. MP, JC, and SR provided statistical analyses and interpretation. MP and JC provided dataset preparation and manuscript drafting. Each author provided critical revision of the manuscript. CBE, PC, and KJP obtained funding for the study. AvG, KJP, PC, and CE provided administrative, technical, or material support.

Ethical Approval

This study was carried out in accordance with the Declaration of Helsinki. The study protocol was approved by the ethics committee of Vaud (CER-VD).

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