

BRIEF REPORT

Treatment Discontinuation Impact on Long-Term (10-Year) Weight Gain and Lipid Metabolism in First-Episode Psychosis: Results From the PAFIP-10 Cohort

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Abstract

Background: Patients with a first episode of psychosis (FEP) are at higher risk of gaining weight and presenting metabolic disturbances, partly related to antipsychotic exposure. Previous studies suggest that treatment discontinuation might have a positive impact on weight in schizophrenia. The aim of this study was to evaluate the effect of treatment discontinuation on weight and metabolic changes in a FEP cohort.

Methods: A total of 209 FEP patients and 57 healthy controls were evaluated at study entry and prospectively at 10-year follow-up. Anthropometric measures and, clinical, metabolic, and sociodemographic data were collected.

Results: Patients discontinuing antipsychotic treatment presented a significantly lower increase in weight and better metabolic parameter results than those still on antipsychotic treatment at 10-year follow-up.

Conclusions: Treatment discontinuation had a positive effect on the weight and metabolic changes observed in FEP patients; however, this effect was not sufficient to reaching a complete reversal to normal levels.

Key Words: Treatment discontinuation, lipid metabolism, weight gain, medication-naïve, second-generation antipsychotic

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Introduction

Patients with schizophrenia spectrum disorders are at higher risk of presenting increments in body weight and related metabolic disturbances, such as dyslipidemia and glucose intolerance, which mediate in the decrease of life expectancy observed in psychosis (Melle et al., 2017). These abnormalities have been observed early in the course of the psychotic disorder (Perez-Iglesias et al., 2007) but usually keep progressing at long-term periods (Mackin et al., 2012, Parabiaghi et al., 2016, Saloojee et al., 2016).

It has been proposed that antipsychotic exposure is one of the main risk factors for this weight gain observed in psychosis (Stahl et al., 2009). Subsequently, recent studies have focused on samples of patients with a first episode of psychosis (FEP) to rule out possible confounding effects of previous exposition to psychopharmacological treatments. As a result, there is mounting evidence of the association between antipsychotic exposure and metabolic disturbances in FEP individuals (Tek et al., 2016), even from the early stages of the disorder, after short periods of antipsychotic exposure (Perez-Iglesias et al., 2007; Josiassen et al., 2010; Perez-Iglesias et al., 2014b). In addition to these early changes, several studies have shown that these weight and metabolic alterations keep progressing at mid- and long-term (1–3 years) (Perez-Iglesias et al., 2007, 2014a; Malla et al., 2016; Bioque et al., 2018; Vazquez-Bourgon et al., 2018). We recently reported a pattern of steady weight gain throughout the 10-year follow-up in a cohort of FEP patients evaluated 10 years after their psychosis breakout (Vázquez-Bourgon et al., unpublished observations). This result is in line with a previous study (Hui et al., 2018).

Taking into account the association between antipsychotic treatment and weight gain, it would be relevant to analyze the impact of treatment discontinuation on the metabolic alterations observed in FEP patients. Treatment discontinuation has been described as a major risk factor for relapse in psychosis (Mayoral-van Son et al., 2016); however, there is almost no evidence regarding the impact of antipsychotic discontinuation on the weight gain in psychosis. Significant reductions in body mass index (BMI) were found after discontinuation of antipsychotic treatment in a small group of hospitalized children and adolescents (Hulvershorn et al., 2017). Despite this, Mackin and colleagues (Mackin et al., 2012) reported that discontinuing antipsychotic medication after several years of exposure was not associated with a reversal of the metabolic disturbances presented in the patients, suggesting that the consolidated metabolic dysregulation associated with the antipsychotic treatment is maintained long term (Mackin et al., 2012). Similarly, Wu and colleagues (Wu et al., 2014) reported that compared with antipsychotic-treated schizophrenia patients, antipsychotic-discontinuation patients showed a smaller BMI, although the differences did not reach statistical significance.

In addition to the scarcity of data in this topic, there are no previous studies, to our knowledge, on FEP patients following a longitudinal prospective approach that analyze the impact of treatment discontinuation on weight and metabolic changes long term (10 years).

This study aimed to explore prospectively the effect of treatment discontinuation on the pattern of weight changes and the occurrence of metabolic disturbances in a FEP cohort followed for the first 10 years of their psychosis. Taking into account the above evidences, we hypothesized that those patients discontinuing antipsychotic treatment would present significantly lower increments in weight and metabolic disturbances

than those patients continuing on antipsychotic treatment after 10 years of the FEP.

Methods

Study Setting

The present study was part of a larger prospective longitudinal study on first-episode, non-affective psychosis: the “First Episode Psychosis Clinical Program 10” (PAFIP-10) study (Ayesa-Arriola et al., 2019).

The study was approved by the local ethics committee for clinical research (CEIC-Cantabria) in accordance with international standards for research ethics. Patients included in the study provided written informed consent for entry initially into PAFIP and for PAFIP-10 reassessment.

Baseline Inclusion Criteria

All referrals to PAFIP between February 2001 and July 2008 were screened against the following inclusion criteria: age 15–60 years; living in the catchment area; experiencing their FEP; no prior treatment with antipsychotic medication or, if previously treated, a total life-time of adequate antipsychotic treatment of less than 6 weeks. DSM-IV criteria for drug or alcohol dependence, intellectual disability, and a history of neurological disease or head injury were exclusion criteria. The diagnoses were confirmed through the use of the Structured Clinical Interview for DSM-IV (First et al., 1996) conducted by an experienced psychiatrist at 6 months from the baseline visit.

Patient Clinical Assessment and Psychopharmacological Treatment

Baseline sociodemographic and clinical information were recorded from interviews with patients or their relatives and from medical records on admission. Clinical data for this study were collected by the same senior consultant psychiatrist (B.C.-F.) at baseline and at the 10-year follow-up.

All patients were, at baseline, randomly assigned to oral antipsychotic medication. Antipsychotic doses could be adjusted as clinically indicated within the prescribed range in an attempt to target the lowest effective dose.

Patients were clustered in 2 groups (“treatment continuation” vs “treatment discontinuation”) based on patients’ self-reports and medical records; patients were included in the “discontinuation group” if they reported not taking antipsychotic treatment at the 10-year reassessment.

Healthy individuals (n=57) without psychiatric illness were recruited as control group and evaluated at baseline and 10 years after. Sociodemographic, clinical, and anthropometric measures were collected. Lipid and glycemic examinations, through laboratory analyses, were also performed at both time-points.

Laboratory Analyses

All determinations were performed at the same site, in our hospital, including both biochemical and endocrinology analysis. All measurements were obtained, after an overnight fast, at baseline and 10-year follow-up. Fasting state as well as treatment compliance were reported by patients and their family members. A full description of the technical methods related to

the laboratory analyses is reported elsewhere (Vázquez-Bourgon et al., unpublished observations).

Statistical Analyses

Statistical analyses were carried out to explore the impact of antipsychotic medication discontinuation on long-term weight and metabolic changes. For this, we compared those patients taking antipsychotic medication at 10-year follow-up ($n=175$) with those who had previously discontinued it ($n=34$) and with the control group ($n=57$). For this purpose, ANCOVA analyses were carried out, where parameter change was used as the dependent variable, participant group (patients on antipsychotic treatment vs discontinuers) was the fixed factor, and baseline BMI, baseline parameter data, age, and sex were used as covariates.

In addition, we calculated the differences in the percentage of participants meeting the criteria for obesity and metabolic disorders from baseline to the 10-year follow-up. To evaluate significant changes in these percentages, we used the McNemar test for repeated measures.

The Statistical Package for Social Science (SPSS) version 22.0 (IBM, Armonk, NY) was used for the statistical analyses. All statistical tests were 2-tailed, and the significance was determined at the .05 level.

RESULTS

Cohort Characteristics

Between February 2001 and July 2008, 307 patients took part in the PAFIP study and were assessed at baseline. Of these, 10 patients died during the follow-up period (including 4 deaths from suicide). Of the 297 remaining participants, 209 (70.4%) completed the 10-year follow-up reassessment (PAFIP-10). Briefly, at program admission, the patients had a mean age of 28.1 years ($SD=8.3$), 54.5% were male, and most of them were White Caucasian (98.6%).

Of the 209 patients in the present study, 30 (14.4%) were initially treated with aripiprazole (a D2 and 5-HT_{1A} receptor partial agonist, and 5-HT_{2A} receptor antagonist), 40 (19.1%) with risperidone (a D₂, 5-HT₂, and NE alpha-2 receptor antagonist), 28 (13.4%) with quetiapine (a D₂ and 5-HT₂ receptor antagonist, and NET -metabolite- reuptake inhibitor), 32 (15.3%) with ziprasidone (a D₂ and 5-HT₂ receptor antagonist), 40 (19.1%) with olanzapine (a D₂ and 5-HT₂ receptor antagonist), and 39 (18.7%) with haloperidol (a D₂ receptor antagonist).

At the 10-year follow-up assessment, 34 patients (16.3%) had previously discontinued the antipsychotic treatment. The mean time to discontinuation was 4.5 years, and the mean time from discontinuation to 10-year follow-up (period without antipsychotic exposure) was 7.4 years ($SD=3.3$). Among those still on antipsychotic treatment, 39 (18.7%) continued with the same treatment initially prescribed, and 29 (17.2%) patients were taking a second antipsychotic medication. A complete analysis of treatment effectiveness and reason for discontinuation in this cohort at 10-year follow-up is the subject of another study currently under preparation.

Both patient groups (on antipsychotic treatment vs discontinuation group) did not differ in most of the main baseline clinical and socio-demographic characteristics (supplementary Table 1). However, it is noteworthy that those patients who continued on antipsychotic treatment at 10-year follow-up were more frequently diagnosed with schizophrenia (vs other schizophrenia-spectrum disorders) and presented higher Scale

for the Assessment of Positive Symptoms (SAPS) score at baseline than those patients who discontinued antipsychotic treatment throughout the 10-year follow-up.

Treatment Discontinuation Effect on Weight and Metabolic Differences After 10 Years From Psychosis Breakout

The ANCOVA analyses comparing the 3 groups (treated patients, discontinued patients, control group) showed significant differences in the long-term changes in weight, BMI, and waist circumference between the 3 groups (all $P<.001$). Results from post-hoc comparisons remained significantly different between the patient groups (treated vs discontinued) and between the treated patients and the control group, but not between the discontinued and the control groups. Weight and waist circumference changes over the 10-year study were progressive between groups, from the control group (the smallest changes), to the discontinuation group, and finally the treated patients group (the greatest changes) (Table 1).

Data from direct comparison (ANCOVA) between the 2 patients groups, excluding the control group from the analyses (supplementary Table 2), showed that apart from the significant differences in weight and BMI changes described above, those patients who discontinued their antipsychotic treatment presented a better progression in metabolic parameters than those still on antipsychotic treatment, with statistical analyses reaching statistical significance for mean changes in high-density lipoprotein (1.44 vs -2.10 mg/dL, $F=4.12$, $P=.044$) and triglycerides-high-density lipoprotein index (0.33 vs 1.27, $F=4.42$, $P=.037$) and trend toward association for mean changes in triglycerides (22.04 vs 48.65 mg/dL, $F=3.04$, $P=.076$), homeostasis model assessment index (0.80 vs 1.13, $F=3.04$, $P=.084$), and insulin (3.23 vs 3.71, $F=3.87$, $P=.051$).

These differences in weight and metabolic changes between patient groups are reflected in the clinical impact; thus, the increment in the percentage of patients meeting criteria for obesity and other metabolic disorders after the 10-year follow-up is remarkably less pronounced in the treatment discontinuation group than in the continuation group (Table 2).

Discussion

This study replicated our previous results (Vázquez-Bourgon et al., unpublished observations) showing a relation between antipsychotic medication exposure and weight gain at long term (10 years) in psychosis. However, it also shows that discontinuing antipsychotic treatment was associated with a smaller increase in weight and waist circumference at long term (10 years) in a sample of patients followed-up after their FEP. Research studies focusing on the effect of antipsychotic discontinuation on weight and metabolic alteration reversibility are scarce. However, these results are in line with indirect data from a previous study comparing adherent and non-adherent schizophrenia patients (Lindenmayer et al., 2009) and showing that non-adherent patients presented significantly lower increments in body weight than adherent patients (1.96 kg vs 2.63 kg, $P=.02$). Similarly, discontinuation of antipsychotic treatment in a small group of hospitalized children and adolescents (Hulvershorn et al., 2017) was associated with reductions in BMI. And Wu and colleagues (Wu et al., 2014) observed that antipsychotic discontinuation patients presented a smaller BMI (23.09 vs 22.28) than the antipsychotic-treated schizophrenia patients, although the differences did not reach statistical significance. In this case, the

Table 1. Differences in Longitudinal Changes (“10-Year” Minus “Baseline” Measures) in Anthropometric and Metabolic Measurements Between Psychosis Patients Regarding Antipsychotic Treatment Status at 10-Year Follow-up

	Patients on antipsychotic treatment	Patients who discontinued treatment	Controls	Stats ^a			P ^b		
	Mean diff (SD)	Mean diff (SD)	Mean diff (SD)						
	A: n=175	B: n=34	C: n=57	df	F	P	A vs B	B vs C	A vs C
Anthropometric measures									
Weight, kg	16.53 (13.06)	8.22 (6.80)	2.89 (7.34)	2; 248	31.11	<.001	<.001	.147	<.001
BMI, kg/m ²	5.88 (4.69)	2.90 (2.45)	1.03 (2.74)	2; 248	30.31	<.001	<.001	.187	<.001
Waist circumference, cm	14.56 (12.19)	7.12 (3.98)	4.68 (7.14)	2; 79	11.82	<.001	.046	1.000	<.001
Lipid parameters									
Cholesterol, mg/dL	21.33 (34.54)	23.33 (30.97)	8.79 (36.52)	2; 210	0.723	.468	1.000	1.000	.693
HDL, mg/dL	-2.10 (12.38)	1.44 (12.93)	2.75 (6.86)	2; 182	5.341	.006	.132	1.000	.015
LDL, mg/dL	13.59 (28.49)	14.96 (26.75)	6.54 (31.44)	2; 179	0.279	.757	1.000	1.000	1.000
Triglycerides, mg/dL	48.65 (76.24)	22.04 (44.83)	-2.75 (52.79)	2; 182	6.644	.002	.181	.706	.003
Glycemic parameters									
Glucose, mg/dL	4.74 (23.11)	0.93 (10.89)	4.42 (16.85)	2; 209	2.926	.056	.772	.961	.073
HOMA index	1.13 (3.37)	0.80 (1.81)	0.16 (0.87)	2; 145	8.478	<.001	.184	.510	<.001
HOMA index, men	1.69 (2.88)	0.57 (1.95)	-0.19 (0.92)	2; 74	5.237	.007	.181	1.000	.015
HOMA index, women	0.45 (3.80)	0.99 (1.76)	0.51 (0.67)	2; 66	4.022	.022	1.000	.252	.018
Triglycerides-HDL index	1.27 (2.14)	0.33 (1.16)	-0.07 (0.97)	2; 178	6.835	.001	.082	1.000	.004
Hormonal levels									
Insulin, μU/mL	3.71 (13.02)	3.23 (6.81)	0.19 (3.59)	2; 148	10.225	<.001	.108	.474	<.001
Insulin, men	5.64 (10.55)	1.90 (7.10)	-0.78 (3.72)	2; 75	6.692	.002	.107	1.000	.005
Insulin, women	1.52 (15.16)	4.43 (6.68)	1.25 (3.27)	2; 68	4.469	.015	1.000	.262	.012
Leptin levels									
Leptin, ng/mL	13.03 (13.39)	9.40 (19.39)	4.66 (4.52)	2; 143	5.709	.004	.691	.382	.003
Leptin, men	8.94 (10.81)	1.42 (5.60)	3.85 (4.64)	2; 72	4.270	.018	.093	1.000	.081
Leptin, women	17.63 (14.58)	16.65 (24.54)	5.54 (4.40)	2; 66	4.384	.016	1.000	.063	.016

Abbreviations: BMI, body mass index; HDL, high-density lipoprotein; HOMA, homeostasis model assessment; LDL, low-density lipoprotein.

^aStatistics: ANCOVA model; parameter change was used as the dependent variable, participant group (patients on antipsychotic treatment vs discontinuers) was the fixed factor, and baseline BMI, baseline parameter data age, and sex were used as covariates.

^bPairwise comparisons based on estimated marginal means; Bonferroni adjustment for multiple comparisons.

lack of statistical significance in the results might be explained by the fact that the mean duration of treatment discontinuation prior to the study was 0.67 years, probably not long enough to reverse the previous long-term metabolic effect of antipsychotic treatment.

Mackin and colleagues (Mackin et al., 2012) reported that discontinuing antipsychotic medication after several years of exposure was not associated with a complete reversal of the metabolic disturbances presented in the patients, suggesting that the consolidated metabolic dysregulation associated with the antipsychotic treatment is maintained long term (Mackin et al., 2012). Our results are in line with this study; FEP patients who had discontinued antipsychotic treatment in our sample presented lower changes in the lipid and glycemic parameters than those patients who continued on antipsychotic treatment, but greater changes than healthy non-psychiatric participants did. However, only statistically significant differences between the treated patients and control group were observed, suggesting that antipsychotic discontinuation was not associated with complete reversal of weight and metabolic changes.

This evidence suggests that antipsychotic exposure does not explain on its own the weight gain and metabolic disturbances observed in FEP patients. The gradual weight gain differences between non-psychiatric healthy controls,

“antipsychotic-discontinuation” patients, and “antipsychotic-treated” patients (3.4, 8.2, and 16.5 kg, respectively) at 10-year follow-up suggest that beyond the effect of antipsychotic medication on weight changes, there are other clinical and social factors contributing to the weight gain in psychosis patients. This is consistent with previous articles showing that cardio-metabolic risk factors and abnormalities are present in early psychosis regardless of antipsychotic exposure (Jensen et al., 2017; Pillinger et al., 2017), thus suggesting that the cardio-metabolic alterations may be in part explained by the underlying illness itself. Other known clinical, social, and personal risk factors, such as unhealthy diet, low physical activity, and substance abuse, are known to contribute to the higher incidence of metabolic alterations in this population (Vancampfort et al., 2017; Firth et al., 2018).

Strengths and Limitations

The main strength of this study is its design, a prospective longitudinal study with an uncommon long-term follow-up (10 years) on a cohort of well-characterized, drug-naïve FEP patients, and its comparison with a prospective sample of healthy individuals. Studying a cohort of drug-naïve patients with a FEP from the early stage of their psychotic disorder facilitates avoiding

Table 2. Comparison of Proportion of Participants with Pathologic Parameters in Weight, Fasting Glucose, and Lipid Levels at Baseline and at 10-Year Follow-up in Each Patient Group

	Baseline	10-year follow-up	% difference	n	P ^a
	% (n)	% (n)			
BMI ≥30 kg/m²					
Discontinued group	3.7 (1)	22.2 (6)	18.5	27	.063
Antipsychotic group	7.3 (11)	38.4 (58)	31.1	151	<.001
Total	6.7 (12)	36.0 (64)	29.3	178	<.001
Glucose >110 mg/dL					
Discontinued group	0 (0)	6.5 (2)	6.5	31	—
Antipsychotic group	1.8 (3)	7.3 (12)	5.5	165	.022
Total	1.5 (3)	7.1 (14)	5.6	196	.007
Insulin (μU/mL); men >15.7, women >17.3					
Discontinued group	0 (0)	10.5 (2)	10.5	19	—
Antipsychotic group	10.7 (12)	34.8 (39)	24.1	112	<.001
Total	9.2 (12)	31.3 (41)	22.1	131	<.001
HOMA; men >3.5, women >3.9					
Discontinued group	0 (0)	10.5 (2)	10.5	19	—
Antipsychotic group	8.2 (9)	33.6 (37)	25.4	110	<.001
Total	7.0 (9)	30.2 (39)	23.2	129	<0.001
Triglyceride/HDL index >3.5					
Discontinued group	8.0 (2)	4.0 (1)	4.0	25	1.000
Antipsychotic group	11.5 (16)	27.3 (38)	15.8	139	<.001
Total	11.0 (18)	23.8 (39)	12.8	164	<.001
Cholesterol >200 mg/dL					
Discontinued group	19.4 (6)	38.7 (12)	19.3	31	.070
Antipsychotic group	24.1 (40)	42.2 (70)	18.1	166	<.001
Total	23.4 (46)	41.6 (82)	18.2	197	<.001
LDL cholesterol >130 mg/dL					
Discontinued group	19.2 (5)	34.6 (9)	15.4	26	.219
Antipsychotic group	25.2 (35)	35.3 (49)	10.1	139	.024
Total	24.2 (40)	35.2 (58)	11.0	165	.006
HDL cholesterol <40 mg/dL					
Discontinued group	23.1 (6)	15.4 (4)	-7.7	26	.625
Antipsychotic group	21.1 (30)	28.2 (40)	7.1	142	.143
Total	21.4 (36)	26.2 (44)	4.8	168	.280
Triglycerides >150 mg/dL					
Discontinued group	3.7 (1)	7.4 (2)	3.7	27	1.000
Antipsychotic group	7.8 (11)	27.7 (39)	19.9	141	<.001
Total	7.1 (12)	24.4 (41)	17.3	168	<.001

Abbreviations: BMI, body mass index; HDL, high-density lipoprotein; HOMA, homeostasis model assessment; LDL, low-density lipoprotein.
^aMcNemar test for repeated measures.

the confounding effect of chronicity and previous exposure to medications with a probable effect on metabolism.

On the other hand, the study presents several important limitations. Patients were not evaluated periodically for research purposes, thus leading to a widely spaced follow-up interval with a lack of clinical and social information in that long period. This may hinder controlling for other factors' effect on weight and precludes proper analyses of weight trajectories. Another limitation of the study is that the data regarding treatment continuation or discontinuation are mainly based on patients and their families' reports, which might explain the low rate of treatment discontinuation observed in this cohort (16%); the use of plasmatic levels of the antipsychotics prescribed would have provided more accurate information of treatment compliance.

Due to the long follow-up period, we were not able to account in the statistical analyses other factors known to contribute to weight changes such as diet and physical activity. Similarly, we were not able to carry out differential antipsychotic medication analysis mainly due to the long-term follow-up and the inability

to control for other environmental and pharmacological confounding factors.

Conclusions

Patients who discontinued antipsychotic treatment prior to the 10-year follow-up presented smaller weight gain and better metabolic progression long term than those who remained on antipsychotic treatment.

Supplementary Materials

Supplementary data are available at *International Journal of Neuropsychopharmacology (IJNPPY)* online.

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Interest Statement

J.V.-B., J.M.-v.S., M.G.-R., R.A.-A., M.J.-R., D.T.-G., and V.O.-G.d.F. report no conflicts of interest. M.B. has received honoraria for his participation as a consultant and/or as a speaker at educational events from Adamed, Ferrer, Janssen-Cilag, Lundbeck, Neuraxpharm, and Otsuka, and a research prize from Pfizer. B.C.-F. has received honoraria for his participation as a consultant and/or as a speaker at educational events from Janssen Johnson & Johnson, Lundbeck, and Otsuka Pharmaceuticals.

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