It is illegal to post this copyrighted PDF on any website.

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

Marianna Piras, PharmD[a]; Céline Dubath, PhD[a]; Mehdi Gholam, PhD[b]; Nermine Laaboub, MSc[a]; Claire Grosu, MSc[a]; Franziska Gamma, MD, MSc[c]; Alessandra Solida, MD[d]; Kerstin Jessica Plessen, PhD[e]; Armin von Gunten, MPhil, MD[f]; Philippe Conus, MD[d]; and Chin B. Eap, PhD[a,g,h,i,*]

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 and blood lipids, glucose, and blood pressure alterations.

Methods: Data for 438 patients taking risperidone and/or its metabolite (paliperidone) for up to 1 year were obtained between 2007 and 2018 from a longitudinal study monitoring metabolic parameters.

Results: For each milligram increase in dose, we observed a weight increase of 0.16% at 1 month of treatment ($P = .002$) and increases of 0.29%, 0.21%, and 0.25% at 3, 6, and 12 months of treatment, respectively ($P < .001$ for each). Moreover, dose increases of 1 mg raised the risk of a ≥ 5% weight gain after 1 month (OR = 1.18; $P = .012$), a strong predictor of important weight gain in the long term. When we split the cohort into age categories, the dose had an effect on weight change after 3 months of treatment (up to 1.63%, $P = .008$) among adolescents (age ≤ 17 years), at 3 (0.13%, $P = .013$) and 12 (0.13%, $P = .036$) months among adults (age > 17 and < 65 years), and at each timepoint (up to 1.58%, $P < .001$) among older patients (age ≥ 65 years). In the whole cohort, for each additional milligram we observed a 0.05 mmol/L increase in total cholesterol ($P = .018$) and a 0.04 mmol/L increase in LDL cholesterol ($P = .011$) after 1 year.

Conclusions: Although of small amplitude, these results show an effect of daily risperidone 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.

J Clin Psychiatry 2022;83(4):21m14110

To cite: Piras M, Dubath C, Gholam M, et al. Daily dose effects of risperidone on weight and other metabolic parameters: a prospective cohort study. *J Clin Psychiatry.* 2022;83(4):21m14110.

To share: https://doi.org/10.4088/JCP.21m14110

© *Copyright 2022 Physicians Postgraduate Press, Inc.*

[a]Unit of Pharmacogenetics and Clinical Psychopharmacology, Centre for Psychiatric Neuroscience, Department of Psychiatry, Lausanne University Hospital, University of Lausanne, Prilly, Switzerland

[b]Center for Psychiatric Epidemiology and Psychopathology, Department of Psychiatry, Lausanne University Hospital, University of Lausanne, Prilly, Switzerland

[c]Les Toises Psychiatry and Psychotherapy Center, Lausanne, Switzerland

[d]Service of General Psychiatry, Department of Psychiatry, Lausanne University Hospital, University of Lausanne, Prilly, Switzerland

[e]Service of Child and Adolescent Psychiatry, Department of Psychiatry, Lausanne University Hospital, University of Lausanne, Lausanne, Switzerland

[f]Service of Old Age Psychiatry, Department of Psychiatry, Lausanne University Hospital, University of Lausanne, Prilly, Switzerland

[g]School of Pharmaceutical Sciences, University of Geneva, Geneva, Switzerland

[h]Center for Research and Innovation in Clinical Pharmaceutical Sciences, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland

[i]Institute of Pharmaceutical Sciences of Western Switzerland, University of Geneva, University of Lausanne, Geneva, Switzerland

**Corresponding author:* Chin B. Eap, PhD, Hôpital de Cery, 1008 Prilly—Lausanne, Switzerland (Chin.Eap@chuv.ch).

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) and 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 nonadherence to treatment, efforts to reduce the use of AAP have been made.[13–15] Nevertheless, they remain the reference medications 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 10 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 (eg, 8 mg/d vs 1 mg/d) after 8 weeks of treatment.[22,23] This dose effect was then confirmed by 1 prospective open-label study, reporting an increase of 0.084 kg for each additional

You are prohibited from making this PDF publicly available.

For reprints or permissions, contact permissions@psychiatrist.com. ♦ © 2022 Copyright Physicians Postgraduate Press, Inc.

It is illegal to post this copyrighted PDF on any website.

Clinical Points

- The atypical antipsychotics risperidone and paliperidone can lead to weight gain and 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.

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 began in 2007 at the Department of Psychiatry of the University Hospital of Lausanne, in collaboration with a private mental health care center (Les Toises; Lausanne, Switzerland). 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 treatment with risperidone and/or paliperidone between 2007 and 2018 with at least 2 weight observations were selected in both cohorts. Clinical follow-up periods not longer than 1 year and not shorter than 3 weeks were used. Different time intervals were taken into account to appreciate the evolution of the metabolic parameters: 1 month (≤ 45 days of treatment); 3 months (> 45 days and ≤ 105 days); 6 months (> 105 days and ≤ 190 days), and up to 1 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 1, 3, and 12 months and then yearly. In addition, weight, waist circumference, and blood pressure were also measured at 2 and 6 months. For hospitalized patients, additional observations collected during the stay were available for weight and/or metabolic parameters. Daily dose intake (DDI) information was extracted from medical files and reported in mg/d 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 2 injections. If patients were receiving both depot and oral forms, the sum between the 2 doses was used without accounting for the different bioavailabilities of the 2 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 comedications (Supplementary Table 2) for treating related somatic diseases were excluded (eg, 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 (≥ vs < 3 mg/d) 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 4 time intervals (1, 3, 6, and 12 months). To appreciate the dose effect, DDI outliers were excluded and doses < 10 mg/d were included. For total, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) cholesterol; triglycerides; glucose; and blood pressure values, the same model was adjusted for age, sex, treatment duration, DDI, and baseline BMI and 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/d. 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 1 month[36] and ≥ 7% along the follow-up). Statistical significance was set at a *P* value ≤ .05, and analyses were performed using Stata16.1 (StataCorp; College Station, Texas) and R environment for statistical computing version 3.6.0.

RESULTS

Patient Characteristics

Four hundred thirty-eight patients starting a follow-up (mean ± SD duration, 153 ± 108 days) on risperidone (374

You are prohibited from making this PDF publicly available.

For reprints or permissions, contact permissions@psychiatrist.com. ♦ © 2022 Copyright Physicians Postgraduate Press, Inc.

It is illegal to post this copyrighted PDF on any website.

Table 1. Cohort Characteristics According to Daily Dose Intake (DDI) Categories[a]

	DDI < 3 mg/d[b] (N = 201)	DDI ≥ 3 mg/d[b] (N = 237)	*P*	Total (N = 438)
DDI (mg/d), mean (SD)	1.6 (0.1)	3.0 (0.1)	**<.001**	3.3 (1.8)
Depot formulations[c,d]				
Yes	61 (25.7)	19 (9.4)	**<.001**	80 (18.3)
No	176 (74.3)	182 (90.6)		358 (81.7)
Age, mean (SD), y	41.5 (22.7)	40.1 (16.7)	.48	40.7 (19.7)
Age category[e]				
Adolescents	27 (13.4)	9 (3.8)	**<.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				
Male	96 (47.8)	126 (53.2)	0.30	222 (50.7)
Female	105 (52.2)	111 (46.8)		216 (49.3)
Follow-up duration (days), mean (SD)	148 (104)	157 (112)	.39	153 (108)
Medical environment				
Ambulatory	92 (45.8)	46 (19.4)	**<.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)	**<.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)
Smoker				
No	113 (56.2)	100 (42.2)	**<.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)	.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)	.18	69.8 (18.1)
BMI > 25 kg/m^2 at baseline[g]				
No	120 (59.7)	141 (59.5)	.73	261 (59.6)
Yes	62 (30.8)	80 (33.8)		142 (32.4)
Missing	19 (9.5)	16 (6.8)		35 (8.0)
BMI > 25 kg/m^2 at last observation				
No	105 (52.2)	131 (55.3)	.83	236 (53.9)
Yes	77 (38.3)	90 (38.0)		167 (38.1)
Missing	19 (9.5)	16 (6.8)		35 (8.0)
Weight gain after 1 mo				
< 5%	152 (75.6)	170 (71.7)	.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)	.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)	**<.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 comedication[i,k]				
No	124 (61.7)	103 (43.5)	**<.001**	227 (51.8)
Yes	77 (38.3)	134 (56.5)		211 (48.2)
Antidepressant comedication[k,l]				
No	137 (68.2)	168 (70.9)	.61	305 (69.6)
Yes	64 (31.8)	69 (29.1)		133 (30.4)
Benzodiazepine comedication[k,l]				
No	113 (56.2)	44 (18.6)	**<.001**	157 (35.8)
Yes	88 (43.8)	193 (81.4)		281 (64.2)
Antihypertensive comedication[k,l]				
No	171 (85.1)	211 (89.0)	.27	382 (87.2)
Yes	30 (14.9)	26 (11.0)		56 (12.8)
Lipid-lowering comedication[k,l]				
No	184 (91.5)	223 (94.1)	.39	407 (92.9)
Yes	17 (8.5)	14 (5.9)		31 (7.1)
Antidiabetic comedication[k,l]				
No	194 (96.5)	231 (97.5)	.76	425 (97.0)
Yes	7 (3.5)	6 (2.5)		13 (3.0)

[a]Values are reported as the number and percentage of patients unless otherwise noted. [b]Patients taking more or less than 3 mg/d for more than 50% of observations during the follow-up. [c]Among 80 patients receiving depot formulations (39 paliperidone and 41 risperidone), only 2 receiving risperidone depot did not have an oral supplementary dose. [d]See Supplementary Table 1 for the exact drug list. [e]Adolescents ≤ 17 years, adults > 17 years and < 65 years, and 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 timepoint in the follow-up. [i]Low risk: haloperidol, pipamperone, flupenthixol, 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 paliperidone. [k]Yes: people with comedication at least once during the follow-up. [l]See Supplementary Table 2 for the exact drug list.

Abbreviation: BMI = body mass index.

You are prohibited from making this PDF publicly available.

For reprints or permissions, contact permissions@psychiatrist.com. ♦ © 2022 Copyright Physicians Postgraduate Press, Inc.

It is illegal to post this copyrighted PDF on any website.

Table 2. Weight Change Over Time[a]

	Weight change 1 month			Weight change 3 months			Weight change 6 months			Weight change 12 months		
Predictor	Estimate	95% CI	*P*	Estimate	95% CI	*P*	Estimate	95% CI	*P*	Estimate	95% CI	*P*
(Intercept)	3.15	1.48 to 4.82	**<.001**	5.05	3.02 to 7.08	**<.001**	7.62	5.17 to 10.07	**<.001**	8.87	6.19 to 11.55	**<.001**
DDI[b]	0.16	0.06 to 0.27	**.002**	0.29	0.18 to 0.39	**<.001**	0.21	0.10 to 0.32	**<.001**	0.25	0.13 to 0.36	**<.001**
Time[b]	1.58	1.32 to 1.84	**<.001**	1.20	1.06 to 1.34	**<.001**	0.80	0.70 to 0.89	**<.001**	0.57	0.51 to 0.63	**<.001**
Sex (female)	−0.38	−1.10 to 0.34	.31	−0.60	−1.49 to 0.29	.19	−0.77	−1.86 to 0.32	.16	−1.01	−2.19 to 0.16	.092
Age[b]	−0.01	−0.02 to 0.01	.54	−0.02	−0.04 to 0.00	.058	−0.04	−0.06 to −0.01	**.008**	−0.04	−0.07 to −0.01	**.003**
Baseline weight[b]	−0.05	−0.07 to −0.03	**<.001**	−0.07	−0.10 to −0.05	**<.001**	−0.09	−0.12 to −0.06	**<.001**	−0.10	−0.13 to −0.07	**<.001**
Schizoaffective disorder[c]	−0.13	−1.14 to 0.87	.80	−0.48	−1.73 to 0.77	.46	0.10	−1.40 to 1.61	.89	−0.25	−1.89 to 1.39	.77
Bipolar disorder[c]	−0.70	−2.03 to 0.64	.31	−0.66	−2.35 to 1.02	.44	−1.08	−3.07 to 0.92	.29	−0.97	−3.17 to 1.22	.39
Depression[c]	0.20	−0.80 to 1.20	.70	0.77	−0.42 to 1.97	.20	0.43	−1.03 to 1.89	.56	0.65	−0.93 to 2.23	.42
Other diagnoses[c]	0.60	−0.37 to 1.56	.23	1.45	0.30 to 2.61	**.014**	1.48	0.08 to 2.89	**.039**	1.56	0.03 to 3.08	**.046**
N patients		337			384			395			411	
Observations		2,095			3,161			3,766			4,301	

[a]Linear mixed models performed for the entire cohort at the 4 time intervals: 1 month, 3 months, 6 months, and 12 months. To understand the magnitude of the results, one can imagine a fictional patient who weighs 60 kg starting risperidone with a DDI of 2 mg. At 1 month, his/her weight would be 60.95 kg (+1.58%). If, during this month, this patient increased DDI from 2 to 3 mg/d, 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 62.16 kg. Moreover, if DDI increased from 2 to 4 mg/d, the total weight increase would be 4.18% (3.6% + 0.29 × 2%), and the weight 62.51 kg.
[b]DDI is expressed in mg/d, time in months, age in years, and baseline weight in kilograms.
[c]Other diagnosis categories were compared to schizophrenia.
Abbreviations: CI = confidence interval, DDI = daily dose intake.

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		
Predictor	Estimate	95% CI	*P*	Estimate	95% CI	*P*	Estimate	95% CI	*P*	Estimate	95% CI	*P*
(Intercept)	3.20	1.50 to 4.90	**<.001**	4.76	2.70 to 6.82	**<.001**	7.19	4.71 to 9.67	**<.001**	8.53	5.82 to 11.23	**<.001**
Time[b]	1.57	1.31 to 1.83	**<.001**	1.19	1.05 to 1.33	**<.001**	0.79	0.70 to 0.88	**<.001**	0.56	0.51 to 0.62	**<.001**
Sex (female)	−0.38	−1.10 to 0.34	.31	−0.61	−1.49 to 0.28	.18	−0.78	−1.86 to 0.31	.16	−1.02	−2.20 to 0.16	.090
Age[b]	−0.01	−0.02 to 0.01	.54	−0.02	−0.04 to 0.00	.058	−0.04	−0.06 to −0.01	**.008**	−0.04	−0.07 to −0.01	**.003**
Baseline weight[b]	−0.05	−0.07 to −0.03	**<.001**	−0.07	−0.10 to −0.05	**<.001**	−0.09	−0.12 to −0.06	**<.001**	−0.10	−0.13 to −0.07	**<.001**
Schizoaffective disorder[c]	−0.13	−1.14 to 0.88	.80	−0.47	−1.72 to 0.78	.46	0.12	−1.39 to 1.62	.88	−0.24	−1.88 to 1.41	.78
Bipolar disorder[c]	−0.70	−2.03 to 0.64	.31	−0.64	−2.32 to 1.04	.46	−1.03	−3.03 to 0.97	.31	−0.93	−3.12 to 1.27	.41
Depression[c]	0.20	−0.80 to 1.21	.69	0.76	−0.44 to 1.95	.21	0.42	−1.04 to 1.88	.57	0.65	−0.93 to 2.23	.42
Other[c]	0.60	−0.37 to 1.56	.22	1.45	0.30 to 2.61	**.014**	1.49	0.08 to 2.90	**.038**	1.56	0.04 to 3.09	**.045**
DDI ≤ 3 mg/d[b]	0.14	−0.08 to 0.36	.22	0.48	0.24 to 0.71	**<.001**	0.47	0.22 to 0.72	**<.001**	0.45	0.19 to 0.72	**.001**
DDI > 3 mg/d[b]	0.16	0.04 to 0.27	**.007**	0.33	0.21 to 0.45	**<.001**	0.27	0.15 to 0.40	**<.001**	0.30	0.17 to 0.43	**<.001**
N patients		337			384			395			411	
Observations		2,095			3,161			3,766			4,301	

[a]Linear mixed models performed for the entire cohort at the 4 time intervals: 1 month, 3 months, 6 months, and 12 months. To understand the magnitude of the results, one can imagine a fictional patient who weighs 60 kg starting risperidone with DDI of 1 mg. At 1 month, his/her weight would be 60.94 kg (+1.57%). If DDI increased from 1 to 2 mg/d, the increase would not affect the weight change. However, if the fictional patient started with 4 mg/d and increased to 5 mg/d within 1 month, his/her weight would be 61.03 kg (+1.73%, ie, 1.57% + 0.16%). For observations within 3 months, the fictional patient's weight would be 61.07 kg after 3 months of treatment (+3.57%, ie, 1.19 × 3). If his/her DDI increased from 1 to 2 mg/d or from 4 to 5 mg/d, his/her weight would be 62.43 kg (+4.05%, ie, 3.57% + 0.48%) or 62.34 kg (+3.9%, ie, 3.57% + 0.33%), respectively.
[b]DDI is expressed in mg/d, time in months, age in years, and baseline weight in kilograms.
[c]Other diagnosis categories were compared to schizophrenia.
Abbreviations: CI = confidence interval, DDI = daily dose intake.

patients) and/or paliperidone (64 patients) were included. Table 1 reports clinical parameters and comedications, dividing patients into those with DDI lower (45.9%) or higher (54.1%) than 3 mg/d. Patients who reached a clinically relevant threshold (≥ 7% of WG) were younger (37.8 vs 42.5 years; $P = .017$), leaner (baseline BMI 22.1 kg/m^2 vs 25.4 kg/m^2; $P < .001$), and had longer follow-ups (176 vs 139 days; $P < .001$).

Weight Change Over Time

Linear mixed effect models were performed on weight change at 1, 3, 6, and 12 months (Table 2). A significant effect of time on weight change was found for each timepoint ($P < .001$), 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 was shown at each timepoint ($P = .002$ at 1 month, $P < .001$ for the others).

You are prohibited from making this PDF publicly available.

For reprints or permissions, contact permissions@psychiatrist.com. ♦ © 2022 Copyright Physicians Postgraduate Press, Inc.

It is illegal to post this copyrighted PDF on any website.

Table 4. Evolution of Metabolic Parameters Over Time and Influence of DDI[a]

Parameter	Variable	Estimate (95% CI)	*P*	N patients	No. of observations
Total cholesterol[b,c]	DDI[d]	0.05 (0.01 to 0.09)	**.018**	290	497
	Time[d]	0.03 (0.01 to 0.06)	**.011**		
LDL cholesterol[b,c]	DDI	0.04 (0.01 to 0.08)	**.011**	289	495
	Time	0.02 (0.00 to 0.04)	**.045**		
HDL cholesterol[b,c]	DDI	−0.01 (−0.03 to 0.01)	.32	290	497
	Time	0.01 (−0.00 to 0.02)	.19		
Triglycerides[c,e]	DDI	0.01 (−0.03 to 0.04)	.60	278	462
	Time	0.01 (−0.02 to 0.03)	.62		
Glucose[c,e]	DDI	0.01 (−0.04 to 0.06)	.75	268	412
	Time	−0.02 (−0.06 to 0.01)	.16		
Systolic blood pressure[f]	DDI	−0.35 (−0.82 to 0.13)	.15	283	1,643
	Time	−0.23 (−0.52 to 0.07)	.13		
Diastolic blood pressure[f]	DDI	−0.60 (−0.95 to −0.24)	**.001**	282	1,642
	Time	−0.14 (−0.36 to 0.08)	0.36		

[a]Linear mixed effect models for all the metabolic variables over 12 months, adjusting for sex, age, diagnoses, and body mass index 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]DDI is expressed in mg/d and time in months.
[e]Only observations for fasting patients were selected.
[f]Results are expressed in mm Hg.
Abbreviations: CI = confidence interval, DDI = daily dose intake.

At 1 month, a 0.16% increase in weight was observed for each additional mg, whereas at 12 months this effect reached 0.25%.

When the piecewise function was applied on DDI (Table 3), at 1 month we observed a DDI effect on WG only for DDI > 3 mg/d ($P = .007$). For each additional mg, the weight increase was 0.16%. For DDI ≤ 3 mg/d, no significant effect on weight change was found ($P = .22$). At 3, 6, and 12 months, both DDI ≤ 3 mg/d and DDI > 3 mg/d had a significant effect on weight change. When adjusting the model for early weight gain (≥ 5% WG in 1 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 = .66, $P = .42$, and $P = .38$ at 3, 6, and 12 months, respectively). Moreover, patients with ≥ 5% WG in 1 month kept gaining more weight than patients who did not reach this threshold (+6.68%, +7.36%, and +7.70% at 3, 6, and 12 months, respectively). Smoking status and psychotropic comedications did not have a significant impact on weight change and were therefore excluded from the model.

An additional analysis was performed on adolescent (age ≤ 17 years), adult (age > 17 and < 65 years), and elderly (age ≥ 65 years) subgroups (Supplementary Table 4). DDI had an increasing impact on weight change at 6 (1.54%, $P = .009$) and 12 (1.63%, $P = .008$) months among adolescents, at 3 (0.13%, $P = .013$) and 12 (0.13%, $P = .036$) months among adults, and at the 4 timepoints among older patients, with a weight increase of 0.76%, 1.37%, 1.58%, and 1.41% for each additional mg, respectively ($P < .001$). Sex subgroups analyses were also performed (Supplementary Table 5), with the dose showing a significant effect on WG at all 4 timepoints for women ($P \leq .001$) and only at 3 months for men ($P = .003$).

Table 5. Logistic Regression[a]

	Weight gain ≥ 5%			Weight gain ≥ 7%		
	Odds ratio	95% CI	*P*	Odds ratio	95% CI	*P*
Mean DDI[b]	1.18	1.04 to 1.35	**.012**	1.12	0.99 to 1.25	.064
Max DDI[b]	1.21	1.09 to 1.34	**<.001**	1.09	1.00 to 1.18	**.043**
No. of observations/ patients		372			438	

[a]Logistic regression on the development of ≥ 5% weight gain after 1 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/d, respectively.
[b]With 1 observation/patient, mean DDI (mg/d) represents 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/d) represents the maximum value.
Abbreviations: CI = confidence interval, DDI = daily dose intake.

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 ($P = .011$ and $P = .045$, 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 ($P = .018$ and $P = .011$, respectively). No significant effect of time nor DDI was observed on the increase of triglycerides and glucose levels and systolic blood pressure and on the decrease of HDL cholesterol levels. A negative effect for DDI was detected for diastolic blood pressure (−0.60 mm Hg for each additional mg, $P = .001$), but with no effect of time ($P = .36$). Psychotropic comedications did not have a significant influence on metabolic parameters and were therefore excluded from the models.

You are prohibited from making this PDF publicly available.

For reprints or permissions, contact permissions@psychiatrist.com. ♦ © 2022 Copyright Physicians Postgraduate Press, Inc.

It is illegal to post this copyrighted PDF on any website.

Logistic Regression

A logistic regression (Table 5) was performed to evaluate the risk of developing ≥ 5% WG after 1 month of treatment, and a dose-significant effect was observed with both the mean (OR = 1.18; $P = .012$) and maximum values (OR = 1.21; $P < .001$) 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; $P = .043$).

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 1 year among patients taking paliperidone only ($P = .005$). For patients taking risperidone only (n = 351), DDI did not have an effect on WG after 1 month ($P = .17$) but had a significant effect on WG after 3, 6, and 12 months ($P < .001$, $P = .007$, $P = .035$, respectively) and on total and LDL cholesterol after 12 months ($P = .002$). 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 1-year naturalistic study design, we aimed to investigate 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 dose 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 (eg, 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 at greater 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 (ie, 438 patients vs 70, 37, 177). Another open-label study with 615 patients did not find a dose-WG correlation.[29] However, the authors divided patients into groups with fixed doses of depot and did not consider the supplementary oral risperidone prescribed to some participants.

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

Dose increases could also heighten the risk of developing WG ≥ 5% after 1 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 (ie, ≥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 3 months. Considering that less than 25 patients were included, the lack of DDI effect at 1 and 3 months could be due to a low statistical power. DDI had a significant effect on WG at 3 and 12 months (with a trend at 1 month, $P = .093$) among adults, and the difference among timepoints may be due to the different patients (eg, with different age and sex) included in each model. On the other hand, a DDI effect on WG was measured in older patients at each of the timepoints, 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 (eg, different comedications introduced and/or stopped, change in 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

You are prohibited from making this PDF publicly available.

For reprints or permissions, contact permissions@psychiatrist.com. ♦ © 2022 Copyright Physicians Postgraduate Press, Inc.

It is illegal to post this copyrighted PDF on any website.

risk factor for AIWG,[8] this result could be explained by the lower age among men (mean ± SD age, 36.5 ± 17.6 years and 45.0 ± 20.7 years in men and women, respectively; $P < .001$). Moreover, our models suggest that young patients are more likely to gain weight, possibly because they are more likely to be antipsychotic-naïve, less likely to have metabolic comorbidities, or less likely 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 in total and LDL cholesterol levels over time but not for HDL cholesterol, triglycerides, glucose, or 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 (eg, 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 (ie, 290 vs 49 and 88 patients) and/or by the different features of patients who were recruited (ie, 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 (eg, diet, physical activity) and substance use (eg, alcohol), which could potentially influence WG and other metabolic parameters, were not available either. Another limitation was the lack of data for plasma risperidone and/or paliperidone concentrations, which would have been of interest considering the large interindividual variability in the metabolism and elimination of these two drugs (eg, 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 and total and LDL cholesterol. However, because risperidone can be prescribed over a large range of doses (typically 1 to 10 mg/d), 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.

Submitted: May 27, 2021; accepted November 8, 2021.

Published online: May 9, 2022.

Potential conflicts of interest: **Dr Eap** received honoraria for conferences or teaching CME courses from Janssen-Cilag, Lundbeck, Otsuka, Sandoz, Servier, Sunovion, Vifor-Pharma, and Zeller in the past 3 years. The other authors report no potential conflicts of interest.

Funding/support: This work has been funded in part by the Swiss National Research Foundation (Drs Eap and Conus: 320030-120686, 324730-144064, and 320030-173211; Drs Eap, Conus, and Plessen: 320030-200602).

Role of the sponsor: The funding sources had no role in the writing of the manuscript or in the decision to submit it for publication.

Acknowledgments: The authors thank the staff at the University Hospital of Lausanne and at the private mental health care center Les Toises who participated in the metabolic monitoring program and all of the participants in PsyMetab and PsyClin.

Supplementary material: Available at PSYCHIATRIST.COM

REFERENCES

1. Annamalai A, Kosir U, Tek C. Prevalence of obesity and diabetes in patients with schizophrenia. *World J Diabetes*. 2017;8(8):390–396.
2. DE Hert M, Correll CU, Bobes J, et al. Physical illness in patients with severe mental disorders. I. prevalence, impact of medications and disparities in health care. *World Psychiatry*. 2011;10(1):52–77.
3. Lawrence D, Hancock KJ, Kisely S. The gap in life expectancy from preventable physical illness in psychiatric patients in Western Australia: retrospective analysis of population based registers. *BMJ*. 2013;346:f2539.
4. Ringen PA, Engh JA, Birkenaes AB, et al. Increased mortality in schizophrenia due to cardiovascular disease: a non-systematic review of epidemiology, possible causes, and interventions. *Front Psychiatry*. 2014;5:137.
5. Singh R, Bansal Y, Medhi B, et al. Antipsychotics-induced metabolic alterations: Recounting the mechanistic insights, therapeutic targets and pharmacological alternatives. *Eur J Pharmacol*. 2019;844:231–240.
6. Abosi O, Lopes S, Schmitz S, et al. Cardiometabolic effects of psychotropic medications. *Horm Mol Biol Clin Investig*. 2018;36(1):/j/hmbci.2018.36.issue-1/hmbci-2017-0065/hmbci-2017-0065.xml.
7. Ward A, Quon P, Abouzaid S, et al. Cardiometabolic consequences of therapy for chronic schizophrenia using second-generation antipsychotic agents in a Medicaid population: clinical and economic evaluation. *P&T*. 2013;38(2):109–115.
8. Gebhardt S, Haberhausen M, Heinzel-Gutenbrunner M, et al. Antipsychotic-induced body weight gain: predictors and a systematic categorization of the long-term weight course. *J Psychiatr Res*. 2009;43(6):620–626.
9. Carliner H, Collins PY, Cabassa LJ, et al. Prevalence of cardiovascular risk factors among racial and ethnic minorities with schizophrenia spectrum and bipolar disorders: a critical literature review. *Compr Psychiatry*. 2014;55(2):233–247.
10. De Hert M, Detraux J, van Winkel R, et al. Metabolic and cardiovascular adverse effects associated with antipsychotic drugs. *Nat Rev Endocrinol*. 2011;8(2):114–126.
11. Barton BB, Segger F, Fischer K, et al. Update on weight-gain caused by antipsychotics: a systematic review and meta-analysis. *Expert Opin Drug Saf*. 2020;19(3):295–314.
12. De Hert M, Yu W, Detraux J, et al. Body weight and metabolic adverse effects of asenapine, iloperidone, lurasidone and paliperidone in the treatment of schizophrenia and bipolar disorder: a systematic review and exploratory meta-analysis. *CNS Drugs*. 2012;26(9):733–759.
13. Donohue J, O'Malley AJ, Horvitz-Lennon M, et al. Changes in physician antipsychotic prescribing preferences, 2002-2007. *Psychiatr Serv*. 2014;65(3):315–322.
14. Dorsey ER, Rabbani A, Gallagher SA, et al. Impact of FDA black box advisory on antipsychotic medication use. *Arch Intern Med*. 2010;170(1):96–103.
15. Weiden PJ, Mackell JA, McDonnell DD. Obesity as a risk factor for antipsychotic noncompliance. *Schizophr Res*. 2004;66(1):51–57.

You are prohibited from making this PDF publicly available.

For reprints or permissions, contact permissions@psychiatrist.com. ♦ © 2022 Copyright Physicians Postgraduate Press, Inc.

It is illegal to post this copyrighted PDF on any website.

16. Kane JM, Correll CU. Past and present progress in the pharmacologic treatment of schizophrenia. *J Clin Psychiatry*. 2010;71(9):1115–1124.
17. Simon V, van Winkel R, De Hert M. Are weight gain and metabolic side effects of atypical antipsychotics dose dependent? a literature review. *J Clin Psychiatry*. 2009;70(7):1041–1050.
18. Carr CN, Lopchuk S, Beckman ME, et al. Evaluation of the use of low-dose quetiapine and the risk of metabolic consequences: a retrospective review. *Ment Health Clin*. 2016;6(6):308–313.
19. Williams SG, Alinejad NA, Williams JA, et al. Statistically significant increase in weight caused by low-dose quetiapine. *Pharmacotherapy*. 2010;30(10):1011–1015.
20. Pillinger T, McCutcheon RA, Vano L, et al. Comparative effects of 18 antipsychotics on metabolic function in patients with schizophrenia, predictors of metabolic dysregulation, and association with psychopathology: a systematic review and network meta-analysis. *Lancet Psychiatry*. 2020;7(1):64–77.
21. Xiang Q, Zhao X, Zhou Y, et al. Effect of CYP2D6, CYP3A5, and MDR1 genetic polymorphisms on the pharmacokinetics of risperidone and its active moiety. *J Clin Pharmacol*. 2010;50(6):659–666.
22. Peuskens J; Risperidone Study Group. Risperidone in the treatment of patients with chronic schizophrenia: a multi-national, multi-centre, double-blind, parallel-group study versus haloperidol. *Br J Psychiatry*. 1995;166(6):712–726, discussion 727–733.
23. Marder SR, Meibach RC. Risperidone in the treatment of schizophrenia. *Am J Psychiatry*. 1994;151(6):825–835.
24. Lane HY, Chang YC, Cheng YC, et al. Effects of patient demographics, risperidone dosage, and clinical outcome on body weight in acutely exacerbated schizophrenia. *J Clin Psychiatry*. 2003;64(3):316–320.
25. Kelly DL, Conley RR, Love RC, et al. Weight gain in adolescents treated with risperidone and conventional antipsychotics over six months. *J Child Adolesc Psychopharmacol*. 1998;8(3):151–159.
26. Hellings JA, Zarcone JR, Crandall K, et al. Weight gain in a controlled study of risperidone in children, adolescents and adults with mental retardation and autism. *J Child Adolesc Psychopharmacol*. 2001;11(3):229–238.
27. Cohen S, Glazewski R, Khan S, et al. Weight gain with risperidone among patients with mental retardation: effect of calorie restriction. *J Clin Psychiatry*. 2001;62(2):114–116.
28. Csernansky JG, Mahmoud R, Brenner R; Risperidone-USA-79 Study Group. A comparison of risperidone and haloperidol for the prevention of relapse in patients with schizophrenia. *N Engl J Med*. 2002;346(1):16–22.
29. Fleischhacker WW, Eerdekens M, Karcher K, et al. Treatment of schizophrenia with long-acting injectable risperidone: a 12-month open-label trial of the first long-acting second-generation antipsychotic. *J Clin Psychiatry*. 2003;64(10):1250–1257.
30. O'Donoghue B, Schäfer MR, Becker J, et al. Metabolic changes in first-episode early-onset schizophrenia with second-generation antipsychotics. *Early Interv Psychiatry*. 2014;8(3):276–280.
31. Lin CH, Kuo CC, Chou LS, et al. A randomized, double-blind comparison of risperidone versus low-dose risperidone plus low-dose haloperidol in treating schizophrenia. *J Clin Psychopharmacol*. 2010;30(5):518–525.
32. Dubath C, Delacrétaz A, Glatard A, et al. Evaluation of cardiometabolic risk in a large psychiatric cohort and comparison with a population-based sample in Switzerland. *J Clin Psychiatry*. 2020;81(3):19m12796.
33. Turkoz I, Bossie CA, Lindenmayer JP, et al. Paliperidone ER and oral risperidone in patients with schizophrenia: a comparative database analysis. *BMC Psychiatry*. 2011;11(1):21.
34. Pinheiro JBD, DebRoy S, Sarkar D. R Core Team. nlme: Linear and Nonlinear Mixed Effects Models. 2021.https://CRAN.R-project.org/package=nlme.
35. Risperdal. Highlights of Prescribing Information. Ortho-McNeil-Janssen Pharmaceuticals; 2009. https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020272s056,020588s044,021346s033,021444s03lbl.pdf. 2008. Accessed July 12, 2020.
36. Vandenberghe F, Gholam-Rezaee M, Saigi-Morgui N, et al. Importance of early weight changes to predict long-term weight gain during psychotropic drug treatment. *J Clin Psychiatry*. 2015;76(11):e1417–e1423.
37. Lee S-Y, Park M-H, Patkar AA, et al. A retrospective comparison of BMI changes and the potential risk factors among schizophrenic inpatients treated with aripiprazole, olanzapine, quetiapine or risperidone. *Prog Neuropsychopharmacol Biol Psychiatry*. 2011;35(2):490–496.
38. Pérez-Iglesias R, Martínez-García O, Pardo-Garcia G, et al. Course of weight gain and metabolic abnormalities in first treated episode of psychosis: the first year is a critical period for development of cardiovascular risk factors. *Int J Neuropsychopharmacol*. 2014;17(1):41–51.
39. Tarricone I, Ferrari Gozzi B, Serretti A, et al. Weight gain in antipsychotic-naive patients: a review and meta-analysis. *Psychol Med*. 2010;40(2):187–200.
40. De Hert M, Dobbelaere M, Sheridan EM, et al. Metabolic and endocrine adverse effects of second-generation antipsychotics in children and adolescents: a systematic review of randomized, placebo controlled trials and guidelines for clinical practice. *Eur Psychiatry*. 2011;26(3):144–158.
41. Rummel-Kluge C, Komossa K, Schwarz S, et al. Head-to-head comparisons of metabolic side effects of second generation antipsychotics in the treatment of schizophrenia: a systematic review and meta-analysis. *Schizophr Res*. 2010;123(2-3):225–233.
42. Scordo MG, Spina E, Facciolà G, et al. Cytochrome P450 2D6 genotype and steady state plasma levels of risperidone and 9-hydroxyrisperidone. *Psychopharmacology (Berl)*. 1999;147(3):300–305.

Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Psychosis section. Please contact Ann K. Shinn, MD, MPH, at ashinn@psychiatrist.com.

See supplementary material for this article at PSYCHIATRIST.COM.

You are prohibited from making this PDF publicly available.

For reprints or permissions, contact permissions@psychiatrist.com. ♦ © 2022 Copyright Physicians Postgraduate Press, Inc.

THE JOURNAL OF
CLINICAL PSYCHIATRY
THE OFFICIAL JOURNAL OF THE AMERICAN SOCIETY OF CLINICAL PSYCHOPHARMACOLOGY

Supplementary Material

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

Authors: Marianna Piras, PharmD; Céline Dubath, PhD; Mehdi Gholam, PhD; Nermine Laaboub, MSc; Claire Grosu, MSc; Franziska Gamma, MD, MSc; Alessandra Solida, MD; Kerstin Jessica Plessen, PhD; Armin von Gunten, MPhil, MD; Philippe Conus, MD; and Chin B. Eap, PhD

DOI Number: 10.4088/JCP.21m14110

List of Supplementary Material for the article

1. Table 1 — List Of Depot Formulations
2. Table 2 — Co-Medications Taken by the Participants
3. Table 3 — Linear Mixed Effect Models for Weight Evolution Over Time, Corrected by Early Weight Gain
4. Table 4 — DDI and Time Effect on Weight Change According to Age Categories
5. Table 5 — DDI Effect on Weight Change According to Sex
6. Table 6 — DDI Effect on Weight Change and Other Metabolic Parameters Among Patients Taking Paliperidone or Risperidone Only

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

© Copyright 2022 Physicians Postgraduate Press, Inc.
It is illegal to post this copyrighted PDF on any website. ♦ © 2022 Copyright Physicians Postgraduate Press, Inc.

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).

It is illegal to post this copyrighted PDF on any website. ♦ © 2022 Copyright Physicians Postgraduate Press, Inc.

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

It is illegal to post this copyrighted PDF on any website. ♦ © 2022 Copyright Physicians Postgraduate Press, Inc.

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.

It is illegal to post this copyrighted PDF on any website. ♦ © 2022 Copyright Physicians Postgraduate Press, Inc.

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.

It is illegal to post this copyrighted PDF on any website. ♦ © 2022 Copyright Physicians Postgraduate Press, Inc.

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.

It is illegal to post this copyrighted PDF on any website. ♦ © 2022 Copyright Physicians Postgraduate Press, Inc.

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.

It is illegal to post this copyrighted PDF on any website. ♦ © 2022 Copyright Physicians Postgraduate Press, Inc.