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Journal: Journal of child and adolescent psychopharmacology

Year: 2018 May

Issue: 28

Volume: 4

Pages: 258-265

DOI: 10.1089/cap.2017.0038

Second-generation antipsychotics in adolescent psychiatric patients: metabolic effects and impact of an early weight change to predict longer term weight gain.

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Key words: weight gain, metabolic syndrome, second generation antipsychotics, weight monitoring.

Running title: Second-generation antipsychotics in adolescents

ABSTRACT:

Background: Important weight gain during the first months of psychotropic drug treatment is a common side effect among adolescent patients. This has a major long term impact on general health and quality of life.

Objectives: To examine the metabolic profile of adolescents at baseline and to determine the potential predictive power of a one month weight gain (WG) on weight changes during longer term second generation antipsychotic (SGA) treatment.

Methods: A retrospective chart review study including patients between 13 and 18 years old and treated with SGA was conducted. Available data at baseline, one, three and twelve months of treatment were recorded.

Findings: 456 patients were included, with a median age of 15 years. 10% of the patients were obese (>95th percentile) and abdominal obesity (>90th percentile) was observed in 12% of patients. In a subgroup of 42 patients with both baseline, one month and three month weight data available, WG>4.5% after one month was found to be the best predictor (sensitivity: 100; specificity: 66; Area Under the Curve: 83) for a WG>15% after three months. After adjusting for potential confounders, a threshold of WG>4% was found as being the best predictor.

Interpretation: A worrisome prevalence of metabolic disorders was observed in an adolescent psychiatric cohort. In such patients, a WG>4% during the first month of treatment should raise concerns about weight controlling strategies. Further research is needed to confirm the present results and to determine the impact of a one month WG on a one year weight change.

INTRODUCTION:

Second-generation antipsychotics (SGA) are commonly prescribed in psychotic syndromes and manic symptoms of bipolar disorder and schizophrenia(Documed 2013). However, despite their better overall tolerance compared to first generation antipsychotics, in particular on neurological and cardiac effects, weight gain (WG) and development of metabolic syndrome induced by SGA are of major concern because of the related long-term increased morbidity and mortality.

Thus, with a two to four fold increased prevalence of metabolic complications in psychiatric patients compared to the general population, cardiovascular diseases are one of the major causes of death in psychiatric patients, contributing largely to the observed decreased life expectancy of 12 to 30 years(Ringen, et al. 2014, Huber-Giseke, et al. 2014). As in the general population, cardiovascular diseases have probably a multifactorial origin (obesity, sedentary lifestyle, unhealthy food and/or smoking are common in psychiatric patients)(De Hert, et al. 2012). However, the contribution of SGA in the development of metabolic disturbances, principally due to an important weight gain, is of major concern, with clozapine and olanzapine inducing strong WG, quetiapine and risperidone inducing a medium WG and aripiprazole, amisulpride and ziprasidone associated with a lower WG risk(Huber-Giseke, Perin, Narring 2014, Leucht, et al. 2013). WG in pediatric or adolescent patients is of major concern and has also been widely described in the literature because of its life course impact. As in adults, a Bayesian meta-analysis on short term WG in pediatric patients showed a significant weight increase for clozapine, aripiprazole, quetiapine, olanzapine and risperidone, in addition to a worsening of metabolic parameters in pediatric patients(Cohen, et al. 2012).

Of note, an important inter individual variability of drug-induced WG is observed, explained, in part, by personal risk factors such as female gender, low baseline body mass index (BMI), younger age or non-Caucasian ethnicities(De Hert, Detraux, van Winkel, Yu, Correll 2012).

This underlines the importance of monitoring metabolic parameters during SGA treatment, to rapidly identify patients with a clinically meaningful WG and to initiate as soon as possible effective weight controlling strategies such as lifestyle change and/or antipsychotic switching if clinically feasible(Citrome, Vreeland 2008).

Post-hoc analysis from clinical trials conducted in adults have shown that a rapid WG during the first weeks of treatment predicts further important WG in patients treated for schizophrenia with olanzapine, ziprasidone and aripiprazole(Hoffmann, et al. 2010, Lipkovich, et al. 2008) and in bipolar patients treated with olanzapine(Lipkovich, et al. 2006). Moreover, we recently demonstrated that a fast (>5%) WG after one month of treatment is the best predictor for an important WG after three (>15%) and 12 (>20%) months of treatment(Vandenberghe, et al. 2015). However, the study included mainly adult and elderly patients (93% were ≥18 years old), and we could not determine whether the 5% threshold could also specifically be used for pediatric patients.

Puberty is a developmental period involving a physiological WG related to hormones influencing the distribution of body fat. Adolescents are, for this reason, more sensitive than adults to metabolic effects during SGA treatment(Vitiello, et al. 2009, Ratzoni, et al. 2002, Safer 2004) and an iatrogenic WG at that developmental stage can be very deleterious on adolescent health(De Hert, et al. 2011). In addition, important WG during SGA treatment is associated with poor treatment adherence (Rettew, et al. 2015) and may also have strong psychological consequences on adolescent development. Of note, the persistence of obesity at adulthood varies from 20-50% when it starts before sexual maturity and from 50-70% when arising before puberty (Romualdo, et al. 2014, Sweeting 2008). Thus, obese children are at-risk for further metabolic complications in adulthood such as dyslipidemia or type 2 diabetes. Predicting important WG during SGA in pediatric patients is therefore of major clinical relevance.

In the present study, we firstly aimed to have an overview of metabolic parameters in a Swiss adolescent cohort from an adolescent psychiatric hospital which is the first study in this class of age in Switzerland. Secondly, we attempted to determine, in a subsample of patients with available longitudinal data, how a weight change after one month of SGA treatment could predict a weight change after a longer period of treatment which has, to our knowledge, never been investigated.

METHODS

Study design

A retrospective chart review study including computerized clinical record of hospitalized patients has been conducted between August 2005 and January 2015 in the adolescent psychiatric inpatient clinic of the University Hospital of Lausanne, Switzerland. Inclusion criteria were adolescents between 13 and 18 years old receiving amisulpride, aripiprazole, clozapine, olanzapine, paliperidone, quetiapine, risperidone and/or sertindole as treatment. Somatic and psychiatric co-medications as well as somatic co-morbidities could not be recorded. There were no exclusion criteria.

Demographic data (age, gender, psychiatric diagnosis, number and duration of hospitalizations and patient height) were recorded at treatment introduction. ICD-10 classification was used to establish psychiatric diagnosis (see supplementary material 1 for more information). Weight was recorded from inpatients and outpatients medical records at baseline, one (±2 days), three (±2 days) and twelve (±7 days) months after treatment introduction. Other metabolic traits (waist circumference (cm), blood pressure (mmHg), venous glycaemia (mmol/L), HDL-Cholesterol (mmol/L), LDL-Cholesterol (mmol/L), triglycerides (mmol/L) and total cholesterol (mmol/L) were documented from medical files at baseline and after one month of treatment. Weight was measured according to the clinical practice of the hospital (patients were wearing minimal underclothing, shoes were removed and professional medical scales were used). Waist circumference was measured between the top of the patient's hip bone and the bottom of patient's ribs. No retrospective or self-estimated patient data were used. Due to an inpatient setting at baseline and one month, all blood samples were drawn in fasting conditions. Obesity (> 95^{th} BMI percentile) was defined by using Centers for Disease Control and Prevention BMI for age percentile growth charts(2009). Abdominal obesity (>90^{th} waist circumference percentile) was defined by using

the American-European percentiles provided by the International Diabetes Federation (IDF). IDF consensus was used to define the metabolic syndrome (MetS)(Zimmet, et al. 2007).

The study was approved by the Ethics Committee of Lausanne University Hospital. Due to the retrospective non-interventional study design, no informed consent form was requested.

Predictive value of an early weight gain: Exploratory statistics

Due to the important number of missing data at three and 12 months, and to consider an eventual dropout bias, baseline demographic was compared between patients with complete (at least baseline, one month and three or 12 months) and incomplete follow-up data. To assess the predictive value of an early WG during the first month of treatment on three and 12 months WG, sensitivity, specificity, positive predictive value (PPV) and negative predictive values (NPV) were calculated using the "pROC" R package(Robin, et al. 2011). Sensitivity is defined as the percentage of correctly predicted high-risk patients among all truly long term high-risk patients. Specificity defines the percentage of patients predicted as low-risk patients among all truly low-risk patients. PPV indicates the percentage of patients with an important three months WG and who were classified as having a high first month WG. NPV indicates the percentage of patients who did not have an important three months WG and were classified as having a low early WG (see supplementary material 2 for more information).

Predictive value of an early weight gain: Confirmatory Analysis

A linear mixed effect model was fitted on the WG percentage observed at three and 12 months after separating patients into two groups based on the best early WG threshold predicting three months WG discovered in the exploratory analysis. The "nlme" package of R(Pinheiro, et al. 2013) was used to fit a linear mixed effect model adjusted for baseline BMI, age, gender and treatment duration (see supplementary material 3 for more information).

RESULTS

Baseline demographics

Data were available for 456 patients (56% male, 44% female, table 1), with a median (Interquartile Range, IQR) age of 15 (2) years and with no significant age differences between both genders. Schizophrenia (F20-F29) and mood disorders (F40-48) were the most frequent diagnosis with a significantly higher schizophrenia prevalence among males (28% vs 13%; p=0.0001) and inversely a higher prevalence of mood disorders among females (38% vs 24%; p=0.003). A small but significant longer hospitalization duration was observed in female patients compared to males (23 vs 20 days; p=0.01). The most frequently prescribed SGA were quetiapine (48%), risperidone (35%) and olanzapine (14%), with no prescription of clozapine or sertindole. Except for quetiapine, which was more prescribed among females (53% vs 41%; p=0.01), no significant gender difference was found.

Prevalence of metabolic disorders

A baseline median (IQR) BMI of 20 (4) kg/m^2 and a prevalence of obesity of 10% were observed, with a significant higher prevalence among males (14% vs 7%, p=0.04). Abdominal obesity was observed in 12% of the patients, without a significant difference between genders. 31% of the patients had hypo HDL-cholesterolemia, 4% hypertriglyceridemia and 9% hyperglycemia, with no gender differences. Of note, a 13 years old male fulfilled the IDF definition of metabolic syndrome.

Short term weight gain as predictors of long term weight gain

After one month of treatment, a median WG of 4% (IQR: 5%) was observed. A median weight increase of 8% (IQR: 10%) was measured after three months and of 11% (IQR: 19%) after 12 months of treatment. Because of missing data, only patients with available weight at both baseline, one month and three months (total n=42) of treatment were included in the analysis for weight predictor (see supplementary material 4 for more information). One month

WG predicting a WG after 12 months could not be determined due to an insufficient number of data (only 19 remaining patients at 12 months).

The best short term predictor, based on the highest AUC, was found to be a WG of >4.5% after one month predicting for WG >15% after three months of treatment. This threshold had a sensitivity of 100%, specificity of 71%, NPV of 100% and a PPV of 40% (table 2). Other short term WG predictors close to the 4.5% threshold were also explored (>3%, >3.5%, >4.5% and >5%). With the exception of the >3% threshold, all other values have an AUC higher than 75, thus clinically relevant for predicting a WG at three months of treatment.

Confirmatory analysis of a short term weight gain

Generalized linear mixed models integrating age, baseline BMI, gender and treatment duration as potential confounders were analyzed in four separate models (table 3). These analyses confirmed the early WG threshold of >4.5% as a significant predictor for a weight change during the first year of treatment ((β): 3.7%, $p_{adjusted}$=0.05). However, using this model adjusted by the same confounders, a value >4% was also found to be the best early WG predictor (β: 4.1%; $p_{adjusted}$=0.03) and was thus retained for further analysis. Of note, an increase of weight was also observed in the group of patients with a WG ≤4% after one month, 75% of such patients gaining more than 4% after three months of treatment (figure 1).

Demographic and metabolic parameters between early and non-early weight gainers

No significant demographic differences were observed between the groups of patients with a one month WG >4% versus ≤4% (table 4). Metabolic traits such as waist circumference, BMI or blood pressure, were also found to be identical between the two groups at baseline. However, patients with a WG >4% at one month had a significant lower median (IQR) baseline level of fasting glucose (4.7 (0.5) vs 5.2 (0.7) mmol/L; p=0.01).

DISCUSSION

In the present cohort of adolescent psychiatric patients, a worrisome obesity prevalence of 10% was observed at baseline, which is higher than the 3.5% obesity prevalence reported in general pediatric and young populations (age range 15-24) in Switzerland(2012). This high prevalence of obesity underlines the higher cumulative risk profile of this adolescent psychiatric population, showing as in adults, the intertwining between mental illness and somatic disorders. Despite this, data on obesity prevalence in psychiatric adolescents similar to the present cohort (e.g. same age range, similar diagnosis) is scarce; prevalence ranging from 6.9% to 16% has been reported by studies with similar mean ages to the present cohort (O'Donoghue, et al. 2014, Kemp, et al. 2013, Fraguas, et al. 2008, de Hoogd, et al. 2012).

Hyperglycemia was observed among 9% of patients at baseline, which is higher than the 5.3% prevalence rate observed in a nationwide German obese adolescent cohort(Hagman, et al. 2014). Regarding psychiatric patients, a retrospective chart review reported a 7.5% prevalence of hyperglycemia in SGA-naïve patients (mean age=13.9) (Panagiotopoulos, et al. 2009), a value closer to the present study, suggesting a higher prevalence rate of hyperglycemia among psychiatric as compared to non-psychiatric adolescent subjects. Of note, it has been reported that diabetic children have an increased risk of neuropsychiatric disorders, the risk increasing in cases of associated obesity or dyslipidemia(Block, et al. 2010). These results are of clinical concern knowing the importance of promoting a healthy state during adolescence to prevent non-communicable diseases during adulthood. Pediatric psychiatric populations therefore deserve greater medical attention to avoid the development of type 2 diabetes and/or of other metabolic disorders.

Differences of psychiatric diagnoses were observed among genders. Schizophrenia was more prevalent in males (28%) than in females (13%), which could be explained by a later age of onset in females(Szymanski, et al. 1995). On the other hand, mood disorders were more

frequent among females (38% versus 24%), confirming previous observations(Birmaher, et al. 1996). Off label use of SGAs in pedopsychiatry is very common and of major concern for patient safety(Winterfeld, et al. 2008). In the present study, the most common prescribed antipsychotics were quetiapine and risperidone, both approved for pediatric use by the Swiss Agency for Therapeutic Products(2015). However, 14% of the patients were treated with olanzapine, a drug without indication for pediatric use in Switzerland(2015), and known to induce, like clozapine, an important WG(Leucht, Cipriani, Spineli, Mavridis, Orey, Richter, Samara, Barbui, Engel, Geddes, Kissling, Stapf, Lassig, Salanti, Davis 2013). Of note, the prescription rate of olanzapine dropped from 53% (17/32 treatments introduced in 2008) to 8% (3/36 treatments introduced in 2009). This could be explained by the introduction (in 2008) within the University hospital of a department guideline for metabolic follow-up during psychotropic drugs known to induce WG (SGA, valproate, lithium and mirtazapine)[(Choong, et al. 2008)], resulting in an increased awareness of metabolic disorders induced by psychotropic treatments.

In the longitudinal cohort, a clinically important WG of 8% was observed after three months of SGA treatment, which is close to the 11.8% WG reported in a previous study with drug naïve adolescents (mean age=13) treated with SGAs for the same treatment duration(Roy, et al. 2010). These values can also be compared with the non-significant weight change (0.65%) in untreated adolescent psychiatric patients (mean age=15.5) during a clinical follow up of three months(Correll, et al. 2009). Of note, a WG of 8.1% after three months of aripiprazole was also reported in a pedopsychiatric cohort (mean age=13.9)(Correll, Manu, Olshanskiy, Napolitano, Kane, Malhotra 2009), emphasizing that drugs with low WG inducing potential in adults can induce strong WG in pedopsychiatric patients. Due to the small cohort size with longitudinal data in the present study, no weight evolution among each SGA could be

calculated. Moreover, these results need to be confirmed in a cohort taking into account BMI changes over time.

An early WG of more than 4% after one month of treatment with SGA was found to be a good predictor in adolescent psychiatric patients for an important WG (>15%) after three months. Patients with >4%WG during the first month had 4.1% more WG over one year compared to patients with ≤4% ($p_{adjusted}$=0.03). This observation is in line with the previously described 5% WG threshold found to predict an important WG at three and 12 months of treatment in a cohort of adult and old age patients(Vandenberghe, Gholam-Rezaee, Saigí-Morgui, Delacrétaz, Choong, Solida-Tozzi, Kolly, Thonney, Fassassi, Ahmed, Ambresin, von Gunten, Conus, Eap 2015). Of note, a 7% WG after six weeks of treatment was defined as clinically significant by the European Association for Study of Diabetes and the European Society of Cardiology(De Hert, et al. 2009). However, this threshold was firstly chosen for its clinical significance and not for its predictive value. The present result suggests that a rapid weight change of more than 4% after four weeks of treatment in pedopsychiatric patients should be a warning for clinicians to further evaluate metabolic consequences of SGA prescription in adolescent patients. Interestingly, baseline BMI and age were found to be similar between patients with more than 4% WG and those with less or equal to 4%, a result which differs from those found in adults patients(Vandenberghe, Gholam-Rezaee, Saigí-Morgui, Delacrétaz, Choong, Solida-Tozzi, Kolly, Thonney, Fassassi, Ahmed, Ambresin, von Gunten, Conus, Eap 2015). This difference can probably be explained by the narrow range of age in the present adolescent cohort, as well as a narrower range of baseline weight probably reflecting a lower number of previous treatments as compared to adult psychiatric patients. On the other hand, in agreement with our previous study(Vandenberghe, Gholam-Rezaee, Saigí-Morgui, Delacrétaz, Choong, Solida-Tozzi, Kolly, Thonney, Fassassi, Ahmed, Ambresin, von Gunten, Conus, Eap 2015), the type of SGA was not found to influence an early WG.

Several limitations of the study have to be discussed. Firstly, the conclusions are limited by the important amount of missing data during drug treatment after the baseline evaluation, which can be explained by the generally short hospitalization of patients in the ward where this study took place, a strict time inclusion criteria of ±2 days at 1 and 3 months as well as ±7 days at 12 months, and also by the late introduction in this ward of clinical recommendations to monitor metabolic parameters during treatment with psychotropic medication. However, and interestingly, they are in agreement with the results found in our previous study with a much larger adult psychiatric cohort. The important number of missing data at one year could explain that no predictor could be found for the one year weight change. Future studies should therefore specifically aim to find predictors for long term WG in pediatric patients starting a SGA treatment. Secondly, weight changes can be due to physiological adolescent growth. To take into account this effect, calculations should be based on %BMI changes with a height measured at each time point. In the present study, only baseline height was available, thus baseline BMI was integrated as confounder into the validation model and relative WG expressed in % was used as the dependent variable. The absence of recorded height after three months of treatment should not influence the present results as this period is a too short to produce a significant increase in height. However, we cannot exclude that some patients had an important growth spurt during this period. Thirdly, no information was available concerning previous treatments, and it was thus not possible to identify antipsychotics-naïve patient. Fourthly, information on SGA dosing was not available. Finally, physical activity, food intake, comorbidities and somatic medication which could interfere with metabolic parameters were not known for the present cohort, and such factors could therefore not be taken into account. Thus, it was not possible to determine if other somatic drugs known to induce weight gain (e.g. insulin, prednisone) were confounding our results.

In conclusion, the present study confirms the presence of several metabolic abnormalities in this cohort of adolescent psychiatric patients, underlining the importance of a systematic weight and other metabolic parameter monitoring during SGA treatment, but also during treatment with other psychotropic drugs with weight gain inducing potential (i.e some first generation antipsychotics, mood stabilizers and antidepressants). In order to identify patients at risk for important WG, complete metabolic parameters should carefully be monitored at baseline and during the first months of treatment according to previously published guidelines(Pringsheim, et al. 2011). Adolescent patients with a weight increase of more than 4% during the first month of treatment appear to be at higher risk for an important (>15%) WG at three months. Considering the major impact of obesity and/or of metabolic symptoms on future general health and quality of life, in particular in this young age group, a particular emphasis should be put on patients at risk, using all available options (e.g. behavioral interventions, diet and physical activity advice), but also possible change in psychotropic medication after a careful re-evaluation of the risk/benefit ratio of psychotropic and/or somatic drug prescription**.**

Author disclosure information:

CBE received honoraria for conferences or teaching CME courses from Astra Zeneca, Forum für Medizinische Fortbildung, Janssen-Cilag, Lundbeck, Merck Sharp & Dohme, Mepha, Otsuka, Servier and Vifor-Pharma in the past 3 years, and for writing a review article for the journal "Dialogues in clinical neurosciences" (Servier). He received an unrestricted educational research grant from Takeda in the past 3 years. Other authors have no financial disclosures.

Funding:

This work has been funded in part by the Swiss National Research Foundation (Chin B. Eap and Philippe Conus: 320030-120686, 324730-144064 and 320030-173211).

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

Previous result presentation:

None.

Acknowledgement:

None.

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Administrative, technical, or material support: All Authors

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Table 1: Clinical and demographic parameters in the overall adolescent psychiatric cohort and comparison between male and female patients.

Variable at baseline	Total sample (n=456)	Female (n=255)	Male (n=201)	p-value[a]
Age, median (IQR), years	15 (2)	15 (2)	15 (2)	0.5
Previous hospitalizations, median (IQR), n	1 (1)	1 (1)	1 (1)	0.9
Hospitalization duration, median (IQR), days	22 (23)	23 (25)	20 (17)	**0.01**
Diagnosis, n/total n (%)				
Psychoactive substance use (F10-F19)	11/456 (2)	4/255 (2)	7/201 (3)	0.2
Schizophrenia (F20-F29)	90/456 (20)	34/255 (13)	56/201 (28)	**0.0001**
Mood disorders (F30-F39)	145/456 (32)	96/255 (38)	49/201 (24)	**0.003**
Stress related disorders (F40-F48)	54/456 (12)	35/255 (14)	19/201 (9)	0.2
Behavioral syndromes (F50-F59)	41/456 (9)	35/255 (14)	6/201 (3)	**<0.0001**
Personality disorders (F60-F69)	16/456 (4)	11/255 (4)	5/201 (2)	0.3
Mental retardation (F70-F79)	2/456 (0)	2/255 (1)	0/201 (0)	0.5
Psychological development (F80-F89)	27/456 (6)	7/255 (3)	20/201 (10)	**<0.0001**
Behavioral and emotional disorders (F90-F98)	70/456 (15)	31/255 (12)	39/201 (19)	**0.04**
Medication, n/total n (%)				
Amisulpride	2/456 (0)	1/255 (0)	1/201 (1)	1
Aripiprazole	7/456 (2)	5/255 (2)	2/201 (1)	0.5
Olanzapine	64/456 (14)	32/255 (13)	32/201 (16)	0.3
Paliperidone	4/456 (1)	1/255 (0)	3/201 (1)	0.3
Quetiapine	219/456 (48)	136/255 (53)	83/201 (41)	**0.01**
Risperidone	160/456 (35)	80/255 (31)	80/201 (40)	0.08
Polymedication[b]	22/456 (5)	11/255 (4)	11/201 (5)	0.7
BMI, median (IQR), kg/m^2	20 (4)	20 (4)	20 (5)	0.6
Obesity, n/total n (%)[c]	34/335 (10)	13/187 (7)	21/148 (14)	**0.04**
Waist circumference, median (IQR), cm	78 (12)	78 (11)	78 (10)	0.7
Abdominal obesity, n/total n (%)[d]	9/72 (12)	5/34 (15)	4/38 (11)	0.7
Hypertension, n/total n (%)[e]	32/418 (8)	12/238 (5)	20/180 (11)	**0.03**
Cholesterol, median (IQR), mmol/L	4 (1)	4.3 (1.2)	3.8 (1)	**0.0002**
HDL-Cholesterol, median (IQR), mmol/L	1.3 (0.4)	1.4 (0.4)	1.2 (0.4)	**0.001**
Hypo HDL cholesterolemia, n/total n (%)[f]	59/189 (31)	30/96 (31)	29/93 (31)	1
Cholesterol / HDL, median (IQR)	3.1 (1.2)	3.1 (1.3)	3.1 (1.2)	0.8
LDL-Cholesterol, median (IQR), mmol/L	2.2 (0.9)	2.3 (0.9)	2.1 (0.9)	**0.02**
Triglycerides, median (IQR), mmol/L	0.9 (0.5)	0.9 (0.6)	0.9 (0.3)	**0.02**
Hypertriglyceridemia, n/total n (%)[g]	8/187 (4)	6/95 (6)	2/92 (2)	0.3
Fasting glucose, median (IQR), mmol/L	4.9 (0.5)	4.9 (0.5)	5 (0.5)	**0.003**
Hyperglycemia, n/total n (%)[h]	19/205 (9)	9/106 (8)	10/99 (10)	0.8
Metabolic syndrome, n/total n (%)[i]	1/72 (1)	0/34 (0)	1/38 (3)	1
First month weight gain, median (IQR), %	4(5)	3(6)	4(4)	0.8
Three months weight gain, median (IQR), %	8(10)	8(9)	8(11)	0.5
One year weight gain, median (IQR), %	11(19)	10(15)	27(24)	**0.04**

[a] p-value were calculated using Wilcoxon rank-sum tests for continuous variables and Fisher's exact tests for categorical variables between both groups. Significant p-values ($p<0.05$) are presented in bold.

[b] Presence of co-prescriptions of amisulpride, aripiprazole, olanzapine, paliperidone, quetiapine or risperidone.

[c] 95th BMI percentile and higher.

[d] For children younger than 16 years: presence of abdominal obesity if waist circumference > 90th percentile. For children older than 16 years: Presence of abdominal obesity if waist circumference ≥ 102 cm for males and ≥ 88 cm for females.

[e] For children younger than 16 years: systolic blood pressure > 130mmHg or diastolic blood pressure > 85mmHg or treatment for hypertension. For children older than 16 years: systolic blood pressure > 130mmHg or diastolic blood pressure > 80mmHg.

[f] For children younger than 16 years: presence of hypo HDL cholesterolemia < 1.03mmol/L. For children older than 16 years: <1.00mmol/L for males and <1.3mmol/L for females

[g] Hypertriglyceridemia : triglycerides ≥ 1.7mmol/L.

[h] Hyperglycemia: glucose ≥ 5.6 mmol/L.

[i] Metabolic syndrome is present if: presence of central obesity and at least two other following factors: hypertension, hypo HDL cholesterolemia, hypertriglyceridemia or hyperglycemia.

Table 2: Predictive statistics for a one month weight gain to predict three month weight gain >15%.

Weight change (%) at 1 Month	PPV	NPV	Sensitivity	Specificity	AUC
3	28	100	100	49	74
3.5	30	100	100	54	77
4	36	100	100	66	83
4.5	40	100	100	71	85
5	50	95	75	85	80

Abbreviations: NPV=Negative predictive value; PPV=positive predictive value; AUC=Area under the curve.

Table 3: Linear mixed effect model fitted on different weight gain threshold (%) over time.

First month weight gain threshold [a]	Difference of weight change (%) between early weight gainers and non-early weight gainers over one year of treatment ($IC_{95\%}$).	p-value
3.5%	3.8% (-0.8 to 8.6)	0.05
4%	4.1% (-0.3 to 8.5)	0.03
4.5%	3.7% (-1 to 8.3)	0.05
5%	2.2% (-3.8 to 7.8)	0.21

[a] Results were obtained by fitting a linear mixed model controlling for age, sex, treatment duration, baseline BMI. 1000 bootstraps were used for the analysis.

Table 4: Demographic baseline characteristics between patients with >4% and ≤4% weight gain during the first month.

Variable at baseline	Total sample (42)	First month weight gain ≤4% (n=22)	First month weight gain >4% (n=20)	p-value[a]
Age, median (IQR), years	15 (2)	16 (2.5)	15 (2)	0.4
Male, n/total n (%)	12/42 (29)	5/22 (23)	7/20 (35)	0.5
Previous hospitalizations, median (IQR), n	2 (2)	2 (1.75)	2 (2)	0.7
Hospitalization duration, median (IQR), days	42 (29)	47 (20)	39 (37)	0.5
Diagnosis, n/total n (%)				
Psychoactive substance use (F10-F19)	1/42 (2)	1/22 (5)	0/20 (0)	1
Schizophrenia (F20-F29)	12/42 (29)	5/22 (23)	7/20 (35)	0.5
Mood disorders (F30-F39)	8/42 (19)	4/22 (18)	4/20 (20)	1
Stress related disorders (F40-F48)	3/42 (7)	2/22 (9)	1/20 (5)	1
Behavioral syndromes (F50-F59)	10/42 (24)	5/22 (23)	5/20 (25)	1
Personality disorders (F60-F69)	2/42 (5)	2/22 (9)	0/20 (0)	0.5
Mental retardation (F70-F79)	0/42 (0)	0/22 (0)	0/20 (0)	0
Psychological development (F80-F89)	1/42 (2)	1/22 (5)	0/20 (0)	1
Behavioral and emotional disorders (F90-F98)	5/42 (12)	2/22 (9)	3/20 (15)	0.7
Medication, n/total n (%)				
Amisulpride	0/42 (0)	0/22 (0)	0/20 (0)	0
Aripiprazole	1/42 (2)	1/22 (5)	0/20 (0)	1
Olanzapine	8/42 (19)	3/22 (14)	5/20 (25)	0.4
Paliperidone	0/42 (0)	0/22 (0)	0/20 (0)	0
Quetiapine	23/42 (55)	13/22 (59)	10/20 (50)	0.8
Risperidone	10/42 (24)	5/22 (23)	5/20 (25)	1
Polymedication[b]	3/42 (7)	3/22 (14)	0/20 (0)	0.2
BMI, median (IQR), kg/m^2	20 (5)	19 (5)	20 (3)	0.9
Obesity, n/total n (%)[c]	3/42 (7)	2/22 (9)	1/20 (5)	1
Waist circumference, median (IQR), cm	74.5 (14.3)	66 (7)	79 (13)	0.08
Abdominal obesity, n/total n (%)[d]	1/14 (7)	0/5 (0)	1/9 (11)	1
Mean arterial pressure, median (IQR), mmHg	83.3 (12.7)	83.3 (9.2)	83.3 (15.5)	0.9
Hypertension, n/total n (%)[e]	3/41 (7)	2/22 (9)	1/19 (5)	1
Cholesterol, median (IQR), mmol/L	4.3 (1)	4.3 (0.7)	3.7 (1.2)	0.1
HDL, median (IQR), mmol/L	1.4 (0.5)	1.5 (0.7)	1.4 (0.4)	0.9
Hypo HDL cholesterolemia, n/total n (%)[f]	6/25 (24)	5/15 (33)	1/10 (10)	0.3
Cholesterol / HDL, median (IQR)	2.7 (1.1)	3.2 (0.9)	2.6 (0.4)	0.1
LDL, median (IQR), mmol/L	2.3 (0.7)	2.4 (0.5)	2 (0.8)	0.08
Triglycerides, median (IQR), mmol/L	0.9 (0.4)	0.9 (0.5)	0.9 (0.4)	0.9
Hypertriglyceridemia, n/total n (%)[g]	0/26 (0)	0/15 (0)	0/11 (0)	0
Fasting glucose, median (IQR), mmol/L	5 (0.7)	5.2 (0.7)	4.7 (0.5)	**0.01**
Hyperglycemia, n/total n (%)[h]	5/26 (19)	5/16 (31)	0/10 (0)	0.1

[a] p-value were calculated using Wilcoxon rank-sum tests for continuous variables and Fisher's exact tests for categorical variables between both groups. Significant p-values ($p<0.05$) are presented in bold.

[b] Presence of co-prescriptions of amisulpride, aripiprazole, olanzapine, paliperidone, quetiapine or risperidone.

[c] 95th BMI percentile and higher.

[d] For children younger than 16 years: presence of abdominal obesity if waist circumference > 90th percentile. For children older than 16 years: Presence of abdominal obesity if waist circumference ≥ 102 cm for males and ≥ 88 cm for females.

[e] For children younger than 16 years: systolic blood pressure > 130mmHg or diastolic blood pressure > 85mmHg or treatment for hypertension. For children older than 16 years: systolic blood pressure > 130mmHg or diastolic blood pressure > 80mmHg.

[f] For children younger than 16 years: presence of hypo HDL cholesterolemia < 1.03mmol/L. For children older than 16 years: <1.00mmol/L for males and <1.3mmol/L for females.

[g] Hypertriglyceridemia : triglycerides ≥ 1.7mmol/L.

[h] Hyperglycemia: glucose ≥ 5.6 mmol/L.

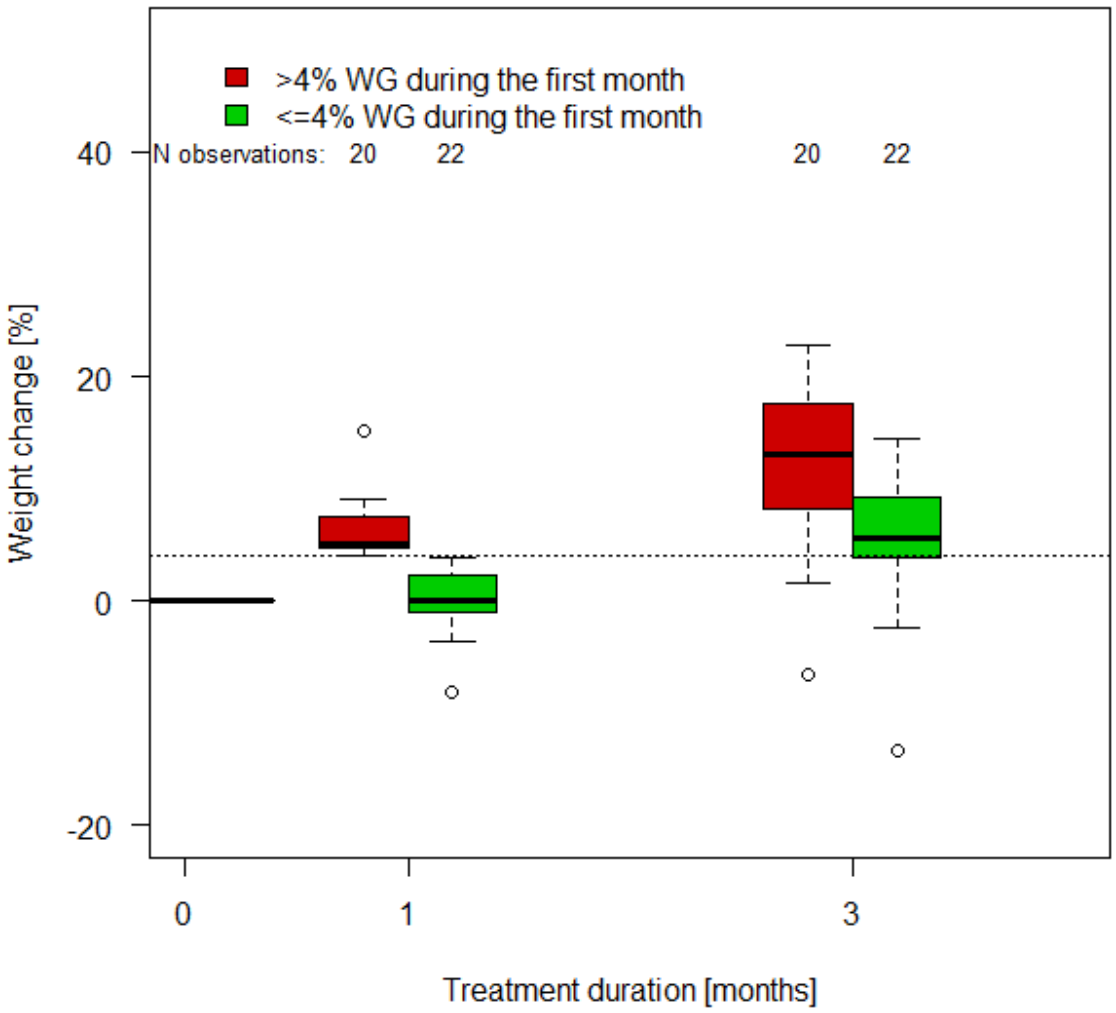

Figure 1: Weight changes at one and three months. Red and green box plots (median and IQR) represent patients with a first month weight gain of more than 4% and less or equal to 4%, respectively. Dotted black line represents a 4% weight increase.

Supplementary data

Supplementary material 1: ICD-10 classification

Supplementary material 2: Exploratory analysis

Supplementary material 3: Confirmatory analysis

Supplementary material 4: Short term weight gain as predictors of long term weight gain

Supplementary material 1: ICD-10 classification

The following clustering was used: F00-F09: Organic mental disorders; F10-19: Mental and behavioral disorders due to psychoactive substance; F20-29: Schizophrenia, schizotypal and delusional disorders; F30-39: Mood disorders; F40-48: Neurotic, stress-related and somatoform disorders; F50-59: Behavioral syndromes; F60-69: Disorders of personality and behavior; F70-79: Mental retardation; F80-89: Disorders of psychological development; F90-98: Behavioral and emotional disorders with onset usually occurring in childhood and adolescence. In presence of more than two psychiatric diagnoses, the main psychiatric diagnosis was retained according to the medical record.

Supplementary material 2: Exploratory analysis

Thresholds for an early WG were examined by 0.5% increments (ranging from 2% to 8%) to find the best predictors for long term WG ranging from 5% to 20% (also with 0.5% increments) at three months of treatment. These analyses allowed to assess the best relation between sensitivity and specificity to find an acceptable threshold for short and long term WG. These analyses were not adjusted for multiple comparisons, covariates or cofactors as they were used only to explore the data and to find the best thresholds which are confirmed in models adjusted by several confounders.

Supplementary material 3: Confirmatory analysis

Due to the important number of missing data at one month and 3 months, cholesterol, glucose and other metabolic traits were not included in the model. The fitted linear mixed effect model(1) had a random effect at the subject level. To be more robust in inferences, a bootstrap analysis(2) was used to evaluate the uncertainty of estimated parameters (evaluated uncertainties are more conservative, but more reliable if there are violations from model assumptions, as normality assumption for residuals). Results were based on 1000 bootstrap replicates at the subject level (subjects were considered to be independently recruited) and increasing the number of bootstraps did not substantially influence the uncertainty of estimated parameters.

Supplementary material 4: Short term weight gain as predictors of long term weight gain

No baseline differences were observed between patients having complete data at three months and patients with missing data excepted that males were less present among patients with complete data (46% vs 29%, p=0.04) and that behavioral syndromes (F50-F59) were more frequently observed among patients with complete three months data (24% vs 7%, p=0.002, data not shown).

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