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Supplementary Material

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

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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

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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

^aList of depot formulations injected in patients included in the present study and the corresponding interval between injections.

^bFormulation 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	Torsemide
Moclobemide	Lorazepam	Simvastatin	Rosiglitazone	Irbesartan	Amiloride
Paroxetine	Lormetazepam		Sitagliptine	Lisinopril	Spirolactone
Reboxetine	Midazolam			Losartan	Hydrochlorothiazide
Sertraline	Nitrazepam			Olmesartan	Indapamide
Trazodone	Oxazepam			Perindopril	Metoprolol
Venlafaxine	Potassium			Ramipril	Nebivolol
Vortioxetine	clorazepate			Telmisartan	Nifedipine
	Prazepam			Trandolapril	Propranolol
	Temazepam			Valsartan	Carvedilol
	Triazolam				Verapamil

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

Predictors	Weight change 1 to 3 months			Weight change 1 to 6 months			Weight change 1 to 12 months		
	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 [$\geq 5\%$] ^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		

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

^bDaily dose intake (DDI) is expressed in mg/day, time in months, age in years and baseline weight in kilograms.

^cDifferent 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	4.26; 3.30 –	0.14; -0.89	5.02; 4.23 –	1.54; 0.39	2.63;	1.63; 0.42 –	0.69; 0.36 –
		-0.39	5.21	-1.17	5.80	-2.70	2.00 – 3.25	2.84	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 –	1.36; 1.05 –	0.13; 0.03 –	1.03; 0.89 –	0.01; -0.10	0.79;	0.13; 0.01 –	0.62; 0.55 –
		0.21	1.67	0.23	1.17	-0.12	0.69 – 0.89	0.25	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 –	1.48; 0.96 –	1.37; 1.03 –	0.45; 0.16 –	1.58; 1.25	0.10; -	1.41; 1.08 –	-0.08; -0.24
		1.10	2.00	1.71	0.74	-1.92	0.11 – 0.30	1.74	-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		

^aLinear 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.

^bAdolescents ≤17 years; adults >17 & <65; elderly ≥65 years.

^cDaily 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

^aDaily dose intake (DDI) is expressed in mg/day.

^bModels 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				

^aDaily dose intake (DDI) is expressed in mg/day.

^bModels were adjusted for time, sex, age, baseline weight and diagnoses.

^cModels were adjusted for time, sex, age, baseline BMI, diagnoses and fasting status.

Abbreviations: CI= confidence interval, N= number.