Title: Daily Dose Effects of Risperidone on Weight and Other Metabolic Parameters: A Prospective Cohort Study.

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Risperidone's daily dose effects on weight and other metabolic parameters: a prospective cohort study.

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Declaration of interests

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ABSTRACT

Background. Atypical antipsychotics can induce metabolic side effects, but whether they are dose-dependent remains unclear.

Objective. To assess the effect of risperidone and/or paliperidone dosing on weight gain, blood lipids, glucose and blood pressure alterations.

Methods. Data for 438 patients taking risperidone and/or its metabolite (paliperidone) for up to one year were obtained between 2007 and 2018 from a longitudinal study monitoring metabolic parameters.

Results. For each mg increase in dose, we observed a weight increase of 0.16% (p=0.002), 0.29%, 0.21% and 0.25% (p<0.001) at one, three, six and twelve months of treatment, respectively. Moreover, dose increases of 1mg raised the risk of a ≥5% weight gain after one month (OR 1.18; p=0.012), a strong predictor of important weight gain in the long term. Splitting the cohort into age categories, the dose had an effect on weight change after three months of treatment (up to 1.63%, p=0.008) among adolescents (≤17 years-old), at three (0.13%, p=0.013) and twelve (0.13%, p=0.036) months among adults (>17 and <65 years-old), and at each time-points (up to 1.55%, p<0.001) among older patients (≥65 years-old). In the whole cohort, for each additional mg we observed a 0.05 mmol/l increase in total cholesterol (p=0.018) and a 0.04 mmol/l increase in LDL cholesterol (p=0.011) after one year.

Conclusion. Although of small amplitude, these results show an effect of risperidone's daily dose on weight gain and blood cholesterol levels. Particular attention should be given to the decision of increasing the drug dose, and minimum effective dosages should be preferred.

Key words: risperidone, paliperidone, dose, daily dose intake, weight gain, metabolic parameters, glucose, lipids, blood pressure.

INTRODUCTION

Compared to the general population, psychiatric patients present a greater prevalence of metabolic disorders [1] such as dyslipidemia, diabetes, and/or visceral obesity, leading to cardiovascular diseases and contributing to decreased life expectancy of more than 10 years [2-4]. Several antipsychotics, antidepressants, and mood stabilizers can induce metabolic alterations, such as weight gain (WG), blood lipid and/or glucose alterations [5,6]. Atypical antipsychotics (AAP), along with female gender, nonwhite ethnicity, low baseline body mass index (BMI <25 kg/m^2) and young age [5,7-10], represent the main risk factors for antipsychotic-induced weight gain (AIWG), which can lead to a clinically relevant threshold (≥7% increase from baseline) [11,12]. Due to their metabolic adverse effects, which can drive patients into partial and/or total non-adherence to treatment, efforts to reduce the use of AAP have been made [13-15]. Nevertheless, they remain nowadays the reference in the treatment of schizophrenia [16]. Given the wide use of AAP, a deeper understanding of the mechanisms leading to AIWG and/or metabolic impairments is essential. Several studies examined the clinically relevant question of a dose-related effect of antipsychotics on metabolic parameters [17], with some results suggesting that WG seems to develop even when low off-label doses are prescribed [18,19]. Since AAPs differ in their metabolic risk profile [20], the dose effect for each individual AAP remains to be studied.

Risperidone is an AAP with a medium-to-high metabolic risk profile [20]. It is mainly metabolized in the liver by the cytochrome P450 2D6 (CYP2D6)[21] into 9-hydroxyrisperidone or paliperidone. The latter is also available for prescription and presents the same metabolic risk profile as risperidone [20]. In 2009, a literature review summarized ten studies focusing on the effect of risperidone dosing on WG [17]. Two randomized controlled trials reported that WG was greater in high dose-fixed groups when compared with low dose-fixed groups (e.g., 8mg/day vs 1mg/day) after eight weeks of treatment[22,23]. This dose effect was then confirmed by one prospective open-label study, reporting an increase of 0.084kg for each additional mg of risperidone during 6 weeks of treatment [24]. The other studies either did not report or did not suggest a correlation between the dose and WG [25-28]. Both risperidone and paliperidone are available as depot formulations and, in an open-label study with patients receiving different depot doses of risperidone every 2 weeks, no difference in WG was observed [29]. To our knowledge, only a few studies have so far examined the influence of risperidone dose on metabolic parameters other than WG, with no significant findings [30,31]. In the present study, we aimed to examine a dose-dependent effect of

risperidone and/or paliperidone on WG and on other metabolic parameters (plasma lipid and glucose levels, blood pressure) in a large cohort of psychiatric patients in Switzerland.

METHODS

Study design

Data were obtained from a longitudinal study (PsyMetab) 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). The Ethics Committee of the Canton of Vaud (CER-VD) approved PsyMetab and recruited patients gave their informed consent for research use of their clinical and genetic data. In addition, CER-VD granted access to data from patients who had a clinical follow-up of metabolic parameters in the Department of Psychiatry of the Lausanne University Hospital from 2007 to the end of 2015 (PsyClin) because of the non-interventional post hoc analysis design. Patients starting a treatment with risperidone and/or paliperidone between 2007 and 2018 with at least two weight observations were selected in both cohorts. Clinical follow-ups not longer than one year and not shorter than 3 weeks were used. Different time intervals were taken into account to appreciate the evolution of the metabolic parameters: one month (≤45 days of treatment); three months (>45 days and ≤105 days); six months >105 days and ≤190 days and up to one year (>190 days and ≤380 days).

Measurements

As previously described [32], within the first week of treatment, data on age, sex, comorbidities, antipsychotic dose and date of first drug intake were collected. Clinical features, such as weight, height, waist circumference, blood pressure, plasma glucose and lipids were measured at baseline and at one, three, twelve months, and then yearly. In addition, weight, waist circumference and blood pressure were also measured at two and six months. Daily dose intake (DDI) information was extracted from medical files and reported in mg/day for both oral and depot formulations. Since there is approximately a 1:2 equivalence between risperidone and paliperidone doses, both oral and depot DDI were transformed into risperidone-equivalent doses [33]. For depot formulations (Supplementary table 1), the administered dose was divided by the expected number of days between two injections. If patients were receiving both depot and oral forms, the sum between the two doses was used without accounting for the different bioavailabilities of the two formulations, since risperidone is metabolized mainly into paliperidone. To appreciate the evolution of weight gain, the change, expressed as the percentage of baseline value over

time, was defined as (value – initial value)/ initial value *100. For the analysis of the evolution of blood metabolic parameters, all patients receiving co-medications (Supplementary table 2) for treating related somatic diseases were excluded (e.g., patients taking lipid-lowering drugs were excluded when cholesterol levels were analyzed).

Statistical analysis

Both demographic and metabolic variables were compared between patients with DDI below and above the median (≥ versus <3mg/day) by Pearson χ^2 for categorical variables and t-test for continuous variables. To evaluate the effect of the dose on weight change, a linear mixed effect model (Rstudio, package "nlme"[34]) was adjusted for age, sex, treatment duration, baseline weight and DDI, and performed at the four time intervals (1, 3, 6 and 12 months). To appreciate the dose effect, DDI outliers were excluded and doses<10 mg/day were included. For total, LDL and HDL cholesterol, triglycerides, glucose and blood pressure values, the same model was adjusted for age, sex, treatment duration, DDI, baseline BMI and it was performed at 12 months. The piecewise function was also applied to DDI, allowing us to estimate the weight changes for lower and higher values than 3 mg/day. Since the prescribed dose also depends on the diagnosis[35], these models were also adjusted for this variable. Logistic regression was also used for analyzing the presence of important WG (≥5% after one month [36] and ≥7% along the follow-up). Statistical significance was set at a p-value ≤0.05 and analyses were performed using Stata16.1 (StataCorp; College Station, Texas) and R environment for statistical computing version 3.6.0.

RESULTS

Patients' characteristics

Four hundred thirty-eight patients starting a follow-up (mean duration ± SD: 153 ± 108 days) on risperidone (374 patients) and/or paliperidone (64 patients) were included. Table 1 reports clinical parameters and co-medications, dividing patients into those with lower (45.9%) or higher (54.1%) DDI than 3mg/day. Patients who reached a clinically relevant threshold (≥7% of WG) were younger (37.8 years old versus 42.5 years old; p=0.017), leaner (baseline BMI 22.1 kg/m^2 versus 25.4 kg/m^2; p<0.001), and had longer follow-ups (176 days versus 139 days; p<0.001).

Weight change over time

Linear mixed effect models were performed on weight change at one, three, six and twelve months (Table 2). A significant effect of time on weight change was found for each time point ($p<0.001$), with 1.58%, 1.20%, 0.80% and 0.57% WG per month at 1, 3, 6 and 12 months, respectively. Concerning DDI, a significant impact on weight change is shown at each time-point ($p=0.002$ at one month, $p<0.001$ for the others). At one month, a 0.16% increase in weight was observed for each additional mg, whereas at twelve months this effect reached 0.25%.

When the piecewise function was applied on DDI (Table 3), at one month we observed a DDI effect on WG only for DDI>3 mg/day ($p=0.007$). For each additional mg, the weight increase was 0.16%. For DDI ≤ 3 mg/day, no significant effect on weight change was found ($p=0.22$). At 3, 6 and 12 months, both DDI ≤3 mg/day and DDI > 3 mg/day had a significant effect on weight change. When adjusting the model for early weight gain (≥5% WG in one month, a strong predictor of further WG in the long-term), no significant effect of DDI on weight change was found (Supplementary table 3, $p=0.66$, $p=0.42$, $p=0.38$ at 3, 6, 12 months, respectively). Moreover, patients with ≥5% WG in one month kept gaining more weight than patients who did not reach this threshold (+6.68%, + 7.36%, +7.70% at 3, 6 and 12 months, respectively). Smoking status and psychotropic co-medications did not have a significant impact on weight change and were therefore excluded from the model.

An additional analysis was performed on adolescent (≤17 years-old), adult (>17 and <65 years-old) and elderly (≥65 years-old) subgroups (Supplementary Table 4). DDI had an increasing impact on weight change at six (1.54%, $p=0.009$) and twelve (1.63%, $p=0.008$) months among adolescents, at three (0.13%, $p=0.013$) and twelve (0.13%, $p=0.036$) months among adults and at the four time-points among older patients, with a weight increase of 0.76%, 1.37%, 1.58% and 1.41% for each additional mg, respectively ($p<0.001$). Sex subgroups analysis were also performed (Supplementary Table 5), with the dose showing significant effect on WG at the four time points for women ($p\leq0.001$), and only at 3 months for men ($p=0.003$).

Other metabolic parameters

At 12 months (Table 4), time had a significant impact on total and LDL cholesterol values, with an increase of 0.03 and 0.02 mmol/l per month, respectively ($p=0.011$ and $p=0.045$, respectively), in the whole cohort including adolescents and elderly patients. DDI also had a significant effect, with a total and LDL cholesterol level increase of 0.05 and 0.04 mmol/l, respectively, for each additional mg

(p=0.018 and p=0.011, respectively). No significant effect of time nor DDI were observed on the increase of triglycerides and glucose levels, of systolic blood pressure and on the decrease of HDL cholesterol levels. A negative effect for DDI was detected for diastolic blood pressure (-0.60 mmHg for each additional mg, p=0.001), but with no effect of time (p=0.36). Psychotropic co-medications did not have a significant influence on metabolic parameters and were therefore excluded from the models.

Logistic regression

A logistic regression (Table 5) was performed to evaluate the risk of developing ≥5% WG after one month of treatment and a dose-significant effect was observed with both the mean (OR 1.18; p=0.012) and maximum values (OR 1.21; p<0.001) of DDI during the follow-up. Concerning the risk of developing a ≥7% WG, a dose-significant effect of DDI was observed when the maximum value of DDI during the follow-up was considered (OR 1.09; p=0.043).

Sensitivity analysis

Since we did not account for the different bioavailability between depot and oral formulations, a sensitivity analysis excluding the 80 patients receiving depot forms was performed, confirming the validity of the results (data not shown).

The effect of the dose on WG was also evaluated among patients taking paliperidone or risperidone only (Supplementary Table 6). Despite the low statistical power (n=28), WG was dose-dependent after one year among patients taking paliperidone only (p=0.005). For patients taking risperidone only (n=351), DDI did not have an effect on WG after 1 month (p=0.17), but had a significant effect on WG after 3, 6 and 12 months (p<0.001, p=0.007, p=0.035, respectively), on total and LDL-cholesterol after 12 months (p=0.002). A negative effect of DDI was also found for blood pressure (both systolic and diastolic) among patients taking risperidone only. Due to the low number of patients on paliperidone only with data available for blood pressure (n=20) or lipid levels (n=23), the effects of the doses were not calculated.

DISCUSSION

Using a one-year naturalistic study design we aimed to look at the dose effect of risperidone and/or paliperidone on both WG and blood metabolic parameters. Along with treatment duration, dose augmentation had an increasing effect on weight. Previous double-blind randomized controlled trials

already showed a risperidone dose-WG association[22,23]. However, while in controlled trials researchers divide the population into different fixed-dose groups, and look at WG after a given time, in our non-interventional prospective study we looked at the effect of the dose (fixed dose, dose increase and/or decrease) on the evolution of weight change over time. Moreover, in double-blind randomized controlled trials, patients receive a fixed dose according to the randomization, while in our case prescribed dose reflected the clinical needs (e.g., severity of the symptoms) of the patients. Our results are also in agreement with a previous prospective study, reporting an increase of 0.084 kg for each mg increase in risperidone dose[24]. Given that younger and/or leaner patients are more at risk of WG [8], we are confident that expressing the WG as a percentage is more reliable than expressing it as a defined-kilogram amount increase [24]. Other studies failed to show a correlation between dose and WG [25,27,28], this discrepancy may be due to our larger sample size giving us better statistical power (i.e., 438 patients vs. 70, 37, 177). Another open-label study with 615 patients did not find any dose-WG correlation [29]. However, the authors divided patients into groups with fixed doses and did not consider the supplementary oral risperidone prescribed to some participants.

When the piecewise function was applied to DDI at one month, a dose effect on WG for DDI>3mg/day was detected, meaning that for each mg increase (e.g., 3 to 4mg/day), weight increased by 0.16%. On the other hand, for DDI≤3 mg/day, a dose effect was observed only at 3, 6 and 12 months but not at one month, probably due to lack of statistical power and/or chance finding. Thus, at 3, 6 and 12 months higher WG estimates are reported for DDI≤3mg/day as compared to higher doses, meaning that increasing DDI from 1mg to 2mg/day led to a greater difference in WG than increasing from 5 to 6mg/day. This could be partially explained by the fact that patients increasing their DDI up to 3 mg/day between 3 and 12 months of therapy were more likely to be antipsychotic-naïve, and/or possibly never received risperidone previously.

Dose increases could also heighten the risk of developing WG ≥ 5% after one month, a strong predictor of additional WG during the follow-up[36]. However, for patients who reached this threshold, DDI did not influence WG at a later stage, suggesting that such patients would keep gaining weight whatever the DDI. Furthermore, the maximum value of DDI during the follow-up, and not the mean value, increased the odds of developing a clinically relevant WG (i.e., ≥7%). This discrepancy is probably due to the significant difference between the mean (3.3 mg) and the maximum value (4.4 mg) of DDI during the

follow-up. Patients with any DDI could, therefore, be prone to developing a clinically relevant WG, especially if they needed higher DDI at some time during the follow-up.

Since lower doses of risperidone are prescribed to adolescent and older patients[35], the effect of DDI on WG was specifically investigated among age categories. Adolescents gained weight all along the follow-up with a DDI effect only after three months. Considering that less than 25 patients were included, the lack of DDI effect at one and three months could be due to a low statistical power. DDI had a significant effect on WG at three and twelve months (with a trend at one month, p=0.093) among adults, the difference among time-points may be due to the different patients (e.g., with different age and sex) included in each model. On the other hand, a DDI effect on WG was measured in the elderly at each time-points, possibly due to a lower clearance.

In agreement with several studies, higher WG was found at the beginning of the treatment[11,36]. It should however be noted that observations could be more reliable within the first 3 months, since at a later stage more confounders could be present (e.g., different co-medications introduced and/or stopped, change of compliance). Discrepant results about the effect of sex on AIWG can be found in the literature, with female patients more likely to develop AIWG [37,38]. In the present study, a trend was found showing women gaining less weight than men but, since young age is also a risk factor for AIWG [8], this result could be explained by the lower age among men (mean, SD 36.5 ± 17.6 years and 45.0 ± 20.7 years in men and women, respectively p<0.001). Moreover, our models suggest that young patients are more likely to gain weight, possibly because they are more likely antipsychotic-naïve, less likely to have metabolic co-morbidities, or to receive drugs with a potential to worsen metabolic parameters [39,40].

Taking into account the entire cohort, a DDI effect was found on the increase of total and LDL-cholesterol levels over time but not for HDL-cholesterol, triglycerides, glucose nor systolic blood pressure. These results could be due to the lower number of observations (glucose/lipid levels are measured less frequently than weight) and/or to a weaker effect of risperidone on blood metabolic parameters than other atypical antipsychotics (e.g., olanzapine) [41]. A negative effect of DDI on diastolic blood pressure was also found, which may be a chance finding. Previous studies failed to show an association between risperidone DDI and other metabolic parameters than WG, including cholesterol [30,31]. This discrepancy with our study could be explained by our greater sample size (i.e., 290 vs. 49 and

88 patients), and/or by the different features of patients who were recruited (i.e., only patients aged 13 to 17 years were enrolled in the above mentioned study [30]).

Several limitations of the present study must be mentioned. First, adherence to treatment could not be ascertained. However, the doses actually administered for hospitalized patients were available, therefore increasing the accuracy of our data. Information on lifestyle (e.g., diet, physical activity) and substance use (e.g., alcohol), which could potentially influence WG and other metabolic parameters were not available either. Another limitation was the lack of data for risperidone and/or paliperidone plasma concentrations, which would have been of interest considering the large inter-individual variability in the metabolism and elimination of these two drugs (e.g., CYP2D6 slow, extensive and ultrarapid metabolizer status) [42]. Moreover, concerning lipids and glucose levels and/or blood pressure determinations, a 12-month follow-up may not have been enough to detect important alterations. We could also not ascertain whether any and/or how many antipsychotic-naïve patients were included, preventing us from further analyzing whether the dose effect on WG differs between these two populations. On the other hand, the principal strength of our study is the naturalistic longitudinal design, which allowed us to analyze the effect of the dose in a real-world setting. In addition, we could analyze the effect of risperidone DDI on both WG and blood metabolic parameters, taking advantage of a large sample size and therefore of a high statistical power.

CONCLUSION

In summary, the present results provide evidence for a small dose effect of risperidone on WG, total and LDL-cholesterol. However, because risperidone can be prescribed over a large range of doses (typically 1 to 10 mg/day), strong DDI increases can contribute to significant worsening of these metabolic parameters over time. Particular attention should, therefore, be given to the decision to prescribe high doses, and minimum effective doses should be preferred.

Clinical Points:

- The atypical antipsychotics risperidone and paliperidone can lead to weight gain, blood lipids and/or glucose alterations, but it was unclear whether such metabolic adverse effects are dose-dependent.

- Despite a small dose effect of risperidone and paliperidone on weight gain and lipid alterations, particular attention should be given to the decision to prescribe high doses and minimum effective doses should be preferred for minimizing metabolic effects.

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Table 1. Cohort characteristics according to daily dose intake (DDI) categories[a]

	DDI <3mg/day[b] **(N=201)**	**DDI ≥ 3mg/day**[b] **(N=237)**	**p-value**	**Total (N=438)**
DDI (mg/day), Mean (SD)	1.6 (0.1)	3.0 (0.1)	**<0.001**	3.3 (1.8)
Depot formulations[c,d]				
Yes	61 (25.7%)	19 (9.4%)	**<0.001**	80 (18.3%)
No	176 (74.3 %)	182 (90.6%)		358 (81.7%)
Age (years), Mean (SD)	41.5 (22.7)	40.1 (16.7)	0.48	40.7 (19.7)
Age-categories[e]				
Adolescents	27 (13.4%)	9 (3.8%)	**<0.001**	36 (8.2%)
Adults	132 (65.7%)	207 (87.3%)		339 (77.4%)
Elderly	42 (20.9%)	21 (8.9%)		63 (14.4%)
Sex				
M	96 (47.8%)	126 (53.2%)	0.30	222 (50.7%)
F	105 (52.2%)	111 (46.8%)		216 (49.3%)
Follow-up duration (days), Mean (SD)	148 (104)	157 (112)	0.39	153 (108)
Medical environment				
Ambulatory	92 (45.8%)	46 (19.4%)	**<0.001**	138 (31.5%)
Hospital	99 (49.3%)	174 (73.4%)		273 (62.3%)
Missing	10 (5.0%)	17 (7.2%)		27 (6.2%)
Diagnoses[f]				
Schizophrenia	66 (32.8%)	127 (53.6%)	**<0.001**	193 (44.1%)
Schizoaffective disorder	10 (5.0%)	44 (18.6%)		54 (12.3%)
Bipolar disorder	10 (5.0%)	17 (7.2%)		27 (6.2%)
Depression	39 (19.4%)	21 (8.9%)		60 (13.7%)
Other	55 (27.4%)	23 (9.7%)		78 (17.8%)
Unknown	21 (10.4%)	5 (2.1%)		26 (5.9%)
Smokers				
No	113 (56.2%)	100 (42.2%)	**<0.001**	213 (48.6%)
Yes	75 (37.3%)	131 (55.3%)		206 (47.0%)
Missing	13 (6.5%)	6 (2.5%)		19 (4.3%)
BMI at baseline (kg/m^2)[g]				
Mean (SD)	23.9 (5.31)	24.3 (5.64)	0.46	24.2 (5.49)
Missing	19 (9.5%)	16 (6.8%)		35 (8.0%)
Weight at baseline (kg)[g,] Mean (SD)	68.6 (19.0)	70.9 (17.4)	0.18	69.8 (18.1)

BMI baseline > 25 kg/m^2[g]				
FALSE	120 (59.7%)	141 (59.5%)	0.73	261 (59.6%)
TRUE	62 (30.8%)	80 (33.8%)		142 (32.4%)
Missing	19 (9.5%)	16 (6.8%)		35 (8.0%)
BMI last observation >25 kg/m^2				
FALSE	105 (52.2%)	131 (55.3%)	0.83	236 (53.9%)
TRUE	77 (38.3%)	90 (38.0%)		167 (38.1%)
Missing	19 (9.5%)	16 (6.8%)		35 (8.0%)
Weight gain after 1 month				
<5%	152 (75.6%)	170 (71.7%)	0.42	322 (73.5%)
≥5%	49 (24.4%)	67 (28.3%)		116 (26.5%)
Important weight gain (≥7%)[h]				
<7%	131 (65.2%)	141 (59.5%)	0.26	272 (62.1%)
≥%7	70 (34.8%)	96 (40.5%)		166 (37.9%)
Previous psychotropic drug[i,j]				
None	76 (37.8%)	50 (21.1%)	**<0.001**	126 (28.8%)
Low-risk profile	7 (3.5%)	23 (9.7%)		30 (6.8%)
Medium-risk profile	23 (11.4%)	31 (13.1%)		54 (12.3%)
High-risk profile	13 (6.5%)	31 (13.1%)		44 (10.0%)
Missing	82 (40.8%)	102 (43.0%)		184 (42.0%)
At risk psychotropic co-medication[i,k]				
No	124 (61.7%)	103 (43.5%)	**<0.001**	227 (51.8%)
Yes	77 (38.3%)	134 (56.5%)		211 (48.2%)
Antidepressant co-medication[k,l]				
No	137 (68.2%)	168 (70.9%)	0.61	305 (69.6%)
Yes	64 (31.8%)	69 (29.1%)		133 (30.4%)
Benzodiazepine co-medication[k,l]				
No	113 (56.2%)	44 (18.6%)	**<0.001**	157 (35.8%)
Yes	88 (43.8%)	193 (81.4%)		281 (64.2%)
Antihypertensive co-medication[k,l]				
No	171 (85.1%)	211 (89.0%)	0.27	382 (87.2%)
Yes	30 (14.9%)	26 (11.0%)		56 (12.8%)
Lipid-lowering co-medication[k,l]				
No	184 (91.5%)	223 (94.1%)	0.39	407 (92.9%)
Yes	17 (8.5%)	14 (5.9%)		31 (7.1%)

Antidiabetic co-medication[k,l]				
No	194 (96.5%)	231 (97.5%)	0.76	425 (97.0%)
Yes	7 (3.5%)	6 (2.5%)		13 (3.0%)

[a]*Values are reported as the number of patients and percentage unless otherwise mentioned.*

[b]*Patients taking more or less than 3mg/day for more than 50% of observations during the follow-up.*

[c]*Among 80 patients taking depot formulations (39 on paliperidone and 41 on risperidone), only 2 taking risperidone depot did not have any oral supplementary dose.*

[d]*See Supplementary Table1 for the exact drug list.*

[e]*Adolescents ≤17 years, adults >17 years and <65 years, elderly ≥65 years.*

[f]*ICD-10 classification: organic disorders, anxiety, personality disorder, and intellectual disability were classified together as "other."*

[g]*First observation in the dataset.*

[h]*At any time-point in the follow-up.*

[i]*Low risk: haloperidol, pipamperone, flupentixol, asenapine, amisulpride, aripiprazole, and lurasidone. Medium risk: zuclopenthixol, levomepromazine, quetiapine, lithium, and mirtazapine. High risk: valproate, olanzapine, and clozapine.*

[j]*In the 30 days before starting risperidone and/or paliperdone.*

[k]*Yes: people with co-medication at least once during the follow-up.*

[l]*See Supplementary Table2 for the exact drug list.*

Table 2. Weight change over time[a].

	Weight change 1 month			**Weight change 3 months**			**Weight change 6 months**			**Weight change 12 months**		
Predictors	*Estimates*	*CI*	*p*	*Estimates*	*CI*	*p*	*Estimates*	*CI*	*p*	*Estimates*	*CI*	*p*
(Intercept)	3.15	1.48 – 4.82	**<0.001**	5.05	3.02 – 7.08	**<0.001**	7.62	5.17 – 10.07	**<0.001**	8.87	6.19 – 11.55	**<0.001**
DDI[b]	0.16	0.06 – 0.27	**0.002**	0.29	0.18 – 0.39	**<0.001**	0.21	0.10 – 0.32	**<0.001**	0.25	0.13 – 0.36	**<0.001**
Time[b]	1.58	1.32 – 1.84	**<0.001**	1.20	1.06 – 1.34	**<0.001**	0.80	0.70 – 0.89	**<0.001**	0.57	0.51 – 0.63	**<0.001**
Sex [F]	-0.38	-1.10 – 0.34	0.31	-0.60	-1.49 – 0.29	0.19	-0.77	-1.86 – 0.32	0.16	-1.01	-2.19 – 0.16	0.092
Age[b]	-0.01	-0.02 – 0.01	0.54	-0.02	-0.04 – 0.00	0.058	-0.04	-0.06 – -0.01	**0.008**	-0.04	-0.07 – -0.01	**0.003**
Baseline weight[b]	-0.05	-0.07 – -0.03	**<0.001**	-0.07	-0.10 – -0.05	**<0.001**	-0.09	-0.12 – -0.06	**<0.001**	-0.10	-0.13 – -0.07	**<0.001**
Schizoaffective disorder[c]	-0.13	-1.14 – 0.87	0.80	-0.48	-1.73 – 0.77	0.46	0.10	-1.40 – 1.61	0.89	-0.25	-1.89 – 1.39	0.77
Bipolar disorder[c]	-0.70	-2.03 – 0.64	0.31	-0.66	-2.35 – 1.02	0.44	-1.08	-3.07 – 0.92	0.29	-0.97	-3.17 – 1.22	0.39
Depression[c]	0.20	-0.80 – 1.20	0.70	0.77	-0.42 – 1.97	0.20	0.43	-1.03 – 1.89	0.56	0.65	-0.93 – 2.23	0.42
Other diagnoses[c]	0.60	-0.37 – 1.56	0.23	1.45	0.30 – 2.61	**0.014**	1.48	0.08 – 2.89	**0.039**	1.56	0.03 – 3.08	**0.046**
N patients	337			384			395			411		
Observations	2095			3161			3766			4301		

[a]*Linear mixed models performed for the entire cohort at the four time intervals: 1 month, 3 months, 6 months and 12 months. To understand the magnitude of the results, one can imagine a 60kg fictional patient starting risperidone with DDI of 2 mg. At one month, his/her weight would be 60.95kg (+1.58%). If, during this month, this patient increased DDI from 2 to 3 mg/day, his/her weight increase would be 1.74% (+1.58%+0.16%), and the weight, therefore, would be 61.04 kg. For observations within 3 months, a weight increase of +1.20% is estimated for each additional month, with a 3.6% total increase after 3 months. In this case, the fictional patient's weight would be 62.16kg. Moreover, if DDI increased from 2 to 4 mg/day, the total weight increase would be 4.18% (3.6%+ 0.29*2%), and the weight 62.51kg.*

[b]*Daily dose intake (DDI) is expressed in mg/day, time in months, age in years and baseline weight in kilograms.*

[c]*Different diagnoses categories were compared to schizophrenic patients.*

Abbreviations: CI= confidence interval, DDI= daily dose intake, F= female, N= number, p= p-value.

Table 3. Piecewise function applied to daily dose intake [a].

	Weight change 1 month			**Weight change 3 months**			**Weight change 6 months**			**Weight change 12 months**		
Predictors	*Estimates*	*CI*	*p*	*Estimates*	*CI*	*p*	*Estimates*	*CI*	*p*	*Estimates*	*CI*	*p*
(Intercept)	3.20	1.50 – 4.90	**<0.001**	4.76	2.70 – 6.82	**<0.001**	7.19	4.71 – 9.67	**<0.001**	8.53	5.82 – 11.23	**<0.001**
Time[b]	1.57	1.31 – 1.83	**<0.001**	1.19	1.05 – 1.33	**<0.001**	0.79	0.70 – 0.88	**<0.001**	0.56	0.51 – 0.62	**<0.001**
Sex [F]	-0.38	-1.10 – 0.34	0.31	-0.61	-1.49 – 0.28	0.18	-0.78	-1.86 – 0.31	0.16	-1.02	-2.20 – 0.16	0.090
Age[b]	-0.01	-0.02 – 0.01	0.54	-0.02	-0.04 – 0.00	0.058	-0.04	-0.06 – -0.01	**0.008**	-0.04	-0.07 – -0.01	**0.003**
Baseline weight[b]	-0.05	-0.07 – -0.03	**<0.001**	-0.07	-0.10 – -0.05	**<0.001**	-0.09	-0.12 – -0.06	**<0.001**	-0.10	-0.13 – -0.07	**<0.001**
Schizoaffective disorder[c]	-0.13	-1.14 – 0.88	0.80	-0.47	-1.72 – 0.78	0.46	0.12	-1.39 – 1.62	0.88	-0.24	-1.88 – 1.41	0.78
Bipolar disorder[c]	-0.70	-2.03 – 0.64	0.31	-0.64	-2.32 – 1.04	0.46	-1.03	-3.03 – 0.97	0.31	-0.93	-3.12 – 1.27	0.41
Depression[c]	0.20	-0.80 – 1.21	0.69	0.76	-0.44 – 1.95	0.21	0.42	-1.04 – 1.88	0.57	0.65	-0.93 – 2.23	0.42
Other[c]	0.60	-0.37 – 1.56	0.22	1.45	0.30 – 2.61	**0.014**	1.49	0.08 – 2.90	**0.038**	1.56	0.04 – 3.09	**0.045**
DDI ≤ 3mg/day[b]	0.14	-0.08 – 0.36	0.22	0.48	0.24 – 0.71	**<0.001**	0.47	0.22 – 0.72	**<0.001**	0.45	0.19 – 0.72	**0.001**
DDI > 3mg/day[b]	0.16	0.04 – 0.27	**0.007**	0.33	0.21 – 0.45	**<0.001**	0.27	0.15 – 0.40	**<0.001**	0.30	0.17 – 0.43	**<0.001**
N patients	337			384			395			411		
Observations	2095			3161			3766			4301		

*[a]Linear mixed models performed for the entire cohort at the four time intervals: 1 month, 3 months, 6 months and 12 months. To understand the magnitude of the results, one can imagine a 60kg fictional patient starting risperidone with DDI of 1 mg. At one month, his/her weight would be 60.94kg (+1.57%). If DDI increased from 1 to 2 mg/day, the increase would not affect the weight change. However, if the fictional patient started with 4 mg/day and increased to 5 mg/day within one month, his/her weight would be 61.03kg (+1.73%, i.e., 1.57% + 0.16%). For observations within 3 months, the fictional patient's weight would be 61.07kg after 3 months of treatment (+3.57%, i.e. 1.19 * 3). If his/her DDI increased from 1 to 2 mg/day or from 4 to 5 mg/day, her/his weight would be 62.43kg (+4.05%, i.e., 3.57% + 0.48%) or 62.34kg (+3.9%, i.e., 3.57% + 0.33%), respectively.*

[b]Daily dose intake (DDI) is expressed in mg/day, time in months, age in years and baseline weight in kilograms.

[c]*Different diagnoses categories were compared to schizophrenic patients.*

Abbreviations: CI= confidence interval, DDI= daily dose intake, F= female, N= number, p= p-value.

Table 4. Evolution of metabolic parameters over time and influence of DDI[a].

	Variable	Estimates; CI	p-value	N patients	N observations
Total cholesterol[b,c]	DDI[d]	0.05; CI(0.01 – 0.09)	**0.018**	290	497
	Time[d]	0.03; CI(0.01 – 0.06)	**0.011**		
LDL cholesterol[b,c]	DDI	0.04; CI(0.01 – 0.08)	**0.011**	289	495
	Time	0.02; CI(0.00 – 0.04)	**0.045**		
HDL cholesterol[b,c]	DDI	-0.01; CI(-0.03 – 0.01)	0.32	290	497
	Time	0.01; CI(-0.00 – 0.02)	0.19		
Triglycerides[c,e]	DDI	0.01; CI(-0.03 – 0.04)	0.60	278	462
	Time	0.01; CI(-0.02 – 0.03)	0.62		
Glucose[c,e]	DDI	0.01; CI(-0.04 – 0.06)	0.75	268	412
	Time	-0.02; CI(-0.06 – 0.01)	0.16		
Systolic blood pressure[f]	DDI	-0.35; CI(-0.82 – 0.13)	0.15	283	1643
	Time	-0.23; CI(-0.52 – 0.07)	0.13		
Diastolic blood pressure[f]	DDI	-0.60; CI(-0.95 – -0.24)	**0.001**	282	1642
	Time	-0.14; CI(-0.36 – 0.08)	0.36		

[a]Linear mixed effect models for all the metabolic variables over 12 months, adjusting for sex, age, diagnoses and BMI at baseline. For each mg increase in DDI, a fictional patient would increase his/her total cholesterol value by 0.05 mmol/l. Moreover, along the follow-up total cholesterol would increase by 0.03 mmol/l per month.

[b]Models were also adjusted for the fasting status of the patients.

[c]Results are expressed in mmol/l.

[d]Daily dose intake (DDI) is expressed in mg/day and time in months.

[e]Only observations for fasting patients were selected.

[f]Results are expressed in mmHg.

Abbreviations: CI= confidence interval, DDI= daily dose intake, N= number.

Table 5. Logistic regression[a].

	Weight gain ≥5%			**Weight gain ≥7%**		
	Odds Ratios	*CI*	*p-value*	*Odds Ratios*	*CI*	*p-value*
Mean DDI[b]	1.18	1.04 – 1.35	**0.012**	1.12	0.99 – 1.25	0.064
Max DDI[b]	1.21	1.09 – 1.34	**<0.001**	1.09	1.00 – 1.18	**0.043**
N observations/patients	372			438		

[a]Logistic regression on the development of ≥5% weight gain after one month of treatment and on the development of ≥7% weight gain within 12 months. The model was adjusted for age, sex and baseline weight. For a fictional patient, the odds of developing ≥5% WG would be dose-dependent, and increase by 1.18 and 1.21 when the mean DDI and max DDI increase by 1 mg/day, respectively.

[b]With one observation/patient, mean DDI (mg/day) represent the mean value of DDI received during the first month of therapy (Weight gain ≥5%) and within 12 months (Weight gain ≥7%), and max DDI (mg/day) represents the maximum value.

Abbreviations: CI= confidence interval, DDI= daily dose intake, N= number.

Online Supplement

Supplementary Table 1: List of depot formulations.

Supplementary Table 2: Co-medications taken by the participants

Supplementary Table 3: Linear mixed effect models for weight evolution over time, corrected by early weight gain.

Supplementary Table 4: DDI and Time effect on weight change according to age categories

Supplementary Table 5: DDI effect on weight change according to sex.

Supplementary Table 6: DDI effect on weight change and other metabolic parameters among patients taking paliperidone or risperidone only.

Supplementary table 1. List of depot formulations[a].

Depot formulations	Interval between injections	Extrapolated risperidone's daily dose
Risperidone suspension (Consta®) 25 mg	14 days	1.8 mg
Risperidone suspension (Consta®) 37.5 mg	14 days	2.7 mg
Risperidone suspension (Consta®) 50 mg	14 days	3.6 mg
Paliperidone suspension (Xeplion®) 100 mg	2nd loading dose / 28 days	1.8 mg
Paliperidone suspension (Xeplion®) 150 mg/1.5mL[b]	1st loading dose / 28 days	2.7 mg
Paliperidone suspension (Xeplion®) 75 mg/0.75mL	28 days	1.3 mg

[a]List of depot formulations injected in patients included in the present study and the corresponding interval between injections.

[b]Formulation used as a loading dose (injected at the beginning of the depot treatment, and followed by a second injection one week after) and maintenance dose (injected every 28 days).

Supplementary table 2. Co-medications taken by the participants.

Antidepressant	**Benzodiazepine**	**Lipid-lowering drugs**	**Antidiabetic**	**Antihypertensive**	
Agomelatine	Alprazolam	Atorvastatin	Glibenclamide	Amlodipine	Aliskirene
Citalopram	Bromazepam	Ezetimibe	Gliclazide	Candesartan	Atenolol
Duloxetine	Clobazam	Fenofibrate	Glimepiride	Diltiazem	Bisoprolol
Escitalopram	Diazepam	Fluvastatin	Insulin	Enalapril	Celiprolol
Fluoxetine	Flurazepam	Pravastatin	Metformin	Felodipine	Furosemide
Fluvoxamine	Ketazolam	Rosuvastatin	Pioglitazone	Lercanidipine	Torasemide
Moclobemide	Lorazepam	Simvastatin	Rosiglitazone	Irbesartan	Amiloride
Paroxetine	Lormetazepam		Sitagliptine	Lisinopril	Spironolactone
Reboxetine	Midazolam			Losartan	Hydrochlorothiazide
Sertraline	Nitrazepam			Olmesartan	Indapamide
Trazodone	Oxazepam			Perindopril	Metoprolol
Venlafaxine	Potassium clorazepate			Ramipril	Nebivolol
Vortioxetine	Prazepam			Telmisartan	Nifedipine
	Temazepam			Trandolapril	Propranolol
	Triazolam			Valsartan	Carvedilol
					Verapamil

Supplementary table 3. Linear mixed effect models for weight evolution over time, corrected by early weight gain.

	Weight change 1 to 3 months			**Weight change 1 to 6 months**			**Weight change 1 to 12 months**		
Predictors	*Estimates*	*CI*	*p*	*Estimates*	*CI*	*p*	*Estimates*	*CI*	*p*
(Intercept)	5.86	2.26 – 9.47	**0.001**	8.93	5.17 – 12.69	**<0.001**	9.83	5.93 – 13.72	**<0.001**
Weight gain [≥5%][a]	6.68	5.25 – 8.11	**<0.001**	7.36	5.75 – 8.97	**<0.001**	7.70	6.02 – 9.37	**<0.001**
DDI[b]	0.05	-0.18 – 0.29	0.66	-0.08	-0.28 – 0.12	0.42	0.08	-0.10 – 0.27	0.38
Time[b]	1.24	0.86 – 1.63	**<0.001**	0.54	0.38 – 0.71	**<0.001**	0.46	0.37 – 0.55	**<0.001**
Sex [F]	-0.73	-2.18 – 0.71	0.32	-0.65	-2.24 – 0.94	0.42	-1.12	-2.76 – 0.52	0.18
Age[b]	-0.06	-0.09 – -0.02	**0.001**	-0.07	-0.11 – -0.04	**<0.001**	-0.08	-0.12 – -0.04	**<0.001**
Baseline weight[b]	-0.08	-0.12 – -0.04	**<0.001**	-0.08	-0.13 – -0.04	**<0.001**	-0.10	-0.14 – -0.05	**<0.001**
Schizoaffective disorder[c]	-1.08	-3.19 – 1.03	0.32	-0.40	-2.62 – 1.81	0.72	-1.24	-3.53 – 1.06	0.29
Bipolar disorder[c]	-1.31	-4.04 – 1.43	0.35	-1.75	-4.57 – 1.08	0.23	-1.30	-4.24 – 1.64	0.39
Depression[c]	0.70	-1.19 – 2.58	0.47	-0.24	-2.34 – 1.85	0.82	0.19	-1.94 – 2.33	0.86
Other diagnoses[c]	1.56	-0.22 – 3.34	0.085	1.04	-0.96 – 3.05	0.31	1.06	-1.01 – 3.12	0.32
N patients	263			301			329		
N observations	1066			1671			2206		

[a]Weight gain[≥5%] variable identifies patients who had at least a 5% weight gain in the first month of therapy. The entire cohort is included. Patients with ≥5% WG at one month keep increasing weight (+6.68% versus patients with <5% WG between days 46 and 105) without a DDI effect.

[b]Daily dose intake (DDI) is expressed in mg/day, time in months, age in years and baseline weight in kilograms.

[c]Different diagnoses categories are compared with schizophrenic patients.

Abbreviations: CI= confidence interval, DDI= daily dose intake, F= female, N= number,

Supplementary table 4. DDI and Time effect on weight change according to age categories[a].

		Weight change							
		1 month		3 months		6 months		12 months	
	Variable	DDI[c]	Time[c]	DDI	Time	DDI	Time	DDI	Time
Adolescents[b]	Estimates; CI	-0.26; -0.91 – 0.39	4.26; 3.30 – 5.21	0.14; -0.89 – 1.17	5.02; 4.23 – 5.80	1.54; 0.39 – 2.70	2.63; 2.00 – 3.25	1.63; 0.42 – 2.84	0.69; 0.36 – 1.02
	p-value	0.43	**<0.001**	0.80	**<0.001**	**0.009**	**<0.001**	**0.008**	**<0.001**
	N patients	20		24		26		29	
	N observations	123		202		232		273	
		DDI	Time	DDI	Time	DDI	Time	DDI	Time
Adults[b]	Estimates; CI	0.10 ;0.02 – 0.21	1.36; 1.05 – 1.67	0.13; 0.03 – 0.23	1.03; 0.89 – 1.17	0.01; -0.10 – 0.12	0.79; 0.69 – 0.89	0.13; 0.01 – 0.25	0.62; 0.55 – 0.68
	p-value	0.093	**<0.001**	**0.013**	**<0.001**	0.91	**<0.001**	**0.036**	**<0.001**
	N patients	258		299		308		321	
	N observations	1452		2183		2639		3105	
		DDI	Time	DDI	Time	DDI	Time	DDI	Time
Elderly[b]	Estimates; CI	0.76; 0.42 – 1.10	1.48; 0.96 – 2.00	1.37; 1.03 – 1.71	0.45; 0.16 – 0.74	1.58; 1.25 – 1.92	0.10; -0.11 – 0.30	1.41; 1.08 – 1.74	-0.08; -0.24 – 0.07
	p-value	**<0.001**	**<0.001**	**<0.001**	**0.003**	**<0.001**	0.37	**<0.001**	0.28
	N patients	59		61		61		61	
	N observations	520		776		895		923	

[a]Linear mixed effect models performed on weight change splitting the cohort into age categories, adjusting by sex, time, diagnoses and baseline weight . *For a 15-year-old 40kg fictional patient starting risperidone, his/her weight after one month would be 41.7kg (+4.26%). DDI increases would not change the weight increase. On the other hand, for a 66-year-old 50kg fictional patient, his/her weight would be 50.74kg after one month (+1.48%), and 51.12kg (+2.24%, i.e., 1.48% + 0.76%) if his/her DDI increased by 1 mg.*

[b]Adolescents ≤17 years; adults >17 & <65; elderly ≥65 years.

[c]Daily dose intake (DDI) is expressed in mg/day and time in months.

Abbreviations: CI= confidence interval, N= number.

Supplementary table 5. DDI effect on weight change according to sex[a].

	Men				Women			
	Estimates; CI	p-value	N patients	N observations	Estimates; CI	p-value	N patients	N observations
Weight change (1 month)[b]	0.08; -0.08 – 0.23	0.32	165	923	0.24; 0.10 – 0.38	**0.001**	172	1172
Weight change (3 months)[b]	0.22; 0.07 – 0.37	**0.003**	190	1412	0.36; 0.20 – 0.52	<**0.001**	194	1749
Weight change (6 months)[b]	-0.01; -0.16 – 0.14	0.91	196	1688	0.41; 0.24 – 0.57	<**0.001**	199	2078
Weight change (12 months)[b]	0.01; -0.13 – 0.16	0.86	204	1924	0.45; 0.28 – 0.63	<**0.001**	207	2377

[a]*Daily dose intake (DDI) is expressed in mg/day.*

[b]Models were adjusted for time, age, baseline weight and diagnoses.

Abbreviations: CI= confidence interval, N= number.

Supplementary Table 6. DDI effect on weight change and other metabolic parameters among patients taking paliperidone or risperidone only [a].

	Risperidone only				Paliperidone only			
	Estimates; CI	p-value	N patients	N observations	Estimates; CI	p-value	N patients	N observations
Weight change (1 month)[b]	0.08; - 0.03 – 0.20	0.17	289	1801	0.10; - 0.12 – 0.32	0.36	20	127
Weight change (3 months)[b]	0.23; 0.11 – 0.35	**<0.001**	329	2707	0.20; - 0.01 – 0.41	0.063	24	204
Weight change (6 months)[b]	0.18; 0.05 – 0.31	**0.007**	337	3153	0.12; - 0.09 – 0.32	0.28	27	249
Weight change (12 months)[b]	0.15; 0.01 – 0.29	**0.035**	351	3488	0.27; 0.08 – 0.46	**0.005**	28	337
Total cholesterol (12 months)[c]	0.07; 0.03 – 0.12	**0.002**	249	424				
LDL cholesterol (12 months)[c]	0.06; 0.02-0.11	**0.002**	248	422				

[a]Daily dose intake (DDI) is expressed in mg/day.

[b]Models were adjusted for time, sex, age, baseline weight and diagnoses.

[c]Models were adjusted for time, sex, age, baseline BMI, diagnoses and fasting status.

Abbreviations: CI= confidence interval, N= number.