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Importance of early weight changes to predict long term weight gain during psychotropic drug treatment

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Key words: weight gain, metabolic syndrome, atypical antipsychotics, mood stabilizers, weight monitoring.

Abstract:

Background: Psychotropic drugs can induce substantial weight gain in particular during the six first months of treatment. The authors aimed to determine the potential predictive power of an early weight gain, following the introduction of weight gain inducing psychotropic drugs on long term weight gain.

Methods: Data were obtained from a one year longitudinal study ongoing since 2007 including 351 psychiatric patients, with metabolic parameters monitored (baseline, one, three, six, nine, 12 months) and with compliance ascertained. International Diabetes Federation and World Health Organization definitions were used to define metabolic syndrome and obesity respectively.

Findings: Prevalence of metabolic syndrome and obesity were 22% and 17%, respectively at baseline, and 32% and 24% after one year. Receiver Operating Characteristic analyses indicate that an early weight gain >5% after a period of one month is the best predictor for important long term weight gain (≥15% after three months, sensitivity: 67%, specificity: 88%; ≥20% after 12 months, sensitivity: 47%, specificity: 89%). This analysis identifies most patients (97% for three months, 93% for 12 months) who had weight gain ≤5% after one month as continuing to have a moderate weight gain after three and 12 months. Its predictive power was confirmed by fitting a longitudinal multivariate model (difference between groups in one year of 6.4% weight increase as compared to baseline, p=0.0001).

Interpretation: Following prescription of weight gain inducing psychotropic drugs, a 5% threshold for weight gain after one month should raise clinician concerns about weight controlling strategies.

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INTRODUCTION:

A high prevalence of obesity (BMI ≥30Kg/m^2, World Health Organization definition) is reported in psychiatric populations, reaching 49% and 55% of bipolar and schizophrenic patients, respectively[1]. Obesity can lead to several metabolic complications such as hypertension and/or lipid profile perturbation, contributing to the reported 20 year shorter life expectancy in psychiatric patients as compared to the general population[2]. Several factors contribute to the high prevalence of metabolic disorders in psychiatry, such as the illness itself as well as life style factors. In addition, atypical antipsychotics, mood stabilizers (e.g. valproate and lithium) and some antidepressants (e.g. mirtazapine) can induce important weight gain (WG)[3,4].

Several factors have been shown to be associated with drug-induced WG, including female gender, low baseline BMI, young age or non-Caucasian ethnicities[5] . A high interindividual variability of drug-induced WG is observed, explained in part by genetic variability (e.g. in *H_1 receptor*, *M_3 receptor* or *CRTC1 genes*)[6,7], underlining the importance of monitoring metabolic parameters.

The Consensus Development Conference on Antipsychotic Drugs and Obesity and Diabetes guideline consider that a WG >5% during treatment should be a sign to reconsider the treatment[8]. However, no notion of time was defined, so that a WG of 5% after one month may be inappropriately compared to a comparable WG after one year of treatment. A joint statement of the European Psychiatric Association, the European Association for Study of Diabetes and the European Society of Cardiology defines a WG of 7% after six weeks of treatment as a clinically significant WG[1]. This 7% threshold was chosen for its clinical significance and not for its predictive value for an important WG during long term treatment. To our knowledge, three studies investigated the predictive values of an early WG (EWG). The first two studies found that a 2kg increase after one month was a good predictor for a 10kg increase after six months in patients treated for schizophrenia with olanzapine, ziprazidone and aripiprazole[9,10]. The third study in bipolar patients treated with olanzapine found that a 2kg WG after 3 weeks will predict a 7% increase after 30 weeks of treatment[11]. Notably, the above-mentioned studies were post-hoc analysis from clinical trials, examining the effect of specific drugs, with

restrictions on the number of drugs which could be prescribed, conditions which are not comparable to usual clinical conditions. In addition, non-observance of the pharmacological treatment is poor particularly during long term treatment[12]. In the above-mentioned studies, compliance was assessed by patient self declaration[13-15], which can be overestimated. Finally, the longest study duration was of 30 weeks, with no long term data (one year).

Because of the high mortality and morbidity associated with obesity, early detection of patients who have a higher risk of developing an important WG during psychotropic treatment is of major clinical relevance. In the present study, we sought to determine, in a cohort of psychiatric patients with compliance ascertained by therapeutic drug monitoring (TDM), how weight change during short term treatment (one month) could predict intermediate (three months) and long term (one year) weight evolution during treatment with psychotropic drugs known to potentially induce important WG. Self-reported increase of appetite and modification of physical activity during the first month after drug introduction were also examined as possible WG predictors.

METHODS

Study design

A longitudinal observational study is ongoing since 2007 in the Department of Psychiatry of the Lausanne University Hospital in which inpatients starting a pharmacological treatment with clozapine, olanzapine, risperidone, quetiapine, aripiprazole, amisulpride, lithium, valproate and/or mirtazapine are included. Baseline clinical data were obtained during hospitalization and follow-up data were obtained in the hospital or in out-patient centers during a medical examination based on the department guideline for metabolic follow-up performed on a routine basis[16]. When a treatment was stopped for more than two weeks, or if a drug was replaced by another drug on the list, the follow-up was restarted from baseline. In case of the introduction of a second studied drug, the follow-up is restarted and the last introduced drug considered as the main treatment (More information in eMethods 1). If two or more follow-ups were available for the same patient, only the longest one was included in the analysis (eFigure 1). Diagnoses were based on the ICD-10 classification ([F00-F09]: organic disorder; [F200-F249] & [F28-F29]: psychotic disorders; [F250-F259]: schizoaffective disorder; [F300-F319]: bipolar disorder; [F3200-F339]: depression; [F10-F19]: drug addiction. Anxiety, personality disorder and mental retardation were classified together in “others” group. Compliance was evaluated by TDM (More information in eMethods 2).The study was approved by the Ethics Committee of the Lausanne University Hospital.

Exploratory statistics:

Mean values were presented with their respective standard error (se) and significance threshold was fixed at $p<0.05$.

To assess the predictive value of an EWG during the first month of treatment on long term WG (LWG) (three and 12 months), sensitivity, specificity , positive predictive value (PPV) and negative predictive values (NPV) were calculated using the “pROC”R package[17]. 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 LWG and who were classified as having a high EWG. NPV indicate the percentage of patients who did not have an important LWG and were classified as having a low EWG.

Thresholds for EWG were examined by 1% increments (from 2% to 8%) to find the best predictors for LWG as defined by a minimal WG of 10%, 15% or 20% at three and 12 months of treatment (More information in eMethods 3). The effect of activity and appetite increase on LWG was analyzed as defined previously.

Confirmatory Analysis:

A linear mixed effect model was fitted on the WG percentage after separating patients into two groups based on their initial WG after one month of treatment, physical activity and appetite increase (eMethods 4).

RESULTS

Demographics:

351 patients were included (selection criteria in eFigure 1). Male subjects (47%), were significantly younger (mean(se): 39(1.6) years) than female (51(1.6) years, $p<0.001$), probably explaining the lower prevalence of obesity in males (9%) than in females (23%, $p=0.003$, eTable 1). No significant differences in other demographic variables were found between genders. Psychotic disorders ([F200-F249] & [F28-F29]) were the most frequent diagnosis (41%) and quetiapine was the most frequently prescribed psychotropic drug (32%, table 1). Data were available for 313 subjects at three months and for 154 subjects at 12 months.

Metabolic parameters:

21% of patients were overweight ([25-30[kg/m^2) and 17% were obese (≥30kg/m^2) at baseline (eTable 2). In patients with one year follow-up, prevalence of patients with normal weight (<25kg/m^2) decreased from 61% to 49% ($p=0.007$, table 2). Mean BMI increase after one year of treatment was dependant on age, being 2.7kg/m^2 in young patients (age:≤25), 2.2kg/m^2 in young adults (age:]25-45]), 1.8kg/m^2 in adult patient (age:]45-65]), and 1kg/m^2 in elderly patients (age:>65, eTable 3). Prevalence of metabolic syndrome (MetS, International Diabetes Federation (IDF) definition) was 22% at baseline and 32% after one year. In patients with baseline and one year data, a trend for an increased prevalence during treatment was observed (from 9% to 23%, $p=0.07$). Other metabolic traits, including their evolutions during treatment, are described in eResults 1.

Short term weight gain as predictors of long term weight gain:

The best EWG predictor (highest Area Under Curve (AUC) values, integrating both sensitivity and specificity of the predictor) was found to be a WG of more than 5% (figure 1) after one month of treatment (mean(se) 31(0.4) days) for predicting a WG of 15% or more after three months of treatment (mean(se) 102(2) days). This threshold had a sensitivity of 67%; specificity of 88%; PPV of 29%; NPV of 97%. Prevalence of a 15% WG after three months was 7.5%. The 5% threshold was also found to be the best predictor for a WG of 20% or more after one year of treatment (mean(se) 393(7)

days; sensitivity: 47%; specificity: 89%; PPV: 30%; NPV: 93%; (eTable 4)). A WG of 20% was observed in 10% of patients after one year. Patients who had a WG >5% at one month and who did not reach a 15% WG at three months (PPV-1) had still a higher WG than patients with ≤5% WG (8.1% versus 2.4%, p=0.000005). However, the difference was not significant anymore after one year (6.1% versus 3.9%, p=0.2). In young adults and adults combined (age:]25-65]), this threshold was also found to be the best predictor for a 20% WG after three months (sensitivity: 100%; specificity: 82%; PPV: 7%; NPV: 100%) and after 12 months (sensitivity: 55%; specificity: 83%; PPV: 30%; NPV: 93%) (eTable 5). Due to an insufficient number of observations, no specific threshold could be calculated in young (age≤25), elderly (age>65) age as well as in different diagnostic and medications groups.

Using this 5% threshold, 18% of patients had a >5% WG after one month. By integrating the 5% threshold in a generalized additive mixed model (figure 2), patients with a EWG >5% had a strong and fast increase of WG during the first three months of treatment, with a much slower increase thereafter (eFigure 2). On the other hand, patients with an EWG ≤5% had a slower but steady one year WG . No differences of age, gender, follow-up duration, illness duration or diagnosis were observed between the two groups. Medication was similar between the two groups except for olanzapine which was present in 24% and 10% of the patients gaining more weight versus those gaining less than 5%, respectively (p=0.006) (table 1). When considering MetS traits at baseline, only BMI was significantly different between both groups (p=0.001), being lower in the >5% group. After one year, a mean BMI increase of 1.2(0.3)kg/m^2 and 3.1(0.8)kg/m^2 was observed in the low and high WG group, respectively (p=0.01) (eTable 6). A stronger decrease of HDL-cholesterol (β:-0.3mmol/l, $P_{adjusted}$<0.0001) and increase of triglyceride (β:1.5mmol/l, $P_{adjusted}$<0.0001) were also observed in the >5% group by using a linear model controlled by several confounders (table 3). In the final linear mixed model with an EWG >5% as predictor, it was confirmed that this threshold was a significant predictor of long-term WG over one year of treatment (difference between groups in one year (β) of 6.4% WG as compared to baseline, $P_{adjusted}$=0.0001). This predictor was also found significant for a stronger LWG in young (age≤25) patients (β:8.7%, $P_{adjusted}$<0.0001), young adults (age:]25-45])

(β:7.3%, $P_{adjusted}$=0.0001), adults (age:]45-65]) (β:7.4%, $P_{adjusted}$=0.005) and elderly (age>65) patients (β:13.6%, $P_{adjusted}$<0.01). This predictor was also found significant in patients with psychotic or schizoaffective disorder (β:7%, $P_{adjusted}$<0.0001), bipolar disorder or depression (β:9.1%, $P_{adjusted}$=0.0006) and in the other diagnoses (β:11.6%, $P_{adjusted}$<0.01). Significant results were also observed in patients treated with amisulpride or aripiprazole (β:6.6%, $P_{adjusted}$=0.003), mirtazapine, lithium, quetiapine or risperidone (β:8.4%, $P_{adjusted}$<0.0001) and finally with clozapine, olanzapine or valproate (β:7.4%, $P_{adjusted}$<0.0001) (eTable 7).

Effect of changes in appetite and physical activity during treatment

Calculations were also made to assess the predictive power value of moderate or high (≥30 minutes/day) physical activity and of an appetite increase during the first month of treatment on LWG (eTable 8 and 9). AUC value indicated no predictive power for both parameters (AUC≈50).

DISCUSSION:

Confirming previous studies in psychiatric patients[18,19], a high prevalence of overweight or obesity (39%) was measured in the present cohort at baseline, even increasing after one year of treatment (50%). Notably, a higher (68%) prevalence of overweight or obesity was measured in another Swiss cohort[20] which is probably explained by the longer treatment duration in the latter cohort (median 2.3 years versus mean 0.65 years). The increase of mean BMI after one year of treatment was dependant on age (decreasing with increasing age), which is in agreement with previous studies showing that being of young age is a risk factor for a stronger increase in BMI[21]. Although WG in elderly patients is subject to controversial results[22,23], in the present study a moderate mean gain of one BMI unit was observed after one year in this group of age, which is in agreement with the CATI-AD study conclusion supporting the importance of metabolic monitoring also in elderly patients[23]. Because of the small cohort size after stratification by the type of drugs prescribed, the frequent polymedication and the previous history of past medications, it was not possible to differentiate the effects of each psychotropic drug separately.

An EWG of more than 5% was found to be the best predictor for a WG of ≥15% after three months and of ≥20% after one year. Of note, AUC values have also been calculated for the previously published threshold of 2kg after one month[9-11], showing similar AUC value than 5% (data not shown). Because an absolute threshold expressed in Kg does not take into account the large variability of baseline weight, a relative threshold expressed in % as presented in this study appears to be more relevant. The high NPV indicates that this measure will correctly predict the future status of most patients (97% for three months, 93% for 12 months) who had a WG less or equal to 5% after one month as continuing to have a moderate WG after three and 12 months. Over one year, these patients had a mean BMI increase of 1.2kg/m^2, which is significantly lower than the 3.1kg/m^2 increase observed in the high EWG group. The low PPV indicates that 71% and 70% of patients with an EWG >5% will not reach the 15% and 20% threshold at three and 12 months. Although WG in this false positive group at three months is still significantly higher than in the low WG group, the

difference was not significant anymore at 12 months indicating the necessity of long term weight monitoring also in the group with low initial WG. Monitoring of metabolic parameters is performed in our department with advice to take into account significant changes of parameters by different means (discussion with the patients, diet and physical activity counselling, drug evaluation and changes). Because such possible interventions were not collected in this post-hoc non-interventional study, it is not known if they could contribute to part of the false positive results.

These predictive parameters are in agreement and complete previous results obtained from clinical trials[9,10,24]. Female gender, young age, low baseline BMI and low triglyceride levels were proposed to predict antipsychotic induced WG[3,19,25,26]. In the present study, only BMI was found to be significantly different between both groups, being lower in the EWG group at baseline. However, triglycerides values increased and HDL-cholesterol values decreased with higher amplitude over one year, showing that these parameters are worsening faster in the early high WG group, paralleling the faster increase of BMIs.

This threshold of more than 5% in the early phase of the treatment remains significant (β:6.4%, $P_{adjusted}$=0.0001) even after adjusting for several confounders. These results indicate the robustness of this predictor, and should motivate clinicians to monitor early weight changes more thoroughly for all patients and not only patients with known risk factors (i.e young patients, drug naive etc). Although not formally demonstrated in the present study, the threshold of more than 5% WG after one month of treatment may also be used to detect some patients who could reach this threshold in a shorter period of time. Thus, very rapid and important WG should be evaluated by the treating physician and nurses independently of the usual time schedules for weight monitoring.

No significant influence of prescribed antipsychotics was found. This is in agreement with a previous study showing that an EWG of 2kg is a good predictor for more WG during 24 to 28 week treatment with olanzapine and aripiprazole, two drugs with important differences in their potential to induce WG[9]. These results suggest that, independently of the prescribed drugs (i.e atypical antipsychotics,

mood stabilizers such as lithium or valproate, or sedative antidepressants such as mirtazapine), the 5% threshold should be used when monitoring WG during treatment.

To our knowledge, only one study previously investigated the role of appetite on long term weight change, concluding that EGW was found to be a better predictor for further WG than appetite increase[27], which is in agreement with the present study. In addition, medium or high physical activity was also a poor predictor. However, the present results do not preclude the use of health promotion intervention including physical activity or behavioral interventions that have shown some effect in psychiatric populations[28].

Several limitations of the present study have to be mentioned. Firstly, the majority of patients were not drug naive and the observed WG was probably also the result of past treatments. However, such patients constitute the majority of psychiatric populations, which therefore might even strengthen the clinical validity of the present finding. Secondly, the follow-up period lasted only one year but previous studies, as well as the present study, show that following drug introduction, most of the WG occurs during this period[29,30]. Thirdly, due to an insufficient number of observations, we could not determine an EWG threshold specifically in young and elderly patients. However, the 5% threshold was significantly associated with important WG in these two age classes. Finally, the results concerning activity and appetite change have to be interpreted with caution because the evaluation was self reported, used a non-validated scale and may be not sensitive enough.

Strengths of the present study was a longitudinal design study with weight monitoring at regular time points during one year when starting a weight inducing psychotropic drug introduction and/or when switching the treatment. In addition, the use of TDM allowed to assess the compliance of the patients, which is an important issue in psychiatric treatment.

In conclusion, this work underlines the importance of weight monitoring at the introduction and after a switch of antipsychotic drugs, mood stabilizers or sedative antidepressants for all patients, independently of their gender, age, initial body weight, previous treatments and/or illness duration. A WG of more than 5% during the first month of treatment should be used by the clinician as one of

the early warning signs to consider those patients as being at higher risk of important WG during long term treatment. A particular emphasis should be put on such patients by using all available strategies (i.e behavioral interventions or even replacing the causative WG inducing drug if clinically possible, after a careful evaluation of the risk/benefit ratio of a drug switch), considering the major impact WG and its consequences have on quality of life and general health of patients.

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Author Contributions: Prof CB. Eap had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: CB. Eap

Acquisition of data: F. Vandenberghe, N. Saigi Morgui, A. Delacrétaz, E. Choong, A. Solida, S. Kolly, S. Fassassi, J. Thonney, A. Hedjal, AE. Ambresin, A. von Gunten, P. Conus

Analysis and interpretation: F. Vandenberghe, M. Gholam-Rezaee

Drafting of the manuscript: F. Vandenberghe, M. Gholam-Rezaee

Critical revision of the manuscript for important intellectual content: all authors

Statistical analysis: M. Gholam-Rezaee, F. Vandenberghe

Obtained funding: CB. Eap, P Conus

Administrative, technical, or material support: A. von Gunten, AE. Ambresin, P. Conus

Additional information:

The original dataset is in possession of Chin B. Eap.

Clinical points (max 60 words):

- Psychotropic drug induced weight gain is associated with high morbidity and mortality.
- Rapid detection of high risk patient is of major clinical significance.
- One month treatment weight gain of more than 5% was found to be a good predictor for important long term weight gain.

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Table 1: Overall demographic parameters (left column) and comparison between early and non early weight gainers:

	All (n=351)	First month weight gain ≤ 5% (n=288)	First month weight gain > 5% (n=63)	P[a]
Age, mean (se), years	46 (1.2)	46 (1.3)	43 (2.6)	0.4
Men, n/total n (%)	164/351 (47%)	131/288 (45%)	33/63 (52%)	0.3
Follow-up duration, mean (se), days	237 (8.18)	240 (8.59)	223 (23.22)	0.1
Illness duration, mean (se), years	8 (0.6)	8 (0.7)	8 (1.2)	0.6
Smoking, n (%)	76 /351 (22%)	64 /288 (22%)	12 /63 (19%)	0.7
Diagnosis, n/total n (%)				
Bipolar disorder	59/351 (17%)	51/288 (18%)	8/63 (13%)	0.5
Depression	61/351 (17%)	49/288 (17%)	12/63 (19%)	0.7
Organic disorders	27/351 (8%)	24/288 (8%)	3/63 (5%)	0.4
Psychotic disorders	143/351 (41%)	113/288 (39%)	30/63 (48%)	0.3
Schizoaffective disorder	26/351 (7%)	22/288 (8%)	4/63 (6%)	0.9
Other	30/351 (9%)	26/288 (9%)	4/63 (6%)	0.6
Not available	5/351 (1%)	3/288 (1%)	2/63 (3%)	0.2
Medication, n/total n (%)				
Amisulpride	36/351 (10%)	29/288 (10%)	7/63 (11%)	0.8
Aripiprazole	30/351 (9%)	27/288 (9%)	3/63 (5%)	0.3
Clozapine	24/351 (7%)	22/288 (8%)	2/63 (3%)	0.3
Lithium	19/351 (5%)	15/288 (5%)	4/63 (6%)	0.8
Mirtazapine	11/351 (3%)	9/288 (3%)	2/63 (3%)	0.9
Olanzapine	44/351 (13%)	29/288 (10%)	15/63 (24%)	**0.006**
Quetiapine	112/351 (32%)	95/288 (33%)	17/63 (27%)	0.4
Risperidone	64/351 (18%)	53/288 (18%)	11/63 (17%)	0.9
Valproate	10/351 (3%)	8/288 (3%)	2/63 (3%)	0.7
Prevalence of metabolic syndrome IDF, n/total n (%)[b]				
Baseline	35/161 (22%)	34/139 (25%)	1/22 (5%)	0.06
After one year treatment	32/100 (32%)	21/79 (27%)	11/21 (52%)	**0.04**
Prevalence of overweight, n/total n (%)				
Baseline: BMI [25-30[, kg/m^2	62 /294 (21%)	21 /237 (22%)	11 /57 (19%)	0.8
One year: BMI [25-30[, kg/m^2	36 /135 (27%)	29 /114 (25%)	7 /21 (33%)	0.4
Prevalence of obesity, n/total n (%)				
Baseline : BMI ≥ 30, kg/m^2	49 /294 (17%)	46 /237 (19%)	3 /57 (5%)	**0.009**
One year: BMI ≥ 30, kg/m^2	33 /135 (24%)	28 /114 (25%)	5 /21 (24%)	1

[a] p-value were calculated using Wilcoxon rank-sum tests for continuous variables and Fisher's exact tests for categorical variables between both group.

[b] Metabolic syndrome is present if: presence of central obesity (M ≥ 94 cm, F ≥ 80 cm) and at least two other following factors: triglycerides ≥ 1.7mmol/l or lipid lowering treatment; glucose ≥ 5.6 mmol/l or type 2 diabetes treatment; blood pressure ≥ 130/85 mmHg or treatment for hypertension; HDL-Cholesterol M ≤ 1.03 mmol/l, F ≤ 1.29 mmol/l.

Table 2: Evolution of metabolic parameters and syndrome at baseline, three months and one year (only patients with one year follow up included) :

	Baseline	3 Months	P[a]	One year	P[a]
Prevalence of normal weight, overweight and obesity, n/total n (%)					
Normal weight: BMI < 25 kg/m^2	71 /116 (61%)	60 /116 (52%)	**0.01**	57 /116 (49%)	**0.007**
Overweight: BMI [25-30[kg/m^2	25 /116 (22%)	32 /116 (28%)	0.2	33 /116 (28%)	0.2
Obese: BMI ≥ 30 kg/m^2	20 /116 (17%)	24 /116 (21%)	0.2	26 /116 (22%)	0.07
Prevalence of abdominal obesity, n/total n (%)					
Waist circumference Men ≥ 94 cm , Women ≥ 80 cm[(b)]	42 /86 (49%)	53 /86 (62%)	**0.02**	53 /86 (62%)	**0.02**
Waist circumference Men ≥ 102 cm, Women ≥ 88 cm[(c,d)]	25 /86 (29%)	28 /86 (33%)	0.50	35 /86 (41%)	**0.02**
Prevalence of HDL hypocholesterolemia, n/total n (%)					
HDL-chol. Men ≤ 1.03 mmol/l, Women ≤ 1.29 mmol/l	18 /61 (30%)	16 /61 (26%)	0.8	17 /61 (28%)	1.00
Prevalence of hypertriglyceridemia, n/total n (%)					
Triglyceridemia ≥ 1.7 mmol/l or lipid lowering treatment	13 /63 (21%)	20 /63 (32%)	0.1	25 /63 (40%)	**0.006**
Prevalence of hyperglycemia, n/total n (%)					
Fasting glucose ≥ 5.6 mmol/l or antidiabetic treatment[(d,b)]	10 /61 (16%)	16 /61 (26%)	0.1	23 /61 (38%)	**0.002**
Fasting glucose ≥ 6.1 mmol/l or antidiabetic treatment[(c)]	7 /61 (11%)	5 /61 (8%)	0.6	9 /61 (15%)	0.7
Prevalence of hypertension, n/total n (%)					
Blood pressure ≥ 130 / 85 mmHg or antihypertensive treatment	14 /80 (18%)	15 /80 (19%)	1	16 /80 (20%)	0.8
Prevalence of metabolic syndrome, n/total n (%)					
ATP-III[e]	3 /35 (9%)	1 /35 (3%)	0.6	6 /35 (17%)	2.00
ATP-III-A[f]	3 /35 (9%)	2 /35 (6%)	1	6 /35 (17%)	0.20
IDF[g]	3 /35 (9%)	6 /35 (17%)	0.5	8 /35 (23%)	0.07

[a] p-value were calculated using McNemar tests between baseline versus three months and baseline versus 12 months.
[b]According to IDF definition.
[c]According to ATP-III (National Cholesterol Education Program's Adult Treatment Panel III) definition.
[d]According to ATP-III-A definition.
[e] Metabolic syndrome is present if at least 3 criterias are present: central obesity (M ≥ 102 cm , F ≥ 88 cm); triglycerides ≥ 1.7mmol/l or lipid lowering treatment; glucose ≥ 6.1 mmol/l or type 2 diabetes treatment; blood pressure ≥ 130/85mmHg or treatment for hypertension; HDL-Cholesterol M ≤ 1.03 mmol/l, F ≤ 1.29 mmol/l.
[f] Same as # but: glucose ≥ 5.6 mmol/l or type 2 diabetes treatment.
[g] Metabolic syndrome is present if: presence of central obesity (M ≥ 94 cm, F ≥ 80 cm) and at least two other following factors: triglycerides ≥ 1.7mmol/l or lipid lowering treatment; glucose ≥ 5.6 mmol/l or type 2 diabetes treatment; blood pressure ≥ 130/85 mmHg of treatment for hypertension; HDL-Cholesterol M ≤ 1.03 mmol/l, F ≤ 1.29 mmol/l.

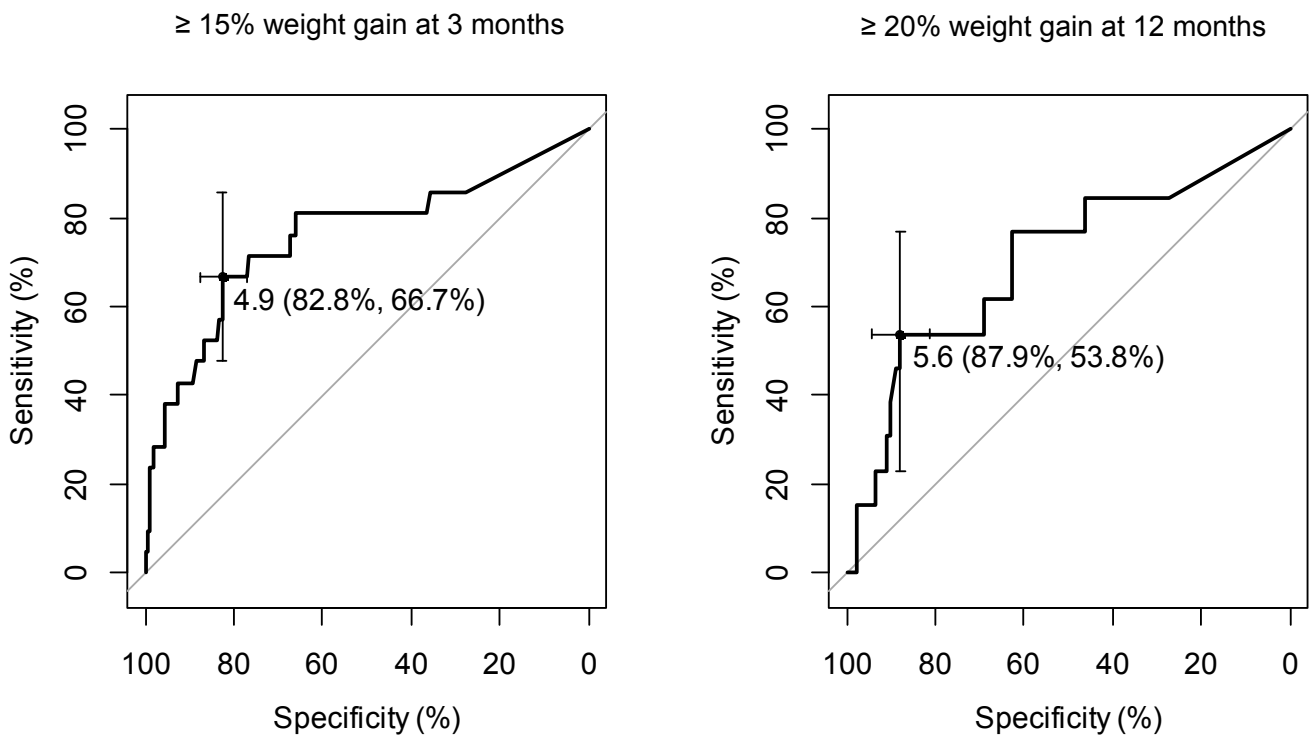

Figure 1: Receiver operating characteristic (ROC) curves indicating the best early weight gain threshold to predict a weight gain ≥ 15% after 3 months and ≥ 20% after one year of treatment.

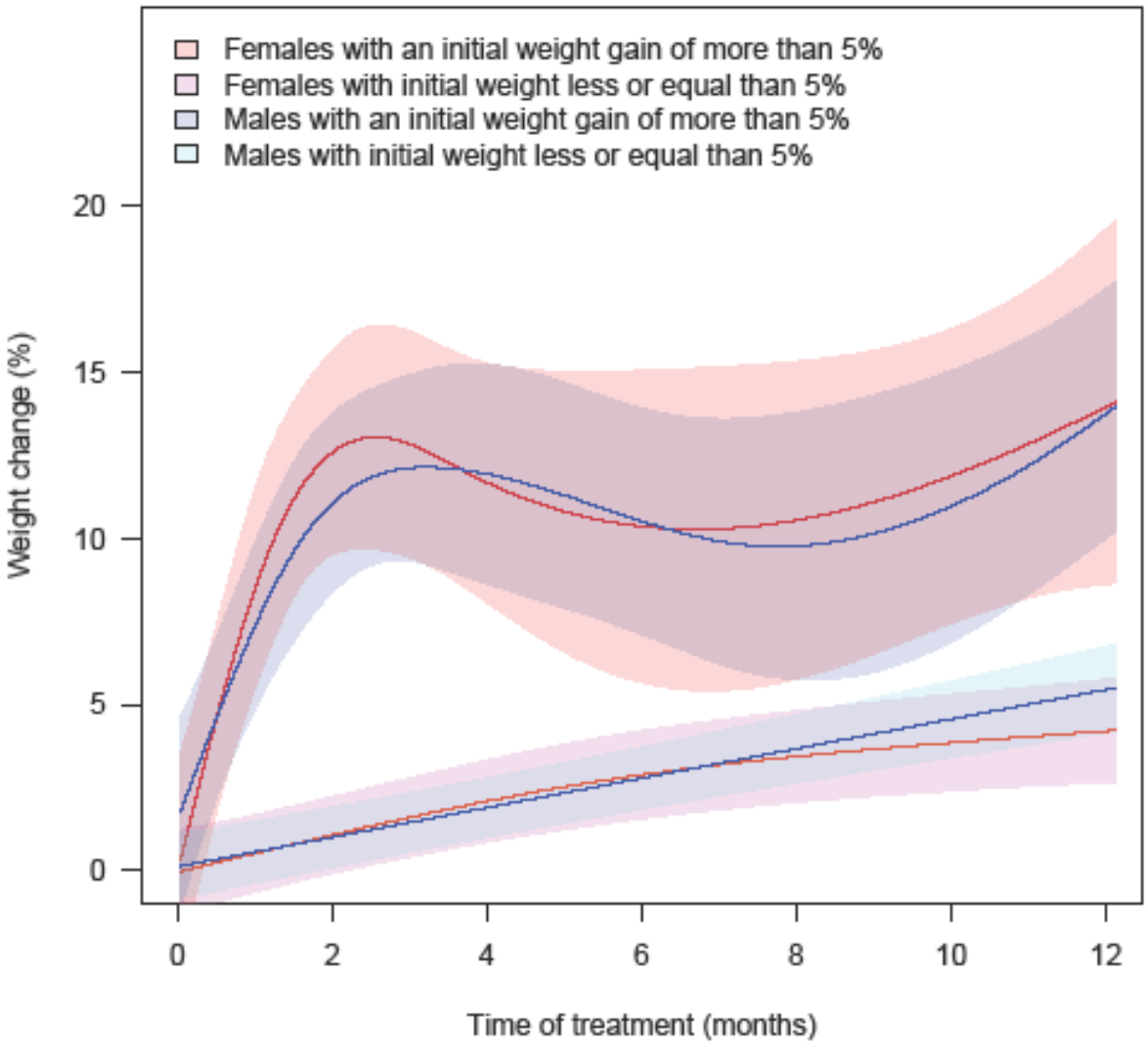

Figure 2: Generalized additive mixed model (GAMM) prediction of weight over a one year period in psychiatric patients having a weight increase of more versus less or equal to 5% after one month following the introduction of weight gain inducing psychotropic drugs. CI_{95} is represented by the shaded area.

Table 3: Linear model comparing one year change of metabolic parameters between early and non early weight gainers:

One year change of:	Difference between ≤ 5% and >5% weight gain group (95%IC).	P
Waist circumference	1.7 cm (-4.8 to 8.2)	0.6
Glucose	0.7 mmol/l (-0.2 to 1.5)	0.1
HDL cholesterol	-0.3 mmol/l (-0.5 to -0.2)	<0.0001
Triglycerides	1.5 mmol/l (0.8 to 2.2)	<0.0001

Results were obtained by fitting a linear model controlling for age, sex, time, baseline BMI, current psychotropic drug.