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ORIGINAL CONTRIBUTION

The effects of antipsychotics on weight gain, weight-related hormones and homocysteine in children and adolescents: a 1-year follow-up study

Inmaculada Baeza[1,5] · Laura Vigo[3] · Elena de la Serna[1,5] · Rosa Calvo-Escalona[1,5] · Jessica Merchán-Naranjo[4] · Pamela Rodríguez-Latorre[4] · Celso Arango[4] · Josefina Castro-Fornieles[1,2,5]

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Abstract To analyze weight gain, metabolic hormones, and homocysteine (Hcys) levels in children and adolescents on antipsychotics (AP) during a year-long follow-up. 117 patients, AP-naïve or quasi-naïve (less than 30 days on AP), were included. Weight, body mass index (BMI), BMI *z*-score (z-BMI), and levels of leptin, insulin, insulin resistance (HOMA-IR), adiponectin, ghrelin, thyroid stimulating hormone (TSH), free thyroxine (FT4), and Hcys were measured at baseline, and at 3, 6, and 12 months, while patients remained on the same AP. Patients (mean age: 14.4 ± 3 years; 64.1 % male) were on risperidone ($N = 84$), olanzapine ($N = 20$) or quetiapine ($N = 13$) from baseline up to 1-year follow-up and significantly increased weight (5.8 ± 4.3 kg at 3-month, 8.1 ± 6.1 kg at 6-month, and 11.6 ± 7.0 kg at 1 year), BMI, and z-BMI. Leptin levels significantly increased from baseline to 3 and 6 months, as did TSH levels from baseline to 3 months, while FT4 levels decreased from baseline to 3 and 6 months. Patients with BMI >85th percentile at baseline ($N = 16$) significantly increased weight, BMI, and z-BMI, more than patients with normal BMI over time. Higher baseline levels of insulin, HOMA-IR, and leptin were associated with increased weight/BMI during follow-up, while higher baseline levels of FT4, adiponectin, and ghrelin were associated with lower weight/BMI during follow-up. All AP were associated with increased weight and BMI/z-BMI in all of the assessments; however, at 1-year assessment, this increase was significantly higher for patients on quetiapine. Both higher baseline levels of insulin, HOMA-IR, and leptin, as well as being overweight/obese at baseline were associated with increased weight/BMI during 1-year follow-up in children and adolescents on AP. Awareness of weight-related parameters in this population may help inform decisions regarding AP prescriptions.

Keywords Antipsychotic · Side effects · Weight gain · Children · Adolescents

✉ Inmaculada Baeza
ibaeza@clinic.ub.es

1 Department of Child and Adolescent Psychiatry and Psychology, SGR-489, Institut Clinic of Neurosciences, IDIBAPS (Institut d'Investigacions Biomèdiques August Pi Sunyer), Hospital Clínic Universitari of Barcelona, Villarroel, 170, Barcelona 08036, Spain

2 Department of Psychiatry and Psychobiology, University of Barcelona, Barcelona, Spain

3 Adolescent Service, Mapther house, Maudsley Hospital, London, UK

4 Child and adolescent Psychiatry Department, School of Medicine, Hospital General Universitario Gregorio Marañón, Universidad Complutense, IISGM, CIBERSAM, Madrid, Spain

5 Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Madrid, Spain

Introduction

Prescribing antipsychotics (AP), essentially second-generation APs, has become a common practice in treating children and adolescents suffering from different psychiatric disorders [1], especially in the last decade [2–4].

Some studies suggest that the child and adolescent population has greater vulnerability to weight gain associated with medication intake [5–7]. Moreover, the younger the child, the greater the weight-gain risk [8]. Other medical problems, such as hyperglycemia, dyslipidemia, and high blood pressure, are associated with weight gain at the metabolic level [5]. All of this may have a negative physical and psychological impact on patients, increasing

morbimortality [9], decreasing the quality of life, and lowering adherence to treatment [10].

There are several possible mechanisms to explain the metabolic abnormalities associated with APs. The main one is the direct effect of the drug antagonizing different brain receptors (H1 and H3 hystaminergic [11], 5HT2A and 2C serotonergic and alpha1 and alpha2 adrenergic receptors [12]), but there is also the effect of various peptide hormones originating in the peripheral system which send signals to the brain through different pathways. It is thought that all of these mechanisms act to increase weight through food intake, resting energy expenditure and physical activity [13]. The most important agents in the regulation of energetic homeostasis and body weight are insulin and leptin [14], although other hormones, such as ghrelin, adiponectin, thyroid hormones as well as the amino acid homocysteine (Hcys), are also involved. Leptin is a hormone that plays a key role in regulating appetite and body weight. It is mainly secreted by adipocytes. Its main function is to regulate energy balance through a negative feedback mechanism involving the hypothalamus and the ventral tegmental area [15]. The production of circulating leptin is related to adiposity. Peripheral administration of leptin reduces appetite and feeding [16]. Insulin is a hormone produced by beta pancreatic cells in the liver. It binds to receptors in the arcuate nucleus of the hypothalamus and, like leptin, provides information on energy status at the peripheral level. Moreover, insulin stimulates leptin's secretion [17]. Ghrelin is a peptide hormone that appears to play a crucial role in regulating energy in the short term. It is secreted by the stomach and binds the growth hormone secretagogue receptor [18]. Ghrelin acts in a manner that is the opposite of leptin and insulin, as its orexygenic effect controls energy balance by increasing fat deposits and food intake [18]. Levels of circulating ghrelin increase before meals and decrease after meals [19]. Insulin seems to decrease ghrelin levels [16]. Adiponectin is a hormone secreted only by fatty cells involved in weight regulation processes by increasing fatty acid oxidation and glucose use [20]. In humans, adiponectin levels are negatively correlated to body weight and insulin levels. Serum adiponectin levels decrease with obesity, insulin resistance, and type II diabetes [21]. Thyroid hormones regulate basal and total energy consumption and could influence body composition [22]. Increases in thyroid stimulating hormone (TSH) levels have been described in obese children and adolescents [23, 24], and leptin might play a role in the relationship between thyroid hormone levels and body composition [25, 26]. As such, an increase of leptin could mediate an increase in thyrotropin-releasing hormone levels (TRH), resulting in an increase of TSH [23]. Hcys is a sulfur-containing amino acid formed during the metabolism of the essential amino acid methionine (one-carbon metabolism, OCM). High levels of Hcys have been consistently associated with cardiovascular risk [27]. Its relationship with being overweight and obesity is controversial in adult studies [28, 29], although higher BMI has recently been associated with higher Hcys levels in children [30].

Studies focusing on the relationship between AP-induced weight gain and the hormones involved in energetic homeostasis mechanisms have considerably increased in recent years. One review [31] states that leptin increases during AP treatment as a consequence of weight gain rather than as a direct effect of AP on leptin levels. Weight gain is also related to increased levels of ghrelin in most [32, 33], but not all [34] studies. It has been reported that ghrelin levels decrease during the first few weeks after beginning AP treatment and increase over time [16]. However, adiponectin has only been associated with weight gain in patients on olanzapine [33, 35].

There is scarce information about the relationship between weight gain and regulating hormones in children and adolescents on AP. It has been reported that body mass index (BMI) and leptin levels increased after 6 weeks on clozapine [36]. Moreover, in an 8-week observational study, despite a mean weight increase of approximately 4 kg, only insignificantly higher leptin levels were found in children and adolescents with psychotic disorders on AP [37]. In a 6-month follow-up study, serum leptin changes were not associated with weight gain in a sample of children with autism on risperidone [38]. In a study of children and adolescents with a mean of 2.9 years on risperidone, it was found that overweight or obese patients had higher insulin levels and insulin resistance than those with normal BMI [39]. To our knowledge, there have been no prospective longer follow-up studies addressing the relationship between weight and hormones in AP-naive or quasi-naive children and adolescents beginning AP treatment.

The main purpose of our study was to analyze weight gain, its relationship to hormones and amino acids associated with weight, and examine their evolution during a 1-year follow-up in a sample of naïve or quasi-naïve children and adolescents on AP treatment.

We hypothesized that patients' weight, BMI, and BMI z-score (z-BMI) would increase from baseline to the different assessments of the follow-up. We also expected that weight gain would be associated with an increase in leptin, insulin, ghrelin, TSH, and Hcys, and a decrease in adiponectin levels.

Method

Subjects

Subjects were recruited from four child and adolescent Psychiatry departments at university hospitals in Spain.

Both inpatients and outpatients visiting at these facilities between May 2005 and April 2007 who met the inclusion criteria were invited to participate in the study (for a full description of the study design, see [40]). Inclusion criteria were: age between 4 and 17 years at the time of first evaluation, with any psychiatric diagnoses according to DSM-IV criteria except for eating disorders; and being AP-naïve (prescribed an AP drug for the first time at baseline) or quasi-naïve (having begun any first AP treatment up to 30 days before baseline). Patients who did not have at least two assessments during the follow-up were not included in the study. There were no exclusion criteria.

For this study, from the whole sample, only patients whose baseline serum leptin levels had been measured were included (only two centers: Hospital Gregorio Marañón, Madrid, and Hospital Clínic, Barcelona, could perform this measurement). Moreover, only patients who continued their AP treatment during the whole follow-up period with the same single AP were included in this analysis. If a patient switched to a different AP or another was added, only the visits prior to that change were included. Additionally, since most patients were on risperidone, olanzapine or quetiapine, three patients who were on different AP were removed from the analysis (Fig. 1). The final sample included 117 subjects.

The study was approved by the ethical committees of all participating clinical centers. Parents or legal guardians of all patients gave written informed consent, and all patients older than 12 years agreed to participate.

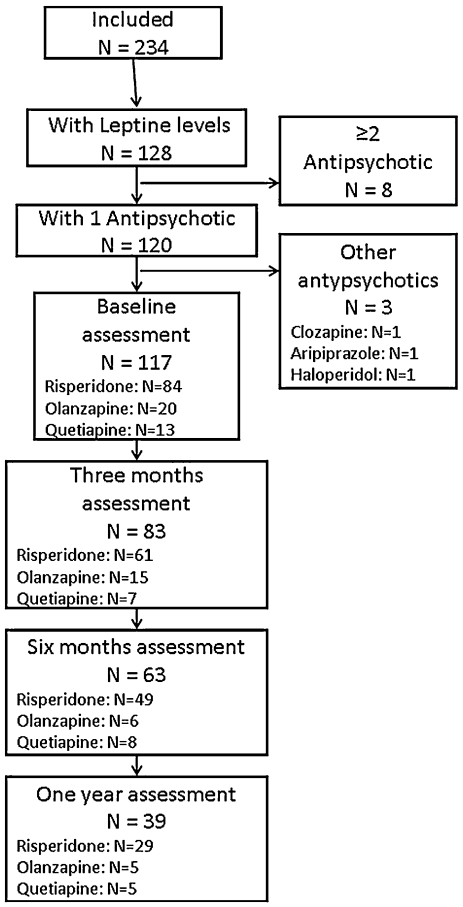

Fig. 1 Participants flow chart

Procedure

Patients were followed up during 1 year, with assessments at baseline, 3, 6, and 12 months, while they were on the same AP. In each evaluation, a blood analysis was performed; weight and height were measured, and AP and other pharmacological treatments were registered (drugs, dosage). AP doses were converted to chlorpromazine equivalents [41].

Assessment

Hormones

Serum leptin, insulin, adiponectin, TSH, and FT4 levels were measured in both centers. Ghrelin and Hcys levels were only measured in patients included in one of the centers (Hospital Clínic, Barcelona).

Leptin was measured with enzyme-linked immunosorbent assay (ELISA) (BioVendor, ref: RD191001100) in one center and by radioimmunoassay (Linco Research, St. Charles, MO, USA) in another. Insulin was measured in both places using a solid-phase, 2-site chemiluminescent immunometric assay (IMMULITE 2000 Insulin, CPS). Insulin resistance was determined using the homeostatic model assessment [HOMA-IR: fasting insulin (μIU/mL) × glucose (mg/dL)/405] [42]. Adiponectin levels were obtained using enzyme-linked immunosorbent assay (ELISA) (BioVendor, ref: RD195023100 and by radioimmunoassay (Linco Research, St. Charles, MO, USA), depending on the center. Both TSH and FT4 were measured using radioimmunoassay (Diagnostic Product Corporation, Los Angeles, CA, USA) at both sites. Ghrelin levels were measured by radioimmunoassay (Ghrelin-Total RIA Kit; Linco Research). Hcys levels were assessed by electrochemiluminiscence immunoassay in an Advia Centaur® analyzer (Siemens Healthcare, Barcelona, Spain).

Height and weight

Weight and height were measured with the same sliding-weight scale at both centers. Height was measured in meters to the nearest 0.1 cm, using a SECA 220 stadiometer. Body weight was measured in kilograms (kg) to the nearest 0.2 kg, wearing light clothes and no shoes, using

platform scales. BMI and z-BMI (standardized BMI adjusted for age and gender) were also calculated, in agreement with standard Spanish tables [43].

Diagnoses

Psychiatric diagnoses were made by child and adolescent psychiatrists in each center, according to DSM-IV-TR criteria, at baseline. Diagnoses were grouped into the following categories: schizophrenia spectrum disorders, bipolar disorders, depressive disorders, disruptive behavior disorders, pervasive developmental disorder, and tic spectrum disorders (for a full description of diagnostic categories and use of AP associated, see [1]).

Data analysis

For descriptive purposes, continuous variables were expressed as means, standard deviations (SD), and ranges, and categorical variables were expressed as frequencies and/or percentages. MANOVA for repeated measures was used to compare the parameters in the different assessments. Student's t test was used to compare assessments one by one when MANOVA for repeated measures was significant.

To assess differences between patients that were overweight/obese (with a BMI ≥85th percentile [44]) at baseline and those who were not, we used Student's t test.

The linear mixed-effects model for longitudinal data (R) was used to analyze the relationship between hormone and Hcys levels at baseline and weight/BMI during the follow-up. We also used linear mixed models to analyze the weight/BMI/z-BMI change at the different assessments according to AP.

Pearson/Spearman correlations were used to assess continuous variables or categorical ones.

All tests were two-tailed. Statistical analyses were carried out with the SPSS 18.0 (Statistical Package for the Social Sciences, Chicago, USA) and R statistics version 3.2.1 (http://www.r-project.org) using linear mixed models with package lme4 (version 1.1-8). Differences of $p < 0.05$ were considered significant.

Results

Sociodemographic characteristics, diagnoses, and treatment at baseline

Table 1 shows the sociodemographic data, diagnoses, and treatment at baseline of the sample. When patients entered the study, 57 (48.7 %) were AP-naïve, and those already on AP had a previous mean exposure of 6.8 ± 6.9 days on medication. The AP dose of quasi-naïve patients at baseline is shown in Table 2.

Table 1 Demographic and clinical characteristics of 117 patients at baseline

Baseline	Total $N = 117$
Age (years ± SD)	14.4 ± 3.0 (range 4–17 years)
Male gender (*N*, %)	75 (64.1)
Ethnicity: caucasian (*N*, %)	106 (90.6)
Current hospitalization (*N*, %)	87 (74.4)
Main diagnostic category (*N*, %)	
Schizophrenia spectrum disorders	34 (29.1)
Disruptive behavioral disorders	32 (27.4)
Bipolar disorders	22 (18.8)
Depressive disorders	15 (12.8)
Tic spectrum disorders	11 (9.4)
Pervasive developmental disorders	3 (2.6)
Psychotropic treatment	
No. of psychotropics (mean ± SD)	1 ± 1.1
Antipsychotics (quasi-naïve patients) (*N*, %)	60 (51.3)
Anxiolitic/hypnotic (*N*, %)	26 (22.2)
Antidepressant (*N*, %)	16 (13.7)
Mood stabilizer (*N*, %)	12 (10.3)
Anticholinergic (*N*, %)	6 (5.1)
Stimulant (*N*, %)	5 (4.3)

From baseline to the different assessments, there was a decrease in the patient sample (Fig. 1). Five (3.4 %) patients were excluded from the study during the follow-up because of AP switch, 2 (1.7 %) for adding a new AP, and 8 (6.8 %) for not having blood analysis results due to technical reasons. Moreover, 36 (30.8 %) patients left the study for medical reasons (mainly, clinical improvements which led to stopping AP treatment), and 27 (23.1 %) for other reasons, such as noncompliance and failure to continue follow-up. The same decrease was found in the subsample for which ghrelin and Hcys were measured (from 33 subjects at baseline to 17 at 3 months, 13 at 6 months, and 8 at 1 year). No differences in age, gender, diagnosis, and baseline hospitalization were found between patients who were excluded or left the study and those who completed it (data not shown).

Evolution of weight, BMI, z-BMI, and levels of laboratory parameters associated with weight

Mean weight, BMI, and z-BMI score significantly increased from baseline to all the posterior assessments ($p < 0.001$ for all the assesments) (Table 3). No differences were found on any BMI and z-BMI assessment when we

Table 2 Mean weight parameters and AP dose at baseline and during follow-up according to AP

Parameter	Baseline $N = 117$[a]	3-month follow-up $N = 83$[b]	6-month follow-up $N = 63$[c]	12-month follow-up $N = 39$[d]
Weight (mean ± SD) (kg)				
Risperidone	53.2 ± 16.7	58.5 ± 19.8	61.6 ± 21.9	65.6 ± 23.6
Olanzapine	55.9 ± 13.9	61.2 ± 8.2	62.4 ± 11.5	62.6 ± 14.7
Quetiapine	57.5 ± 8.2	62.9 ± 8.5	66.1 ± 10.5	76.2 ± 11.6
BMI (mean ± SD) (kg/m^2)				
Risperidone	20.4 ± 3.6	22. 2 ± 4.3	22.9 ± 4.9	23.7 ± 5.3
Olanzapine	20.3 ± 3.3	22.2 ± 2.3	23 ± 1.8	22.7 ± 2.7
Quetiapine	20.3 ± 3.0	22.4 ± 3.8	23.7 ± 4.7	26.4 ± 6.3
z-BMI (mean ± SD)				
Risperidone	−0.1 ± 1.3	0.5 ± 1.3	0.7 ± 1.4	1 ± 1.3
Olanzapine	−0.2 ± 0.9	0.3 ± 0.7	0.6 ± 0.5	1 ± 1.3
Quetiapine	−0.3 ± 0.8	0.3 ± 1.1	0.7 ± 1.3	1.4 ± 1.8
AP dose (mean ± SD)(mg/day)				
Risperidone	2.2 ± 1.5	3 ± 2.4	2.8 ± 2.6	2.2 ± 1.8
Olanzapine	13.5 ± 7	10.7 ± 5.7	7.5 ± 4.2	6 ± 2.2
Quetiapine	291.7 ± 241.7	421.4 ± 429	353.3 ± 423.9	490 ± 324.8
CPZ equivalent dose (mean ± SD)(mg/day)				
Risperidone	168.1 ± 114.2	226.7 ± 183.1	208.7 ± 192.1	163.3 ± 134.7
Olanzapine	284.2 ± 147.2	224.5 ± 120.1	157.9 ± 88.1	126.3 ± 47.1
Quetiapine	204.2 ± 169.2	295 ± 300.3	247.3 ± 296.7	343 ± 227.4

BMI body mass index, *AP* antipsychotic, *CPZ* chlorpromazine

[a] Quasi-naïve patients on risperidone $N = 32$, olanzapine $N = 10$ and quetiapine $N = 6$

[b] Patients on risperidone $N = 61$, olanzapine $N = 12$ and quetiapine $N = 7$

[c] Patients on risperidone N = 49, olanzapine $N = 6$ and quetiapine $N = 8$

[d] Patients on risperidone $N = 29$, olanzapine $N = 5$ and quetiapine $N = 5$

compared patients who at baseline were using stimulants ($n = 5$) vs. those not using them ($N = 112$), or between patients who were taking any concomitant psychotropic medication ($N = 47$) vs. those not taking any ($N = 70$) (data not shown). AP dose and its chlorpromazine equivalents at all of the assessments are shown in Table 2.

Mean leptin levels increased from baseline to 3- and 6-month visits with statistical significance ($F = 3.233$, $p = 0.047$). Mean TSH levels significantly increased from baseline to 3- and 6-month assessments ($F = 3.424$, $p = 0.034$), while FT4 levels significantly decreased from baseline to 3-month evaluation ($F = 3.000$, $p = 0.025$) (Table 3 shows the complete comparison data). The other mean levels of laboratory parameters measured did not significantly change across the assessments (Table 3).

When we divided the sample by gender, mean leptin levels were significantly higher in female than in male subjects at baseline (15.4 ± 14.4 vs. 7 ± 11.4 ng/mL, $t = 3.459$, $p = 0.001$), 3-month (42.4 ± 25.3 vs. 17.4 ± 8.2 ng/mL, $t = 2.900$, $p = 0.014$) and 12-month assessments (20.9 ± 12.7 vs. 6.8 ± 7 ng/mL, $t = 3.969$, $p < 0.001$). No other differences were found among the other parameters.

Differences in weight gain and BMI/z-BMI increase depending on the AP prescribed

Weight gain and BMI/z-BMI increase from baseline to 3-, 6-, and 12-month assessments varied according to the AP prescribed, as shown in Table 4. Patients on different AP showed different degrees of weight gain and BMI/z-BMI increase at all of the assessments. However, only from baseline to the 12-month assessment was there statistically significant data, with patients on quetiapine gaining a mean of 9.5 kg more than those on risperidone, and 7.7 kg more than those on olanzapine ($t = 2.403$, $p = 0.0217$) (Table 4).

In patients on quetiapine, a relationship was detected between weight gain and BMI/z-BMI increase from baseline to 12-month and mean daily dose at 12-month assessment ($R = 0.975$, $p = 0.005$ for all the analyses). No such relationship was found for risperidone or olanzapine.

Evolution of parameters in baseline overweight/obese subjects compared to normal BMI subjects

In overweight/obese subjects ($n = 16$, 13.7 % from the whole sample, at baseline; $n = 14$, 16.9 %, at 3-month;

Table 3 Mean weight and hormone levels at baseline and follow-up in the whole sample

Parameter	Baseline $N = 117$[1]	3-month follow-up $N = 83$[2]	6-month follow-up $N = 63$[3]	12-month follow-up $N = 39$[4]	F	p value
Weight (mean ± SD) (kg)	54.4 ± 15.5	59.3 ± 17.6	62.2 ± 19.9	66.6 ± 21.5	37.750	*<0.001*[a]
BMI (mean ± SD) (kg/m^2)	20.4 ± 3.5	22.2 ± 4	23 ± 4.7	23.9 ± 5.2	28.434	*<0.001*[b]
z-BMI (mean ± SD)	−0.2 ± 1.2	0.4 ± 1.2	0.7 ± 1.3	1 ± 1.3	24.509	*<0.001*[b]
Leptin levels (mean ± SD) (ng/mL)	10 ± 13.2	13 ± 13.5	13.9 ± 12.4	10.4 ± 10.6	3.233	*0.047*[c]
Insulin levels (mean ± SD) (µg/mL)	10.7 ± 6.0	11.9 ± 7.2	13.2 ± 11.4	10.3 ± 5.6	2.294	0.111
HOMA-IR (mean ± SD)	2.2 ± 1.3	2.6 ± 1.8	2.7 ± 2	2.1 ± 1.3	2.154	0.127
Adiponectin levels (mean ± SD) (ng/mL)	11.5 ± 4.6	11 ± 7.8	10.3 ± 5.8	10.8 ± 6.6	2.733	0.086
Ghrelin levels (mean ± SD) (ng/mL)	1154.8 ± 397.4	1089.9 ± 367.7	1138.5 ± 368.9	1085 ± 467.6	*	*
TSH levels (mean ± SD) (µU/mL)	2.5 ± 2.6	2.4 ± 1.4	2.3 ± 1.4	2.3 ± 1.5	3.424	*0.034*[d]
FT4 levels (mean ± SD) (ng/dL)	1.3 ± 0.4	1.1 ± 0.2	1.1 ± 0.3	1.1 ± 0.3	3.000	*0.025*[e]
Hcys (mean ± SD) (µmol/L)	9.0 ± 3.7	7.9 ± 2.6	8.5 ± 4.3	7.5 ± 1.8	0.413	0.763

BMI body mass index, *HOMA-IR* insuline resistance, *TSH* thyroid stimulating hormone, *FT4* free thyroxine, *Hcys* homocysteine

[a] Baseline < 3-month, $p < 0.001$; baseline < 6-month, $p < 0.001$; baseline < 12-month, $p = <0.001$

[b] Baseline < 3-month, $p < 0.001$; baseline < 6-month, $p < 0.001$; baseline < 12-month, $p < 0.001$

[c] Baseline < 3-month, $p < 0.001$; baseline < 6-month, $p = 0.002$; baseline < 12-month, $p = 0.066$

[d] Baseline < 3-month, $p = 0.001$; baseline < 6-month, $p = 0.913$; baseline < 12-month, $p = 0.374$

[e] Baseline < 3-month, $p = 0.003$; baseline < 6-month, $p = 0.021$; baseline < 12-month, $p = 0.742$

[1] Except for Ghrelin levels, $N = 30$ and for Hcys levels, $N = 52$

[2] Except for Ghrelin levels, $N = 17$ and for Hcys levels, $N = 33$

[3] Except for Ghrelin levels, $N = 13$ and for Hcys levels, $N = 20$

[4] Except for Ghrelin levels, $N = 8$ and for Hcys levels, $N = 13$

* It is not possible to calculate due to the low sample size

Statistically significant values are in italic

$n = 11$, 17.5 %, at 6-month; and $n = 7$, 17.9 %, at 12-month visits), mean levels of leptin and HOMA-IR were significantly higher in all of the assessments compared to normal BMI subjects. Moreover, mean levels of insulin were significantly higher at 3 and 12-month visits in overweight/obese subjects compared to those with normal BMI (Table 5).

From baseline to 3, 6, and 12 months, overweight/obese as well as normal BMI patients increased in weight, BMI, and z-BMI, with a significant interaction of time by group (weight, $F = 31.261$, $df = 3.31$, $p < 0.001$; BMI, $F = 26.268$, $df = 3.31$, $p < 0.001$ and z-BMI, $F = 24.816$, $df = 3.31$, $p < 0.001$). Thus, overweight/obese patients at baseline had a significantly higher increase in weight/BMI and z-BMI than normal BMI subjects during the follow-up (Fig. 2).

Regarding laboratory parameters, only insulin ($F = 5.289$, $df = 3.17$, $p = 0.009$) and HOMA-IR ($F = 5.434$, $df = 3.17$, $p = 0.008$) increased in each of the assessments with a significant interaction of time by group (Fig. 2). Baseline overweight/obese patients had significantly higher levels of insulin and HOMA-IR than did normal BMI subjects during the follow-up.

Baseline parameters and weight and BMI at follow-up

Some laboratory parameters at baseline were associated with an increase in weight at follow-up. Baseline insulin levels ($t = 2.41$, $p = 0.01$) and HOMA-IR ($t = 3.31$, $p = 0.001$) were associated with weight, with an increase of one insulin unit being associated with a mean increase of 1.16 kg. Baseline leptin levels ($t = 4.22$, $p = 0.0001$) were also linked to an increase in weight (an increase of one leptin unit being associated with a mean increase of 0.19 kg). The same baseline parameters were associated with BMI at follow-up (insulin levels: $t = 3.40$, $p < 0.001$; HOMA-IR: $t = 4.45$, $p < 0.001$ and leptin levels: 6.02, $p < 0.001$).

The same statistical test showed that other baseline laboratory parameters were associated with lower weight at follow-up. Higher FT4 ($t = -7.194$, $p < 0.001$), adiponectin ($t = -3.77$, $p < 0.001$), and ghrelin levels ($t = -3.849$ $p < 0.001$) were all linked to a decrease in weight at follow-up.

Pearson/Spearman correlations showed no direct link between cumulative doses of AP at each assessment and the increase in weight and BMI from baseline to 3-, 6- or 12-month assessments. First or second degree

Table 4 Weight gain and BMI/z-BMI increase over time according to the AP prescribed

Parameter	Risperidone	Olanzapine	Quetiapine	*t*	*p*
Weight (mean ± SD) (kg)					
From baseline to 3-month follow-up ($N = 83$)[1]	5.4 ± 0.5	6.8 ± 1.7	7.1 ± 3.4	1.131[a] 0.785[b]	0.262[a] 0.785[b]
From baseline to 6-month follow-up ($N = 63$)[2]	7.7 ± 0.9	10.1 ± 3.6	11.9 ± 5.9	0.894[a] 0.762[b]	0.375[a] 0.440[b]
From baseline to 12-month follow-up ($N = 39$)[3]	10.3 ± 1.3	12.1 ± 4.5	19.8 ± 7.7	0.571[a] 2.403[b]	0.571[a] *0.022*[b]
BMI (mean ± SD) (kg/m^2)					
From baseline to 3-month follow-up ($N = 83$)[1]	1.8 ± 0.2	2.5 ± 0.7	3 ± 1.3	1.646[a] 0.793[b]	0.104[a] 0.430[b]
From baseline to 6-month follow-up ($N = 63$)[2]	2.4 ± 0.3	3.6 ± 1.3	4.4 ± 2.2	1.205[a] 0.980[b]	0.233[a] 0.331[b]
From baseline to 12-month follow-up ($N = 39$)[3]	3 ± 0.5	3.9 ± 1.7	6.5 ± 2.9	0.774[a] 2.340[b]	0.444[a] *0.032*[b]
z-BMI (mean ± SD)					
From baseline to 3-month follow-up ($N = 83$)[1]	0.5 ± 0.1	0.7 ± 0.2	0.8 ± 0.4	1.428[a] 0.816[b]	0.157[a] 0.417[b]
From baseline to 6-month follow-up ($N = 63$)[2]	0.6 ± 0.1	0.9 ± 0.4	1.2 ± 0.6	1.428[a] 0.816[b]	0.157[a] 0.417[b]
From baseline to 12-month follow-up ($N = 39$)[3]	0.8 ± 0.1	1 ± 0.4	1.7 ± 0.7	0.660[a] 1.540[b]	0.513[a] *0.038*[b]

BMI body mass index

[a] Patients on risperidone compared to those on olanzapine

[b] Patients on risperidone compared to those on quetiapine

[1] Patients on risperidone $N = 61$, olanzapine $N = 12$ and quetiapine $N = 7$

[2] Patients on risperidone $N = 49$, olanzapine $N = 6$ and quetiapine $N = 8$

[3] Patients on risperidone $N = 29$, olanzapine $N = 5$ and quetiapine $N = 5$

Statistically significant values are in italic

family background of obesity also did not correlate with the increased weight or BMI in the different visits (data not shown).

Discussion

Our study found that higher baseline levels of insulin, HOMA-IR, and leptin were significantly associated with higher weight/BMI during the 1-year follow-up; while higher baseline levels of FT4, adiponectin, and ghrelin were linked to lower weight/BMI during the follow-up in children and adolescents on treatment with the same single AP (risperidone, olanzapine or quetiapine). Weight, BMI, and z-BMI increased from baseline to 3, 6, and 12 months, and at the same time, leptin levels significantly increased from baseline to 3 and 6-month assessments. TSH levels significantly increased from baseline to 3 and 6-month visits, and FT4 levels significantly decreased from baseline to 3-month assessment. Moreover, different degrees of weight gain and BMI/z-BMI increase were found for each of the prescribed AP at all of the assessments. However, only at 1-year follow-up were these differences significant, with quetiapine being associated with significantly greater increases than risperidone or olanzapine.

Weight significantly increased in our sample from baseline to the follow-up assessments (5.8 ± 4.3 kg at 3 months, 8.1 ± 6.1 kg at 6 months, and 11.6 ± 7.0 kg at 1 year). Weight gain in children and adolescents on AP has been consistently reported [8, 45] in studies with follow-up periods ranging from 4 weeks to 2 years. Nevertheless, few studies have had a 1-year or longer follow-up [7]. Additionally, our study was unique in that it focused on patients who were on the same single AP during the entire follow-up. As a result, our findings do not exactly confirm those of other studies, because AP polypharmacy seems to confer a higher risk for weight gain in children and adolescents [46].

Concomitant treatment in addition to AP could also play a role in weight gain, and exposure to two or more medications appears to be a predictor of being overweight [8]. However, in our study, we did not find that patients with concomitant psychotropic drugs had different BMI or z-BMI than those without them. Moreover, among patients with concomitant treatment with only stimulants (which could decrease appetite and produce weight loss [47]), no differences were observed in BMI or z-BMI compared to

Table 5 Weight and metabolic parameters in normal BMI and overweight/obese patients

Parameter	Normal BMI	Overweight/obese	*t*	*p* value
Weight (mean ± SD) (kg)				
Baseline	51.8 ± 13.2	68.6 ± 21	4.313	*<0.001*
3-month	56.7 ± 15.3	72.4 ± 22.6	3.214	*0.002*
6-month	58.9 ± 17.1	77.2 ± 26.5	2.900	*0.005*
12-month	62 ± 18.1	87.1 ± 26.3	3.052	*0.004*
BMI (mean ± SD)				
Baseline	19.5 ± 2.5	25.6 ± 4	8.258	*<0.001*
3-month	21.2 ± 2.9	27.4 ± 4.6	6.432	*<0.001*
6-month	21.8 ± 3.5	28.9 ± 5.4	5.606	*<0.001*
12-month	22.4 ± 3.7	31 ± 5.5	5.043	*<0.001*
z-BMI (mean ± SD)				
Baseline	−0.45 ± 0.9	1.6 ± 0.8	8.363	*<0.001*
3-month	0.1 ± 1	2.2 ± 1	8.024	*<0.001*
6-month	0.2 ± 1	2.6 ± 1	7.525	*<0.001*
12-month	0.5 ± 0.9	3 ± 1	6.511	*<0.001*
Leptin levels (mean ± SD) (ng/mL)				
Baseline	8.2 ± 11.2	22.4 ± 18.3	4.242	*<0.001*
3-month	10.8 ± 11.8	23.2 ± 16.7	3.162	*0.002*
6-month	12.4 ± 11.6	23 ± 15.2	2.145	*0.037*
12-month	9.5 ± 10.7	17.8 ± 9.1	1.462	0.155
Insulin levels (mean ± SD) (µg/mL)				
Baseline	10.2 ± 5.2	14.5 ± 9.4	2.526	*0.013*
3-month	10.4 ± 5.1	19 ± 10.5	4.555	*<0.001*
6-month	12.3 ± 11.7	18.2 ± 10.1	1.409	0.165
12-month	9.6 ± 4.1	15.9 ± 9.8	2.280	*0.031*
HOMA-IR levels (mean ± SD)				
Baseline	2.1 ± 1.2	2.9 ± 1.9	2.225	*0.028*
3-month	2.2 ± 1.2	4.3 ± 2.6	4.460	*<0.001*
6-month	2.4 ± 1.8	4.1 ± 2.6	2.305	*0.025*
12-month	2 ± 0.9	3.6 ± 2.2	2.545	*0.017*
Adiponectin levels (mean ± SD) (ng/mL)				
Baseline	11.4 ± 4.8	11.2 ± 3.1	−0.115	0.909
3-month	11 ± 8.3	11 ± 6.3	0.015	0.988
6-month	10.7 ± 6.1	7.2 ± 2.5	−0.1249	0.219
12-month	11.1 ± 7.1	8.2 ± 1.4	−0.684	0.500
Ghrelin levels (mean ± SD) (ng/ml)				
Baseline	1235.4 ± 409.3	808.67 ± 48.4	−1.650	0.111
3-month	1113.1 ± 378.7	916.5 ± 294.9	−0.699	0.495
6-month	1138.5 ± 368.9	–	–	–
12-month	1095.9 ± 504	1.009	−0.161	0.877
TSH levels (mean ± SD) (µU/mL)				
Baseline	2.5 ± 2.8	2.5 ± 1.5	−0.065	0.948
3-month	2.4 ± 1.4	2.6 ± 1.2	0.517	0.607
6-month	2.3 ± 1.5	2.6 ± 1.1	0.572	0.570
12-month	2.1 ± 1.5	3.3 ± 1.2	1.633	0.114
T4 levels (mean ± SD) (µU/mL)				
Baseline	1.3 ± 0.4	1.3 ± 0.3	0.260	0.796
3-month	1.1 ± 0.2	1.1 ± 0.2	0.068	0.946
6-month	1.1 ± 0.3	1.2 ± 0.1	1.080	0.285
12-month	1.1 ± 0.3	1.2 ± 0.2	0.981	0.335
Hcys levels (mean ± SD) (µmol/L)				
Baseline	9 ± 4	9.1 ± 2.3	−0.170	0.866
3-month	7.8 ± 2.7	8.6 ± 2.4	0.393	0.697
6-month	8.5 ± 4.5	8.3 ± 2.1	−0.061	0.952
12-month	7.3 ± 1.7	10.5	1.855	0.091

BMI body mass index, *HOMA-IR* insuline resistance, *TSH* thyroid stimulating hormone, *FT4* free thyroxine, *Hcys* homocysteine

Statistically significant values are in italic

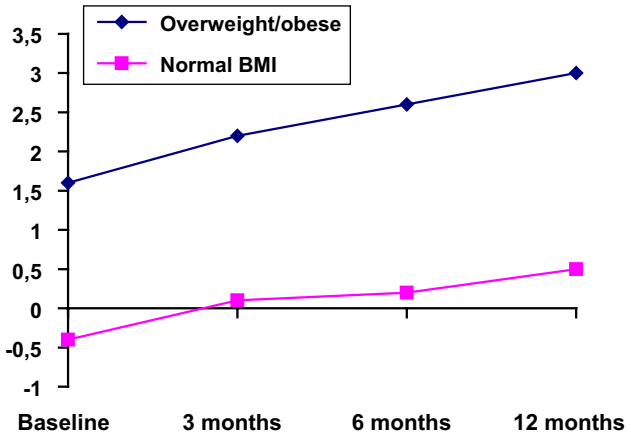

Fig. 2 Change over time of mean BMI *z*-scores in normal BMI (BMI < 85th percentile) and overweight/obese (BMI ≥ 85th percentile) patients at baseline. *Axis*: x = assessment visits; y = BMI *z*-scores. Time: $F(3, 31) = 55.501$, $p < 0.001$. Group × Time interaction: $F(3,31) = 8.131$, $p < 0.001$

the rest of the sample in any of the assessments. The fact that only 5/117 (4.3 %) patients were on stimulants in our sample does not allow this finding to have sufficient statistical power, but other authors have also reported similar results [48].

In our study, leptin levels increased during the first 6 months of treatment. A significant increase was found between baseline and 3 and 6 months, while a decrease was found from 6- to- 12-month assessments. We also found a relationship between baseline leptin levels and the mean increase in weight/BMI during follow-up. In child and adolescent samples, shorter follow-up studies have not found a relationship between increased weight and serum leptin

levels [37, 38], except for one study [34] where BMI and serum leptin levels increased from baseline to week 6 of treatment with clozapine. However, the association between weight and leptin levels is consistently observed in adult studies [32]. Increases in leptin levels during AP treatment could be a result of weight gain rather than a direct effect of atypical AP on leptin physiology [32]. Increased leptin levels in healthy subjects imply that fat stores are sufficient, and that the subject should decrease food intake. However, in patients on AP, it is possible that the ability of hyperleptinemia to decrease food intake is lost [36]. AP could interfere with the neural processing of leptin by blocking 5-HT2C, which modifies appetite and feeding behavior [49]. In fact, most obese subjects are resistant to the effects of endogenous leptin [16], and AP treatment could cause a similar resistance.

Moreover, we found that female patients had higher leptin levels in almost all of the assessments (baseline, 3, and 12 months), which is consistent with other studies in children and adolescents not on AP [50, 51]. It has been reported that higher levels of leptin in adolescent girls are associated with an increase of fat mass during puberty, compared to the increase of lean mass in boys [52]. No studies are found in the literature, which examine AP use in this population and the possible gender-specific effects of leptin levels.

Thyroid hormones significantly changed in the short-term follow-up. TSH levels increased from baseline to 3- and 6-month assessments, although this could be explained as a consequence of weight gain rather than a cause of it [23]. FT4 levels significantly decreased from baseline to 3-month visits, but not in later assessments. This could be explained by the decreasing sample size over time. The decrease in FT4 levels could be associated with the increased TSH levels as a possible adaptive process [22]. Moreover, baseline FTA levels were associated with a decrease in mean weight/BMI. Thyroid hormones have been related to the mechanism of weight gain [22], and this has been widely described in obese children and adolescents [23]. In our study, only FT4 and not TSH levels were related to the increase of weight/BMI, although this may be due to the linear correlation described for TSH with FT3 levels, but not with FT4 in pediatric subjects [53]. Other authors [54] have studied the relationship between TSH and weight in children with obesity, and reported a positive correlation between TSH and FT3 levels and z-BMI, but not FT4. Margari et al. [55] described an increase in FT3 levels in children and adolescents after 6 months on risperidone, but they did not study the possible association with increased weight and BMI. Unfortunately, we did not measure FT3 in our study.

The other parameters analyzed (insulin, HOMA-IR, adiponectin, ghrelin, and Hcys) were not significantly different from baseline to the other assessments in the whole sample. However, higher baseline insulin levels/HOMA-IR were linked to an increase of mean weight/BMI at follow-up. This is consistent with higher insulin levels/HOMA-IR described in children and adolescents on AP at 6-month follow-up [45] and insulin levels in longer follow-up [39]. Moreover, higher baseline adiponectin and ghrelin levels were associated with a mean decrease in weight/BMI at follow-up. Among adults, adiponectin has been associated with weight gain in patients on olanzapine in some studies [33, 35], but not others [31]. Studies of ghrelin have also shown controversial results in studies ranging from 1 week to 1 year of follow-up [31]. All previous studies have been conducted with adult patients only.

We found no changes in Hcys levels during the assessment and no relationship between baseline Hcys and weight/BMI at follow-up. Nevertheless, Yakub et al. [30] described a relationship in children between high Hcys levels and increased weight. Moreover, in adults with a first episode of psychosis, increased BMI and higher levels of Hcys after 12 weeks on AP have been described, and changes in Hcys levels were associated with changes in BMI [56]. In our study, it is possible that the negative results relate to the fact that Hcys measures were obtained for only a limited number of subjects.

We also found that different AP had a different impact on weight gain and BMI increase, with patients on quetiapine showing greater gains at 1-year assessment than those on risperidone or olanzapine. Supporting our results, Correll et al. [5] described, in a naturalistic 12-week study, that patients on quetiapine increased more weight than those on aripiprazole or risperidone; However, no patients in that study were on olanzapine. A review of weight gain in children and adolescents on AP [8] reported that olanzapine appears to cause the most significant weight gain, with quetiapine being associated with lower weight gain than olanzapine or risperidone treatment [8]. In a comprehensive review of controlled or prospective studies of AP treatment in children and adolescents with psychotic or bipolar spectrum disorders [3], olanzapine has also been associated with the highest increased weight. The authors suggested a ranking for SGA-induced weight in the pediatric population of olanzapine $\geq$ clozapine > risperidone $\geq$ quetiapine > aripiprazole = ziprasidone. Our group has also previously reported a follow-up study in children and adolescents where risperidone, olanzapine, and quetiapine were all associated with a 7 % increase in patients' weight at 6 months, although both risperidone and olanzapine were associated with a higher proportion of patients showing this 7 % gain than was quetiapine. Moreover, patients on quetiapine had reached their maximum weight after the first 3 months of treatment, while those on risperidone and olanzapine continued to gain weight up to end point [45].

Olanzapine and quetiapine have a similar receptor-binding profile [57], and this could play a role in their potential to produce weight gain.

In our sample, baseline overweight/obese patients showed greater increases in weight, BMI, and z-BMI than patients with normal BMI. This is contrary to previous adult studies which report that patients with lower baseline BMI are at increased risk of weight gain [48]. In children and adolescents, controversial data on this issue have been reported [8]. We also observed differences in leptin and insulin levels as well as HOMA-IR between overweight/obese and normal BMI patients. Other authors have observed higher levels of leptin [58] and of insulin and HOMA-IR [59] in obese children. In fact, insulin and leptin are interrelated, since insulin stimulates the secretion of leptin [17]. We did not find differences in TSH levels between overweight/obese and normal BMI subjects, in contrast to the increased TSH in obese patients that has been widely reported [23]. Because changes in TSH seem to be more a consequence than a cause of obesity [23], it is possible that obese/overweight patients on AP have a different pattern of adaptive response to weight gain. Other laboratory parameters showed no differences between overweight/obese and normal BMI patients.

In our study, we did not find any correlation between family background of obesity and increased weight, BMI or z-BMI over time. This differs from one adolescent study which reports a correlation between paternal BMI and weight gain after 12 weeks on AP [60]. We also found no correlation between weight gain and the other parameters studied. This contrasts with Sporn et al. [36] who found in children and adolescents with schizophrenia correlations between an increased BMI and a decrease in ghrelin and adiponectin levels after 6 weeks on clozapine, stating that these changes, also seen in obese subjects, probably represent secondary compensatory changes resulting from weight gain.

Limitations and strengths

Several limitations to our study deserve mention: the sample size was reduced during the follow-up; we did not measure FT3 levels or other OCM markers, such as folic acid and vitamin B12; we did not have a single laboratory to perform all of the necessary measurements, and leptin and adiponectin levels were analyzed using two different methods; and we did not register the dietary habits or physical activity of patients. Moreover, it is a naturalistic study where AP was prescribed by clinical criteria, and our results cannot be compared to randomized or controlled studies.

However, among its strengths are the prospective design, with 12 months of follow-up; the homogeneity of the sample, with AP-naïve or quasi-naïve children and adolescents; the repeated measurements of laboratory parameters (not only at baseline and end point); and its naturalistic design, which can offer more generalizable results, similar to clinical practice.

To sum up, we found an increase from baseline to 1 year in weight, BMI, and z-BMI in a sample of children and adolescents treated with a single AP. Increases in leptin and TSH and decreases in FT4 levels were observed. Higher baseline levels of insulin, HOMA-IR, and leptin, were all associated with increased weight/BMI during the follow-up, as was being overweight/obese at baseline. Higher baseline levels of FT4, adiponectin, and ghrelin were associated with lower weight/BMI during the follow-up. Additionally, weight gain and BMI/z-BMI increase at 1-year assessment were significantly higher for patients on quetiapine.

Further studies, especially ones with different AP and longer follow-up periods, are needed to confirm these results. Increased awareness of the role of these biochemical parameters could help improve the management of weight gain in children and adolescents on AP, a problem with significant physical and emotional coonsequences in this population.

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Compliance with ethical standards

Conflict of interest IB has received honoraria and travel support from Otsuka and Janssen, research support from Fundación Alicia Koplowitz and grants from the Spanish Ministry of Health, Instituto de Salud Carlos III. RCE has a grant from the Spanish Ministry of Health, Instituto de Salud Carlos III, and has received travel support from Shire. CA is a consultant for AstraZeneca, Bristol Myers Squibb, Janssen-Cilag, Pfizer and Servier; has received grants/support from the Spanish Ministry of Health, Instituto de Salud Carlos III, the European Comission, Fundación Alicia Koplowitz, Astra-Zeneca, Bristol Myers Squibb. JCF has been a consultant for Eli Lilly and has received grants from the Spanish Ministry of Health, Instituto de Salud Carlos III, the European Comission and Fundació La Marató de TV3. LV, ES, JMN and PRL declare no conflicts of interest.

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