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# Aripiprazole dose associations with metabolic adverse effect: Results from a longitudinal study

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ABSTRACT

*Objective:* Weight gain, blood lipids and/or glucose dysregulation can follow aripiprazole treatment onset. Whether aripiprazole dosage is associated with an increase in these metabolic parameters remains uncertain. The present study investigates aripiprazole dose associations with weight change, blood glucose, lipids, and blood pressure.

*Methods:* 422 patients taking aripiprazole for a minimum of three weeks to one year were selected from PsyMetab and PsyClin cohorts. Associations between aripiprazole dose and metabolic outcomes were examined using linear mixed-effect models.

*Results:* Aripiprazole dose was associated with weight change when considering its interaction with treatment duration (interaction term: −0.10, $p < 0.001$). This interaction resulted in greater weight gain for high versus low doses at the beginning of the treatment, this result being overturned at approximately five months, with greater weight increase for low versus high doses thereafter. LDL and HDL cholesterol levels were associated with aripiprazole dose over five months independently of treatment duration, with an average of 0.06 and 0.02 mmol/l increase for each 5 mg increment, respectively ($p = 0.033$ and $p = 0.016$, respectively). Furthermore, mean dose increases were associated with greater odds (+30 % per 5 mg increase) of clinically relevant weight gain (i.e., ≥7 %) over one year ($p = 0.025$).

*Conclusion:* Aripiprazole dose was associated with one-year weight changes when considering its interaction with treatment duration. Increasing its dose could lead to metabolic worsening over the first five months of treatment, during which minimum effective doses should be particularly preferred.

## 1. Introduction

Antipsychotic drugs, including aripiprazole, are prescribed for treating several psychiatric disorders such as schizophrenia, mania associated with bipolar disorders and major depressive disorder (Chokhawala and Stevens, 2022). Weight gain, blood lipids and/or glucose dysregulation can follow antipsychotic treatment onset and can degenerate into significant clinical conditions such as obesity and/or dyslipidemia (Correll et al., 2011; Delacrétaz et al., 2018). Several mechanisms underlie the antipsychotic-induced metabolic adverse

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effects, the antagonisms at the serotonin 5-$HT_{2C}$ and histamine $H_1$ receptors probably having a role (Kroeze et al., 2003; Matsui-Sakata et al., 2005; Reynolds et al., 2006), and several risk factors, which can be genetic, epigenetic and non-genetic (e.g., age, baseline weight, smoking, diet, physical activity and socioeconomic status) have been described (Delacrétaz et al., 2019; Dubath et al., 2021a; Musil et al., 2015). Nevertheless, whether changes in antipsychotic dosing can increase or decrease such metabolic adverse effects and to what extent remains unclear nowadays, with previous studies suggesting different drug-dependent dose effects (Dubath et al., 2021b; Piras et al., 2022a; Sabé et al., 2023; Schoretsanitis et al., 2022; Viktoria Simon, 2009).

The atypical antipsychotic aripiprazole is a partial agonist at the dopamine $D_2$ and the serotonin 5-$HT_{1A}$ receptors, an antagonist at serotonin 5-$HT_{2A}$ and 5-$HT_{2C}$ receptors, and is mainly metabolized by the cytochrome (CYP) 3A4 and CYP2D6 into its active metabolite dehydroaripiprazole (Casey and Canal, 2017). Aripiprazole is known to induce milder metabolic adverse effects when compared to other atypical antipsychotics. A 26-week randomized double-blind trial comparing 161 patients receiving olanzapine and 156 receiving aripiprazole reported occurrences of 37 % and 14 % clinically relevant weight gain (i.e., ≥7 % weight gain from baseline) and a mean weight change of +4.23 kg and − 1.37 kg, respectively (McQuade et al., 2004).

Despite the milder metabolic risk, significant weight gain can follow aripiprazole treatment onset. For example, a longitudinal study including 109 aripiprazole-treated patients with early psychosis reported an average of +7 kg in weight gain over a median treatment duration of 15 months (Shymko et al., 2023). Therefore, additional research is needed to investigate aripiprazole-induced metabolic adverse effects. To our knowledge, only a few studies reported an association between aripiprazole dose and the induced metabolic alterations. A meta-analysis including ten placebo-controlled studies and 2694 patients with a median treatment duration of 4 weeks reported a linear weight increase and a plateau effect for aripiprazole doses ≤ and > than 10 mg/day, respectively, resulting in a mean weight gain of 0.97 kg for a dose of 30 mg/day (Wu et al., 2022). Moreover, a meta-analysis including 2231 patients reported a greater incidence of weight gain among patients receiving 10 or 5-to-10 mg/day when compared with patients receiving 3.5 mg/day (Seshadri et al., 2021). On the other hand, results from five placebo-controlled trials reported that aripiprazole dose was not associated with an increase in the induced adverse effects among 932 included patients (i.e., weight increase nor lipids and/or glucose alterations) (Marder et al., 2003), and another study including 3097 patients suggested that aripiprazole dose was not associated with diabetes occurrence (Ulcickas Yood et al., 2011).

In order to elucidate whether dosing changes of aripiprazole might affect metabolic adverse effects and to what extent, this study aims to investigate the association between aripiprazole's dose and weight gain, blood glucose, lipids, and blood pressure in a Swiss cohort of psychiatric patients.

## 2. Methods

### 2.1. Study design and participants

Data were obtained from PsyMetab and PsyClin cohorts, two longitudinal studies accepted by The Ethics Committee of the Canton of Vaud (CER-VD). PsyMetab is an ongoing longitudinal study 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) and the Department of Psychiatry of the Geneva University Hospital. While patients gave their consent to be enrolled in PsyMetab, for the PsyClin study the CER-VD gave access to clinical data of patients followed at the Department of Psychiatry of Lausanne University Hospital from 2007 to the end of 2015, because of the non-interventional post hoc analysis design. From both studies, 424 patients newly starting aripiprazole treatment who had at least two weight observations and an aripiprazole treatment duration between three weeks to one year were included. Two patients with outlying clinical profiles (i.e., one with a considerable weight increase due to pregnancy, and one with considerable weight decreases due to a major depressive episode with anorexia) were excluded from the dataset, resulting in 422 aripiprazole-treated patients included in the present study. According to the International Classification of Diseases-10 (ICD-10), included patients could be diagnosed with schizophrenia or schizoaffective disorders (F20-F25 and F28-F29, $N = 212$), bipolar disorder (F30-F31, $N = 74$), depression (F32-F33, $N = 69$), or other diagnoses (F00-F19, F34- F99, $N = 62$).

### 2.2. Measurements

Clinical and metabolic data, as age, sex, aripiprazole dose, prescribed co-medications and previous weight-inducing psychotropic drugs (see Supplementary Table 1), weight, height, smoking status, clinical environment (i.e., in- or out- patients) and blood sampling results were gathered from clinical files at several time points (i.e., treatment onset, after one, three and twelve months of treatment), according to the metabolic monitoring guidelines of the Department of Psychiatry of Lausanne University Hospital. Additional observations of weight and/or other metabolic parameters were available for hospitalized patients. For aripiprazole depot formulations, the usual posology for one injection being one month, the daily dose was calculated by dividing the total depot dose by thirty, (e.g., for 400 mg depot formulation, the total daily dose would be calculated as 400 mg/30 days, i.e., 13.33 mg/day for the 30 days from the injection day). The varying bioavailability levels were not considered, given that mild differences are reported for the oral and intramuscular formulations (i.e., bioavailability of 0.85 and 0.98, respectively), and since aripiprazole is mainly metabolized into its active metabolite dehydroaripiprazole (Boulton et al., 2008; Casey and Canal, 2017). If patients received both depot and oral formulations, doses were summed (e.g., for patients receiving 400 mg depot formulation and an oral supplement of 5 mg of aripiprazole, the total dose would be (400 mg/30 day) + 5 mg = 18.33 mg/day).

### 2.3. Statistical analysis

Clinical variables were compared between patients taking average doses below or above the median dose (i.e., 10 mg) using the Wilcoxon test for continuous variables and the Pearson $\chi^2$ or Fisher test for categorical variables as appropriate. Linear mixed-effects models on weight change over one year (i.e., calculated as percentage change from the first available weight observation) were fitted adjusting for treatment duration, dose, sex, age, weight at baseline, treatment setting (inpatients vs outpatients), smoking status, psychiatric diagnoses, previous weight-inducing psychotropic-drug prescription, and weight-inducing psychotropic co-medication. Since most of the patients had blood lipids, glucose or blood pressure observations only up to five months of treatment (e.g., <15 % of patients had cholesterol observations after five months), linear mixed-effects models for these metabolic outcomes (i.e., blood glucose, lipids, and blood pressure) were fitted over five months of treatment. These models were adjusted for treatment duration, dose, sex, age, body mass index (BMI) at baseline, medical environment (inpatients vs outpatients), smoking status, psychiatric diagnoses, previous weight-inducing psychotropic-drug prescription, and weight-inducing psychotropic co-medication. No significant interaction between the dose and treatment duration was found and it was therefore excluded in the latter models. Patients taking non-psychiatric medications related to metabolic outcomes were excluded when analyzing the outcomes evolution (i.e., patients taking antidiabetic, antihypertensive, lipid-lowering drugs were excluded when analyzing glucose, blood pressure and lipid evolutions, respectively, see Supplementary Table 1). Given the outlying clinical profile associated with doses above the maximum recommended dose per day (i.e., >30 mg/day), observations reporting a dose >30 mg/day were excluded, representing ~2 % of total

observations. Logistic regression was used to establish whether the dose could increase the odds of developing clinically relevant weight gain (i.e., ≥7 % of weight gain from baseline), obesity (i.e., BMI ≥ 30 kg/m$^2$), hyperglycemia (i.e., fasting glucose ≥5.6 mmol/l), hypercholesterolemia (i.e., total cholesterol ≥5.2 mmol/l and LDL cholesterol ≥4.1 mmol/l), hypocholesterolemia (i.e., HDL ≤1.03 mmol/l for men and ≤ 1.29 mmol/l for women), hypertriglyceridemia (i.e., fasting triglycerides ≥1.7 mmol/l) and hypertension (i.e., systolic blood pressure ≥ 140 mmHg and diastolic blood pressure ≥ 90 mmHg). The models were adjusted for the mean dose over the follow-up, sex, age, body mass index (BMI) at baseline, treatment setting (inpatients vs outpatients), smoking status, psychiatric diagnoses, previous weight-inducing psychotropic-drug prescription, and weight-inducing psychotropic co-medication. Analyses were done using Stata 17.0 (StataCorp; College Station, Texas) and the statistical software package R-4.0.2. Statistical significance was set at a $p$-value ≤0.05.

## 3. Results

Patients taking, on average, doses >10 mg/day (Table 1) were younger ($p < 0.001$), mostly diagnosed with schizophrenia or schizoaffective disorder ($p < 0.001$), had longer follow-ups ($p = 0.001$) and were also more likely to receive psychotropic co-medications ($p < 0.001$) and to have received a previous psychotropic drug ($p < 0.001$).

An association between aripiprazole dose and weight change was found only when considering an interaction between treatment duration and aripiprazole dose (interaction term: −0.10, $p < 0.001$, Table 2). This interaction showed that high doses were associated with greater weight increase versus low doses at the beginning of the treatment, and that, reversely, low doses were associated with greater weight increase versus high doses after five months of treatment approximately (Fig. 1). Concerning the other co-variates, women gained less weight than men on average (i.e., −0.86 %, $p = 0.041$), baseline weight was negatively associated with weight changes (i.e., −0.06 % for each additional baseline kg, $p < 0.001$), and smokers gained more weight than non-smokers on average (+0.99 %, $p = 0.017$) according to Model 1 of Table 2.

No significant interaction between the dose and sex or age categories was found (data not shown). Since switching to aripiprazole might be a pharmacological strategy to reduce psychotropic-induced weight gain (Weiden, 2007), a stratified analysis including only patients with and without records of previous psychotropic treatment was also performed, confirming an interaction between the dose and treatment duration (data not shown). Moreover, since young age is also a risk factor for psychotropic-induced weight gain, a sensitivity analysis considering only 23 young adults without record of previous psychotropic treatment was also performed, showing a lack of association between the dose and weight changes, even when considering its interaction with treatment duration (data not shown). Since the varying bioavailability levels of the oral and depot formulations were not considered, a sensitivity analysis excluding the 15 patients receiving aripiprazole injection was also performed, confirming the results reported in Table 2 (data not shown). Moreover, since we included patients from two different cohort studies, two sensitivity analyses were performed either by adjusting for the cohort of origin, or excluding the 30 PsyClin patients, both confirming our results (data not shown). Likewise, a sensitivity analysis including all the prescribed doses (i.e., up to 45 mg/day) was performed, confirming a significant interaction between time and dose (data not shown).

Linear mixed-effect models on metabolic outcomes over five months of treatment (i.e., most of the patients had blood lipids, glucose or blood pressure observations only up to five months of treatment as previously mentioned) showed a positive association between the dose, LDL and HDL cholesterol levels (Table 3), with 0.06 and 0.02 mmol/l increase for each 5 mg increment in aripiprazole dose, respectively ($p = 0.033$ and $p = 0.016$, respectively), and a trend was found for total cholesterol ($p =$

**Table 1**
Demographic and clinical data for patients receiving an average dose of aripiprazole of ≤10 or > 10 mg/day.

| | ≤10 mg ($N$ = 211) | >10 mg (N = 211) | P-value | Total[a] ($N$ = 422) |
|---|---|---|---|---|
| Dose (mg/day)[b] | 6.7 (5.0–9.9) | 15 (14–19) | <0.001 | 10 (6.7–15) |
| Age (Year) | 39 (29–52) | 33 (25–45) | <0.001 | 36 (26–48) |
| Sex | | | 0.051 | |
| Female | 120 (56.9 %) | 99 (46.9 %) | | 219 (51.9 %) |
| Age categories[c] | | | 0.073 | |
| Young adults | 34 (16.1 %) | 52 (24.6 %) | | 86 (20.4 %) |
| Adults | 161 (76.3 %) | 148 (70.1 %) | | 309 (73.2 %) |
| Elderly | 16 (7.6 %) | 11 (5.2 %) | | 27 (6.4 %) |
| Smoking status | | | 0.24 | |
| Smokers | 113 (53.6 %) | 126 (59.7 %) | | 239 (56.6 %) |
| Psychiatric diagnoses[d] | | | <0.001 | |
| Schizophrenia and Schizoaffective disorders | 70 (33.2 %) | 142 (67.3 %) | | 212 (50.2 %) |
| Others | 141 (66.8 %) | 69 (32.7 %) | | 210 (49.8 %) |
| Follow-up duration (Days) | 96 (51–180) | 140 (58–230) | 0.001 | 100 (55–200) |
| Baseline weight (Kg)[e] | 72 (64–84) | 74 (64–86) | 0.19 | 73 (64–85) |
| Baseline BMI (Kg/m$^2$) [e] | 25 (22–29) | 25 (22−30) | 0.71 | 25 (22–29) |
| Missing | 9 (4.3 %) | 4 (1.9 %) | | 13 (3.1 %) |
| Medical environment | | | <0.001 | |
| Inpatients | 27 (12.8 %) | 93 (44.1 %) | | 120 (28.4 %) |
| Previous psychotropic drug[f,g] | | | <0.001 | |
| Yes | 121 (57.3 %) | 178 (84.4 %) | | 299 (70.9 %) |
| Psychotropic co-medication[g] | | | <0.001 | |
| Yes | 41 (19.4 %) | 81 (38.4 %) | | 122 (28.9 %) |
| Antidiabetic co-medication[h] | | | 0.57 | |
| Yes | 5 (2.4 %) | 8 (3.8 %) | | 13 (3.1 %) |
| Antihypertensive co-medication[h] | | | 0.56 | |
| Yes | 12 (5.7 %) | 16 (7.6 %) | | 28 (6.6 %) |
| Lipid lowering co-medication[h] | | | 0.29 | |
| Yes | 5 (2.4 %) | 10 (4.7 %) | | 15 (3.6 %) |

[a] Continuous variables are reported as median (Q1-Q3) and categorical variables as number (%).
[b] Median dose was 10 mg/day. All patients with depot formulations (N = 15) were included in the >10 mg/day group.
[c] Young adults: age 16–24 years; adults: age 25–64 years; elderly: age 65–82 years.
[d] International Classification of Diseases-10: organic disorders, anxiety, personality disorder, intellectual disability, dementia, substance use disorder, depression and bipolar disorder were classified together as "other." For five patients in the "other" category, diagnostic data were missing.
[e] First available observation.
[f] Patients with records of previous weight-inducing psychotropic drugs according to clinical files. Information on whether those patients switched psychotropic drugs or interrupted the previous treatment was unavailable. Data on whether patients without record of previous psychotropic drugs were psychotropic-naïve were unavailable.
[g] Weight-inducing psychotropic drugs. See Supplementary Table 1 for drug list.
[h] See Supplementary Table 1 for drug list.

**Table 2**
Dose and time effects of linear mixed-effect models on weight change.

| Weight change over one year[a] | | | |
|---|---|---|---|
| *Variables* | Estimates | 95 % CI | p |
| *Model 1*[b] | | | |
| Treatment duration (Month) | 0.17 | 0.10 to 0.24 | <0.001 |
| Dose (5 mg) | 0.13 | −0.08 to 0.34 | 0.23 |
| *Model 2* | | | |
| Treatment duration (Month) | 0.49 | 0.31 to 0.67 | <0.001 |
| Dose (5 mg) | 0.45 | 0.18 to 0.71 | 0.001 |
| Treatment duration (Month) * Dose (5 mg)[c] | −0.10 | −0.15 to −0.05 | <0.001 |
| N patients[c] | 422 | | |
| N observations | 1941 | | |

Abbreviations: CI: confidence interval; p:*p*-value.

[a] Three linear mixed-effect models including the same number of patients and observations until follow-up day 365. Models were also adjusted for age, sex, baseline weight, smoking status, treatment setting, psychiatric diagnoses, weight-inducing psychotropic co-medications and previous weight-inducing psychotropic drug.

[b] A 50 kg patient starting aripiprazole would gain 0.25 kg after 3 months of treatment (i.e., +0.17*3).

[c] A sensitivity analysis was performed excluding patients with short follow-ups (i.e., 30 or 45 days), confirming our results.

0.057). The dose was not associated with glucose or triglyceride levels ($p = 0.55$ and $p = 0.26$, respectively), nor with systolic or diastolic blood pressure ($p = 0.13$ and $p = 0.27$, respectively). Treatment duration was not associated with any of the previously mentioned metabolic parameters. Moreover, no significant interaction between the dose and treatment duration was found and it was therefore excluded from the latter models. Since the models for other metabolic outcomes were performed over five months of treatment, a sensitivity analysis was performed on weight changes over five months of treatment, showing no dose effect on weight changes (data not shown).

Increases in the mean dose over the follow-up were associated with +30 % odds for each 5 mg increase ($p = 0.025$) of developing clinically relevant weight gain (i.e., ≥7 %), with patients who gained ≥7 % in weight receiving higher doses than patients who did not reach this threshold (Wilcoxon rank-sum test $p = 0.041$, data not shown). On the other hand, no association with increased odds of developing obesity, hyperglycemia, dyslipidemias, or hypertension was found (data not shown).

## 4. Discussion

With a one-year longitudinal study design including patients newly starting aripiprazole treatment, the association between aripiprazole dose and weight changes was investigated. When excluding the interaction between the dose and treatment duration from our models, aripiprazole dose was not associated with weight changes. This result

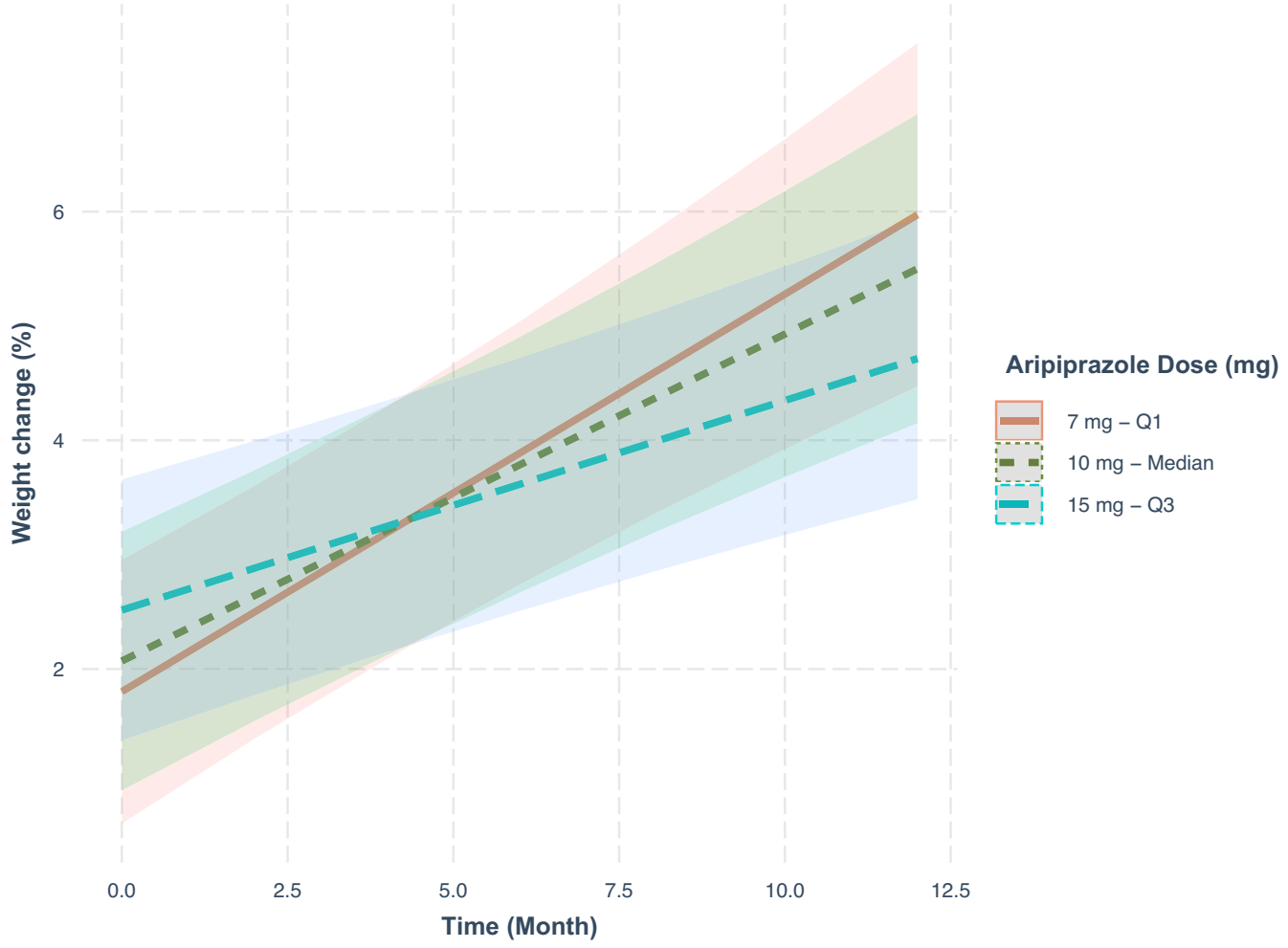


**Fig. 1.** Dose and treatment duration interaction according to Model 2, Table2.
Fig. 1. Representation of the interaction between aripiprazole dose and treatment duration according to Table 2 Model 2.

**Table 3**
Dose and time effects of linear mixed-effect models on other metabolic parameters.

| *Variables* | Estimates | 95 % CI | p |
|---|---|---|---|
| *Glucose*[a,b,c] | | | |
| Treatment duration (Month) | −0.02 | −0.08 to 0.03 | 0.39 |
| Dose (5 mg) | 0.02 | −0.05 to 0.09 | 0.55 |
| N patients | 275 | | |
| N observations | 472 | | |
| *Total cholesterol*[a,d,e] | | | |
| Treatment duration (Month) | −0.00 | −0.04 to 0.03 | 0.81 |
| Dose (5 mg) | 0.06 | −0.00 to 0.12 | 0.057 |
| N patients | 327 | | |
| N observations | 619 | | |
| *Cholesterol LDL*[a,d,e,f] | | | |
| Treatment duration (Month) | −0.00 | −0.04 to 0.03 | 0.83 |
| Dose (5 mg) | 0.06 | 0.00 to 0.11 | 0.033 |
| N patients | 321 | | |
| N observations | 594 | | |
| *Cholesterol HDL*[a,d,e,g] | | | |
| Treatment duration (Month) | −0.01 | −0.02 to 0.00 | 0.12 |
| Dose (5 mg) | 0.02 | 0.00 to 0.04 | 0.016 |
| N patients | 327 | | |
| N observations | 612 | | |
| *Triglycerides*[a,b,e] | | | |
| Treatment duration (Month) | −0.01 | −0.05 to 0.04 | 0.79 |
| Dose (5 mg) | 0.04 | −0.03 to 0.10 | 0.26 |
| N patients | 305 | | |
| N observations | 546 | | |
| *Systolic blood pressure*[h] | | | |
| Treatment duration (Month) | −0.44 | −1.09 to 0.21 | 0.19 |
| Dose (5 mg) | 0.71 | −0.20 to 1.62 | 0.13 |
| N patients | 336 | | |
| N observations | 899 | | |
| *Diastolic blood pressure*[h] | | | |
| Treatment duration (Month) | −0.44 | −0.93 to 0.05 | 0.077 |
| Dose (5 mg) | 0.38 | −0.30 to 1.07 | 0.27 |
| N patients | 336 | | |
| N observations | 899 | | |

Abbreviations: CI: confidence interval; p:p-value.
[a] Expressed in mmol/l.
[b] Non-fasting observations were excluded.
[c] From the 422 selected patients, we included patients with available glucose data that were not taking antidiabetic drugs.
[d] Model adjusted also for fasting status.
[e] From the 422 selected patients, we included patients with available lipids data that were not taking lipid-lowering drugs. The LDL cholesterol of a fictive patient would increase by 0.06 mmol/l for each additional 5 mg of aripiprazole.
[f] When excluding patients from the PsyClin cohort or adjusting for the cohort of origin, similar results were found. When excluding patients with short follow-ups (i.e., 30 or 45 days), only a trend-significancy level was found ($p = 0.081$ and 0.088, respectively).
[g] Similar results were found when adjusting for the cohort of origin (i.e., PsyMetab or PsyClin), or when excluding patients with follow-ups shorter than 45 days. Trend-significancy results were found when excluding patients from the PsyClin cohort ($p = 0.062$) or patients with follow-ups shorter than 30 days ($p = 0.059$).
[h] From the 422 selected patients, we included patients with available blood pressure data that were not taking antihypertensive drugs. Blood pressure is expressed in mmHg.

agrees with five placebo-controlled trials (Marder et al., 2003), and it highlights that aripiprazole dose was also not associated with weight increase in the present uncontrolled real-world setting, in which aripiprazole dose prescription was due to clinical needs and not to randomization. On the other hand, our results are in contrast with a meta-analysis reporting greater weight increase among patients receiving 10 or 5-to-10 mg versus 3.5 mg of aripiprazole (Seshadri et al., 2021), the difference in results probably due to the varying dosage ranges included in the two analyses (i.e., up to 30 mg in the present one). Nevertheless, to the best of our knowledge, the present study also suggests for the first time that aripiprazole dose is associated with weight changes in a time-dependent fashion. Indeed, Fig. 1 shows greater weight gain for high versus low doses at the beginning of the treatment, this result being overturned at approximately five months, with greater weight increase for low versus high doses thereafter. Aripiprazole is a low metabolic-risk medication that has been associated with an attenuation in weight gain after switching from other psychotropic drugs (Piras et al., 2022b). Thus, since patients receiving high (>10 mg) doses were more likely to have been treated with previous psychotropic drugs than patients receiving low doses (≤10 mg, see Table 1), aripiprazole onset could have led to an attenuation of their weight gain, resulting in lower weight increase for high versus low doses after approximately five month of treatment. Nevertheless, the latter results call for further studies specifically investigating the long-term effect of aripiprazole dose. Indeed, most of the included patients had a treatment duration between approximately 2 and 6 months (i.e., quartile 1 and 3 of treatment duration were 55 and 200 days, respectively), with patients taking lower doses on average having shorter follow-ups than patients taking higher doses. Moreover, among patients with records of previous psychotropic treatment, we could not ascertain whether patients were directly switching from another psychotropic drug, or whether there was a wash-out period between the two treatments, which could have been associated with different weight change patterns. Finally, aripiprazole dose was also associated with greater odds of reaching clinically relevant weight gain (i.e., ≥7 %), probably because patients who gained ≥7 % in weight received higher doses than patients who did not reach this threshold.

Interestingly, in a previous one-year longitudinal study including patients treated with clozapine (i.e., one of the antipsychotics most associated with weight gain (Pillinger et al., 2019)), we reported an increasing effect of clozapine dose on weight changes after a first adaptation to clozapine treatment (i.e., three months) (Piras et al., 2023). Conversely, in the present study, we showed for the first time that high doses of aripiprazole (i.e., one of the antipsychotics least associated with weight gain (Pillinger et al., 2019)) were associated with less weight increase than low doses after five months of treatment. Thus, these differences further underlie the metabolic-risk gap between high- (e.g., clozapine) and low-risk (e.g., aripiprazole) drugs. Of note, the differing sizes of the predicted weight increase per month (i.e., time effect on weight changes) in the present study (i.e., +0.17 %, see Model 1 of Table 2) and in the clozapine study (i.e., +0.50 %) are comparable with a previous two-year longitudinal study including both patients taking low- (+0.26 %) and high-risk drugs (+0.67 %), respectively (Piras et al., 2022b). Given the different cohorts included in the clozapine study and the present study, a direct comparison of the different dose effect sizes (i.e., dose effect on weight changes) cannot be made due to different sample sizes and patient features. Thus, it would be interesting to compare different dose effect sizes in further studies including a homogeneous cohort of patients taking high- and low-risk drugs.

No interaction of the dose with age and sex was found, suggesting the effect of dose increases on weight change was independent of different ages and sex. However, since the present cohort was composed mainly of adults (i.e., 73 %), further studies including age- and sex-categorized cohorts should be considered. Although different weight patterns might follow switching to and/or starting aripiprazole (Piras et al., 2022b) as previously mentioned, we found similar results when considering only patients with and without records of previous weight-inducing psychotropic treatment. However, we could not ascertain whether patients were switching to aripiprazole or whether they were antipsychotic-naïve, with possible missing data on previous psychotropic prescription. Moreover, the additional sensitivity analysis including only 23 young adults without record of previous psychotropic drugs showed no association of the dose with weight change, even when considering its interaction with time, probably due to the low sample size. Thus, further studies including only naïve patients or patients switching from other psychotropic drugs should be considered to ascertain whether the dose has different effects between these two groups of patients, and to elucidate the long-term effect of the dose (i.e.,

after five months, since most of the included patients had a treatment duration up to 6 months as previously mentioned).

Due to missing data, the association between the dose and blood lipids, glucose or blood pressure was investigated over five months of treatment, in which LDL and HDL cholesterol levels were positively associated with aripiprazole dose. This result is in contrast with five placebo-controlled studies not finding this association (Marder et al., 2003), with the discrepancy of the results probably due to the differing study durations (i.e., only four-to-six weeks in the previously mentioned trials and five months in the present study). Moreover, although the dose was associated with a worsening in LDL cholesterol, which can follow the onset of several antipsychotic treatments, it was also associated with an improvement in HDL cholesterol. This result may be due to the metabolic amelioration that can follow a switch to aripiprazole or the onset of aripiprazole as a co-psychotropic treatment. Indeed, increases in HDL cholesterol were found in a previous open-label study including patients switching from several antipsychotics to aripiprazole (Kim et al., 2009), and in another open-label trial including patients that added aripiprazole to a previously-introduced clozapine treatment (Henderson et al., 2006). On the other hand, the dose was not associated with weight changes over five months, confirming the absence of an independent dose effect on weight changes. Moreover, no association was found between the dose and glucose or triglycerides, probably due to the short treatment duration (i.e., five months, as previously mentioned) and/or the low metabolic effect of aripiprazole. Finally, aripiprazole dose was not associated with increased odds of developing a metabolic disease such as hyperglycemia, this result being in line with a previous work indicating no dose dependence for diabetes occurrence (Ulcickas Yood et al., 2011). Due to the lack of data on blood pressure, glucose or lipids, further studies should elucidate the long-term effect of aripiprazole dose on these outcomes (i.e., after five months of treatment).

Several limitations of the present study must be mentioned. Confounding variables, such as diet, physical exercise, alcohol consumption, and chlorpromazine equivalent doses of psychotropic co-medications, which could have affected weight changes, were not available. Moreover, although information on the dose administered was available for inpatients, adherence to treatment, which could have also affected weight changes (i.e., prescription of higher doses for non-adherent patients), could not be ascertained. In addition, since aripiprazole is metabolized by CYP2D6, which can lead to inter- and intra-variabilities in drug exposure, it would have been interesting to measure the plasma concentrations. In the same way, many drugs can interact with CYP3A4, aripiprazole's secondary metabolism pathway, so that co-medications, other than antipsychotics, could also lead to heterogeneous exposure. Data on antipsychotic-naïve status, on whether we included first-episode patients, on illness duration and clinical response, or on whether patients were undergoing a switch from another treatment to aripiprazole (e.g., due to excessive weight gain) were also unavailable and could have influenced the weight gain associated with intake of aripiprazole as previously mentioned. Moreover, as previously discussed, given the low number of included patients with treatment durations up to one-year, and since previous studies reported a flattening of weight change over treatment duration with antipsychotics, independently of their doses (Bazo-Alvarez et al., 2020), the present results should be confirmed by further studies focusing on the long-term effect of both aripiprazole dose and treatment duration on metabolic adverse effects. On the other hand, the main advantage of the present study was the large sample size proceeding from real-world, naturalistic settings, in which previously-treated and psychotropic-naïve patients with heterogeneous confounding behaviors (e.g., adherence to treatment) are included, with the main novelty being the association between aripiprazole dose and weight change in a time-dependent fashion.

## 5. Conclusion

Over the first five months of treatment, aripiprazole dose was associated with increases in blood lipids and weight. Thus, increasing aripiprazole dose could lead to metabolic worsening, so that minimum effective doses should be preferred particularly during the first five months of treatment.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2024.07.007.

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## CRediT authorship contribution statement

**Marianna Piras:** Writing – original draft, Formal analysis, Data curation. **Iris Popovic:** Writing – original draft, Formal analysis, Data curation. **Setareh Ranjbar:** Writing – review & editing, Methodology, Formal analysis. **Claire Grosu:** Writing – review & editing, Project administration. **Nermine Laaboub:** Writing – review & editing, Project administration. **Othman Sentissi:** Writing – review & editing, Project administration. **Mohamed H. Lakhal:** Writing – review & editing, Project administration. **Franziska Gamma:** Writing – review & editing, Project administration. **Kerstin J. Plessen:** Writing – review & editing, Project administration, Funding acquisition. **Armin von Gunten:** Writing – review & editing, Project administration. **Philippe Conus:** Writing – review & editing, Project administration, Funding acquisition. **Chin B. Eap:** Writing – review & editing, Supervision, Project administration, Funding acquisition, Conceptualization.

## Declaration of competing interest

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

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### *Author contributions*

CBE had full access to the data in the study and takes responsibility for its integrity and accuracy. Study conceptualization and design was provided by CBE. Project administration was provided by MP, NL, CG and by OS, ML, FG, KJP, AvG and PC. MP, IP and SR provided statistical analyses and interpretation. MP and IP provided data curation and manuscript original drafting. Each author provided a critical review of the manuscript. CBE, PC and KJP obtained funding for the study. OS, FG, AvG, KJP, PC, and CBE provided administrative, technical, or resources support.

*Ethics statement*

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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