Journal of Psychiatric Research 46 (2012) 540–548

Contents lists available at SciVerse ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/psychires

Psychotropic drug-induced weight gain and other metabolic complications in a Swiss psychiatric population

Eva Choong [a,1], Guido Bondolfi [b,1], Manuela Etter [b], Françoise Jermann [b], Jean-Michel Aubry [b], Javier Bartolomei [b], Mehdi Gholam-Rezaee [c], Chin B. Eap [a,d,*,1]

[a] Unit of Pharmacogenetics and Clinical Psychopharmacology, Centre for Psychiatric Neuroscience, Department of Psychiatry, University Hospital Centre and University of Lausanne, Prilly, Lausanne, Switzerland
[b] Department of Mental Health and Psychiatry, University Hospital of Geneva, Switzerland
[c] Centre of Psychiatric Epidemiology and Psychopathology, Department of Psychiatry, University Hospital Centre, Prilly, Lausanne, Switzerland
[d] School of Pharmaceutical Sciences, University of Geneva, University of Lausanne, 1211 Geneva 4, Switzerland

ARTICLE INFO

Article history:
Received 10 June 2011
Received in revised form
16 December 2011
Accepted 9 January 2012

Keywords:
Antipsychotics
Mood stabilizers
Predictors
Long-term
Weight gain
Body mass index
Cardiovascular risks

ABSTRACT

Purpose: To describe the weight gain-related side-effects of psychotropic drugs and their consequences on metabolic complications (hypercholesterolemia, obesity) in a Swiss cohort of psychiatric patients.
Method: This cross-sectional observational study was performed in an out-patient psychiatric division with patients having received for more than 3 months the following drugs: clozapine, olanzapine, quetiapine, risperidone, lithium, and/or valproate. Clinical measures and lifestyle information (smoking behaviour, physical activity) were recorded.
Results: 196 inclusions were completed. Weight gain (≥10% of initial weight) following drug treatment was reported in 47% of these patients. Prevalence of obesity (BMI ≥ 30), hypercholesterolemia (≥6.2 mmol/L) and low HDL-cholesterol (<1.0 mmol/L in men, <1.3 mmol/L in women) were present in 38%, 21%, and 27% of patients, respectively. A higher standardised dose, an increase of appetite following medication introduction, the type of medication (clozapine or olanzapine > quetiapine or risperidone > lithium or valproate), and the gender were shown to be significantly associated with evolution of BMI.
Conclusion: High prevalence of obesity and hypercholesterolemia was found in an out-patient psychiatric population and confirms drug-induced weight gain complications during long-term treatment. The results support the recently published recommendations of monitoring of metabolic side-effects during treatment with atypical antipsychotics. Moreover, the weight gain predictors found in the present study could help to highlight patients with special health care management requirement.
© 2012 Elsevier Ltd. All rights reserved.

1. Introduction

Weight gain-related side-effect was shown for several therapeutic classes including anti-HIV drugs, antidepressants (in particular the tricyclics), second generation antipsychotics (SGA) or so-called atypical antipsychotics, and some mood stabilizers (MS). Recent publications have drawn attention to the risk of developing metabolic complications with SGA including weight gain, diabetes or dyslipidemia (American Diabetes Association, American Psyhiatric Association, American Association of Clinical Endocrinologists, North American Association for the Study of Obesity, 2004; Allison and Casey, 2001; De Hert et al., 2009; Stahl, 2008). The magnitude of weight gain-related side-effect is compound-dependent with clozapine and olanzapine being frequently associated with the highest weight gain (Allison et al., 2001; Basson et al., 2001; Hasnain et al., 2009; Komossa et al., 2010; Leucht et al., 2009; McIntyre et al., 2001; Meyer, 2007; Newcomer and Haupt, 2006; Tschoner et al., 2007; Wirshing et al., 1999). Expectedly, longer SGA treatment durations are associated with increased risks of weight gain (Zheng et al., 2009). In addition, other drugs such as valproate and lithium, two MS, can equally contribute to metabolic complications in psychiatric patients, especially through an increase in body weight (Documed, 2010; Vieweg et al., 2008).

Drug-induced weight gain is a challenging issue for physicians. Not only because it can jeopardise the patients self-confidence and increase the risk of relapse by compromising treatment compliance

* Corresponding author. Hôpital de Cery, 1008 Prilly, Lausanne, Switzerland. Tel.: +41 21 643 64 38; fax: +41 21 643 64 44.
E-mail address: chin.eap@chuv.ch (C.B. Eap).
[1] Both authors contributed equally to this study.

0022-3956/$ – see front matter © 2012 Elsevier Ltd. All rights reserved.
doi:10.1016/j.jpsychires.2012.01.014

(Weiden et al., 2004), but it could also be considered as the first step towards the development of obesity and other metabolic complications, which can ultimately reduce life expectancy by several years (Isomaa et al., 2001; Lakka et al., 2002; Stahl, 2008). Thus, an increase in the natural mortality rate of 1.5–2-fold as compared to the general population was reported for depressed, bipolar and schizophrenic patients (Angst et al., 2002; Laursen et al., 2007), which appears to be mainly due to a two-fold excess of cardiovascular risk factors (Birkenaes et al., 2007; Cohn and Remington, 2003; McEvoy et al., 2005; Musselman et al., 1998; Osby et al., 2000; Van der Kooy et al., 2007). In addition, several studies reported a higher prevalence of metabolic syndrome in various psychotic disorders including bipolar and schizophrenic patients as compared to the general population (Birkenaes et al., 2007; Correll et al., 2008; Fiedorowicz et al., 2008; Sicras et al., 2008; Van Winkel et al., 2008b). As a consequence, consensus reports have recommended to closely monitor potential iatrogenic weight gain side-effects and other metabolic complications in psychiatric patients receiving SGAs (American Diabetes Association, American Psyhiatric Association, American Association of Clinical Endocrinologists, North American Association for the Study of Obesity, 2004; De Hert et al., 2009).

The major aims of the present study were to estimate the prevalence of obesity and hypercholesterolemia, two metabolic complications, in a chronic psychiatric population from Switzerland and to evaluate the influence of SGA, of MS and of others covariables on weight gain in patients in whom drug intake was ensured.

2. Materials and methods

2.1. Subjects

Patients were recruited between 18 and 65 years old and receiving one or several of the following psychotropic drugs for at least 3 months: clozapine, olanzapine, quetiapine, risperidone, lithium, and/or valproate. No exclusion criterion was set for this study. All concomitant medications were allowed. The study was conducted in two out-patient psychiatric centres of Geneva University hospital (Jonction and Servette). Diagnosis was made by their current psychiatric physician according to the ICD-10 diagnostic scale.

Enrolments were made between June 2006 and May 2008 during one of the patients routine follow-up examinations. The visit could take place at any time during the day regardless of the drug and food intake. This cross-sectional study performed in a naturalistic setting was approved by the Ethics Committee of the University of Geneva. All patients gave written consent to participate in the study after oral and written information. In the case of a patient with a legal tutor, the approval of the tutor was also obtained.

2.2. Measurements

Body weight and height were measured during the interview while sex, age, comedications, previous and current psychotropic treatment were extracted from the medical record. Baseline weight was considered as the weight prior to the use of the current psychotropic treatment (i.e. SGA and/or MS). Baseline weight and those measured during the current psychotropic treatment were retrospectively obtained from the medical file and were used to calculate the weight gain. Different lifestyle factors, tobacco consumption, physical activity defined as any daily sport and/or walking activity (to go to work, to the bus, climbing stairs, etc.), for less or more than 1 h were based on the patient declarations. Self-reported appetite modification (decreased appetite, no change, increased appetite), baseline weight and weight change after 1, 3, and 6 months under SGA and MS treatment were obtained directly from the patient.

Blood samples were collected and samples were sent to the unit of pharmacogenetics and clinical psychopharmacology and stored at −20 °C until analysis. Measurements of SGA concentrations were performed by liquid chromatography–mass spectrometry as previously described (Albrecht et al., 2004; Choong et al., 2009). The validated method for risperidone determination allows the simultaneous dosage of quetiapine and clozapine (data available on request). Plasma levels of olanzapine were not available for the 31 patients treated with olanzapine, due to its instability after long-term storage even at −20 °C (Choong et al., 2009; Heller et al., 2004). 19 patients reported weight gain while 12 patients reported no change of weight following the introduction of olanzapine. Because we could not control for compliance, all 31 patients were excluded from the statistical analysis of drug-induced weight gain but were included in the epidemiological analysis. Measurement of lithium plasma levels was performed with an ion specific electrode apparatus (EasyLyte, Medica, Châtel-St-Denis, Switzerland). Total cholesterol (CHOLtot), HDL-cholesterol (HDL) and valproate plasma levels were quantified by a Cobas Integra 400 (Roche Diagnostic, Basel, Switzerland).

Body mass index (BMI) was calculated as weight/height^2 (kg/m^2) and was considered as normal (BMI 18.5 to <25 kg/m^2), overweight (BMI 25 to <30 kg/m^2), obese (BMI $\geq$ 30 kg/m^2) and target levels for CHOLtot and HDL were defined as CHOLtot $\leq$6.2 mmol/L, and HDL as $\geq$1.3 mmol/L for women and as $\geq$1.0 mmol/L for men according to the National Cholesterol Education Program (National Institute of Health, 2002). Dyslipidemia criteria were met when CHOLtot levels and/or HDL were outside the target limits and/or when a lipid lowering agent was prescribed. As blood samples were taken randomly regardless of the fasting period, triglycerides were not measured in the present study.

An 10% increase of baseline weight was considered as an important weight gain. An arbitrary threshold at 10% of the minimal therapeutic drug plasma concentration (Baumann et al., 2004) (i.e. 35, 7, 2 ng/mL, 0.05 mmol/L and 5 mg/L for clozapine, quetiapine, risperidone + hydroxy-risperidone, lithium, and valproate) was chosen to ensure psychotropic drug intake.

2.3. Statistical analysis

Dose standardization (i.e. z-score transformation to obtain a mean of 0 and a standard deviation of 1, obtained by the mean dose subtracted from the raw dose and divided by the standard deviation of the dose) was carried out for each medication and each inclusion site, which permits using this standardised dose in the analyses regardless of the medication type. Thus a mean of 0 indicated that the administered dose was equal to the mean dose of the centre. The weight gain analyses were tested in patients for whom psychotropic drug intake was ensured.

Non-parametric tests, Pearson's chi-squared and Fisher exact tests were used to assess any association between clinical outcomes in continuous traits (weight gain, CHOLtot levels, HDL levels) and in categorical traits (BMI categories (BMI < 25, 25–30, $\geq$30 kg/m^2), obesity (BMI $\geq$ 30), important weight gain (>10% of baseline weight), dyslipidemia, and studied medication with covariables (gender, age, diagnosis, smoking status, standardised doses, treatment duration, etc.). Moreover, categorised variables, such as important weight gain, were analysed using logistic regressions by controlling the model with a specification link test for single-equation models (linktest command in Stata) (Pregibon, 1979,

1980; Tukey, 1949). Finally, correlations between continuous traits were performed using the Spearman correlation test (r_s). Measurements are given as median with the interquartile range unless otherwise stated.

Because of the complicated evolution trend of weight gain, a generalized additive mixed-model was used which allows a semi-parametric flexible trend for weight gain versus time (Wood, 2006). The test was performed to fit the response variable (i.e. BMI which was log transformed to obtain parametric data), taking into account several covariates (age, age at the beginning of the treatment, gender, standardised dose, current studied medication, comedication with a potential impact on weight (concomitant drugs potentially causing an increase in weight: other SGA, mirtazapine, clomipramine, mianserine, cetirizine, tibolone; concomitant drugs potentially causing a decrease in weight: fluoxetine, venlafaxine, metformin, topiramate (Documed, 2010), treatment durations, physical activity, smoking behaviour, alteration of appetite following MS or SGA introduction, and initial BMI). The validity of the model was assessed by graphical residual diagnostics. The psychotropic drugs were considered separately or grouped into 3 categories according to their expected effects on weight: clozapine with olanzapine, risperidone with quetiapine, lithium with valproate (Leucht et al., 2009; McIntyre and Konarski, 2005; Newcomer, 2005; Tschoner et al., 2007) or according to their therapeutic classes (SGA vs. MS). The medication with the longest treatment duration was considered as the influential medication in the analyses while the other drug(s) of interest (clozapine, olanzapine, quetiapine, risperidone, lithium, and/or valproate) were considered as concomitant drugs potentially causing an increase in weight.

The significance threshold is fixed at p-value of ≤ 0.05. Statistical analyses were performed using Stata 10 (StataCorp, College Station TX, USA) and using R environment for statistical analysis version 2.11.1 for model-fitting purposes (R Development Core Team, 2010).

3. Results

3.1. Patient characteristics

Among the 200 included patients, 4 were withdrawn (not completed report form ($n = 1$), treatment duration shorter than 3 months ($n = 1$), treatment not taken into account in the protocol (i.e. amisulpride, $n = 2$). The whole cohort is composed of 86% Caucasians, 55% male, with a median age of 40 y (range: 33–47) for men and 43 y (range: 35–49) for women. The two most common ICD-10 diagnosis found in the studied population were: mood affective disorder (ICD-10: F30–F39; $n = 89$), and schizophrenia, schizotypal and delusional disorders (F20–F29; $n = 87$). The other diagnostics were as followed: F40–F48 ($n = 7$), F60–F69 ($n = 6$), F00–F09 ($n = 3$), F10–F19 ($n = 2$), F80–F89 ($n = 1$), and 1 patient with an unknown diagnostic. The median of current SGA and/or MS treatment duration was 2.3 years (range: 0.9–5.6). SGA were prescribed to 69% of the patients and the remaining 31% were receiving a MS. No significant difference of prescription was found between genders ($p > 0.1$). The population characteristics are summarised in Table 1.

Among the 196 patients, 18% of the patients had a second study medication and 3% had in total 3 studied drugs. The most frequent associations were quetiapine–lithium ($n = 8$), risperidone–lithium ($n = 5$), and valproate–clozapine ($n = 8$). Prescription of more than 1 studied drug is higher for MS (48%) than SGA (11%, $p < 0.001$). The present cohort had in majority experienced other antipsychotic drugs since the psychiatric onset before the current medication (called from hereafter previous treatment): 26% had previously experienced a MS and 57% a SGA with 4% and 16% of patients declared having experienced 2 different MS or SGA, respectively. No previous treatment was recorded for 67 patients. Regarding the current prescription, patients receiving concomitant drug(s) potentially altering weight are listed in Table 2 (Documed, 2010).

Table 1
Patient characteristics data are expressed as number (percentage) of patients or as median (interquartile range).

Characteristics	Drugs													
	Clozapine		Olanzapine		Quetiapine		Risperidone		Lithium		Valproate		All	
	$n = 28$		$n = 31$		$n = 35$		$n = 42$		$n = 35$		$n = 25$		$n = 196$	
Sex, male	13	(46)	20	(65)	19	(54)	24	(57)	21	(60)	11	(44)	108	(55)
Caucasian ethnicity	24	(86)	28	(90)	31	(89)	29	(69)	34	(97)	23	(92)	169	(86)
Smoker	15	(54)	16	(52)	20	(57)	25	(60)	23	(66)	18	(72)	117	(60)
Age, median (range), y	35	(29–44)	41	(33–46)	45	(38–51)	40	(35–47)	44	(34–49)	44	(40–49)	41	(34–48)
Treatment duration, median (range), y	4.8	(1.7–7.8)	1.8	(1.1–7.0)	1.1	(0.7–3.7)	1.7	(0.8–4.6)	3.1	(1.0–10.9)	1.7	(0.9–3.7)	2.3	(0.9–5.6)
Dose, median (range), mg/day[a]	300	(200–350)	10	(5–15)	200	(100–400)	2	(1–4)	24	(22–30)	1500	(1000–1500)		
[mg/2 weeks][a]								[38 (37.5–50)]						
Concomitant studied drug[b]	6	(21)	1	(3)	2	(6)	6	(14)	20	(57)	9	(36)	44	(22)
Cholesterol mmol/L														
median (range)	5.3	(4.4–6.1)	5.5	(4.8–6.2)	4.9	(4.4–5.8)	5.3	(4.6–6.1)	5.5	(4.6–6.3)	4.9	(4.4–6.1)	5.3	(4.5–6.1)
level at risk[c]	5	(18)	7	(23)	3	(9)	10	(24)	11	(31)	6	(24)	42	(21)
HDL-cholesterol mmol/L														
median (range)	1.2	(1.0–1.6)	1.2	(1.1–1.4)	1.3	(1.0–1.5)	1.2	(1.1–1.5)	1.4	(1.2–1.7)	1.2	(0.9–1.6)	1.3	(1.0–1.6)
level at risk[c]	9	(32)	9	(29)	9	(26)	12	(29)	4	(11)	10	(40)	53	(27)
BMI kg/m^2[c]														
median (range)	28	(24–31)	29	(25–31)	29	(25–32)	27	(24–31)	26	(23–32)	29	(25–32)	28	(24–31)
<25	10	(36)	9	(29)	8	(23)	14	(33)	15	(43)	7	(28)	63	(32)
25–30	9	(32)	10	(32)	12	(34)	14	(33)	7	(20)	7	(28)	59	(30)
≥30	9	(32)	12	(39)	15	(43)	14	(33)	13	(37)	11	(44)	74	(38)
Weight gain>10% during the present drug treatment	10	(53)	12	(75)	6	(30)	16	(47)	16	(50)	7	(33)	67	(47)

[a] Lithium is expressed as mmol/day. Risperidone was prescribed in oral form ($n = 27$, 1st row) in mg/day and in injectable form ($n = 15$, 2nd row in bracket) in mg/2weeks.
[b] Number of patients with prescription of more than 1 studied drug (i.e. clozapine, olanzapine, quetiapine, risperidone, lithium, valproate).
[c] Total cholesterol ≥6.2 mmol/L and cholesterol-hdl <1 mmol/l for men and <1.3 mmol/l for women are considered as cardiovascular risk factors, BMI is considered as normal when <25, overweight when 25–30 and obese when BMI ≥ 30 kg/m^2.

Table 2
Comedications potentially altering weight recorded in the patients' medical file. The number of patients taking a certain comedication is indicated.

Potential weight effect	Comedications and number of patients
One comedication potentially causing an increase of weight	amisulpride $n = 10$ aripiprazole $n = 3$ mirtazapine $n = 8$ clomipramine $n = 4$ mianserine $n = 1$ cetirizine $n = 1$ tibolone $n = 1$
Two comedications potentially causing an increase of weight	mirtazapine with amisulpride, $n = 1$
One comedication potentially inducing weight loss	fluoxetine $n = 3$ venlafaxine $n = 24$ metformin $n = 3$ topiramate $n = 4$
Two comedications potentially inducing weight loss	fluoxetine with topiramate, $n = 1$
Two comedications potentially altering weight in an opposing way	venlafaxine with aripiprazole $n = 1$ venlafaxine with mirtazapine $n = 3$ topiramate with mirtazapine $n = 1$ metformin with amisulpride $n = 1$

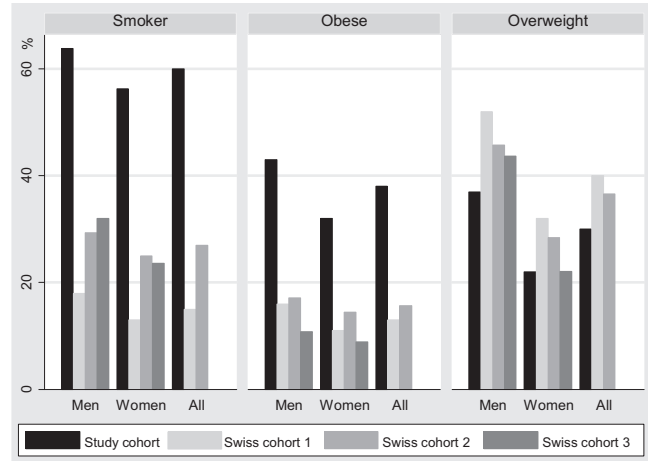

Fig. 1. Prevalence (%) of smoking, obesity and overweight by gender in the study cohort of psychiatric patients and in other Swiss general population cohorts. Note that data for men and women combined in Swiss cohort 3 is not available. Swiss cohort 1 (Chiolero et al., 2008), Swiss cohort 2 (Firmann et al., 2008), Swiss cohort 3 (Office féderal de la statistique, 2009).

Finally, some patients were also receiving pharmacological treatments in relation to the metabolic syndrome, with a lipid lowering agent, antihypertensive, or antidiabetic drugs prescribed to 4% (4 women; 4 men), 7% (5 women; 9 men) and 6% (7 women; 4 men) of patients, respectively.

3.2. Obesity and dyslipidemia

The median BMI in the whole group is 27.9 kg/m^2 (range: 24.2–31.4), which is in line with other European studies with schizophrenic patients (Bobes et al., 2007) and patients with mood disorders (McElroy et al., 2002; Salvi et al., 2008; Sicras et al., 2008). Approximately 30% of patients were overweight ($n = 59$, 22% of women and 37% of men) and 38% were obese ($n = 74$, 32% of women and 43% of men). As expected, median BMI was higher in males compared to females (25.8 kg/m^2, range: 22.5–31.0 for women compared to 28.4 kg/m^2, range: 25.5–31.6 for men, $p = 0.015$) (Schokker et al., 2007) and higher frequencies for overweight status (37% vs 22%) and for obesity (43% vs 32%), were found in male than in female patients, respectively ($p < 0.001$ in both cases). No significant differences between patients taking MS and those taking SGA were found regarding obesity on a whole ($p = 0.6$) or for patients receiving a single drug ($p = 0.8$). Although no control group was included in the present study, we found an approximately twice higher prevalence of obesity when compared to several Swiss general population cohorts, with prevalence between 5 and 14% for women and 11–18% for men of similar or slightly older age (Fig. 1) (Fondation Suisse de Cardiologie, 2002; Office féderal de la statistique-Neuchâtel Suisse, 2009; Chiolero et al., 2008; Firmann et al., 2008). On the other hand and interestingly, the prevalence of overweight patients in the present cohort is similar to or slightly lower than the general population (Fig. 1).

High CHOLtot levels were observed in 21% of the patients (20% in women, 22% in men), and low HDL levels were observed in 27% of patients (30% in women, 25% in men) (Table 1) (National Institute of Health, 2002). Taking into account that lipid lowering agents were prescribed to 4% of patients, dyslipidemia (see Materials and Methods) was observed in up to 47% of patients (43% in women, 57% in men). Finally, 60% of patients were smokers (median number of cigarettes per day, range: 20, 20–30 cigarettes), which adds another cardiovascular risk factor.

3.3. Weight gain during treatment

3.3.1. Patients' self-estimation

Self-reported body weights were evaluated for reliability in the subset of patients for whom body weights were recorded in the medical files. Estimated baseline body weight and at different time points after treatment initiation were thus compared to body weight found in medical records for 29 patients (mean treatment duration: 2 years; range: 0.25–14 years). An excellent concordance was found ($r_s = 0.97$, $p < 0.0001$) between weight modification estimated by the patient (median: 6 kg; range: 3–11 kg) and the one recorded in the medical file (median: 6 kg; range: 1–10 kg). Moreover, baseline self-reported and recorded body weight were not found to be significantly different ($p = 0.3$).

Regarding the patients estimation on the drug being responsible for their greatest weight gain (during the past and current treatment prescription), 58%, 54%, 43%, 32%, 26% and 21% of patients receiving olanzapine, clozapine, risperidone, valproate, quetiapine and lithium, respectively, stated that this drug was the drug which induced the most severe weight gain.

3.3.2. Weight gain in marginal analyses

Weight modification from drug initiation to inclusion in the study was available for 157 patients. Among them, 126 had available blood levels that were above the minimal threshold (see Materials and Methods) and were subsequently tested for the weight gain analyses. Wide interindividual variability was found for weight change (range: −29 kg to +51 kg, min/max) with a median treatment duration of 2.5 (range: 0.9–5.6) years. Marginal analyses with weight gain and several covariables are shown in Table 3. A trend was found between additional medication on the drug-induced weight gain with 5 kg ($n = 89$, range: 1–13) and 9 kg ($n = 37$, range: 5–13) in patients receiving one and more than one drug, respectively ($p = 0.054$) while the duration of treatment was not significantly different between these groups ($p = 0.3$).

Moreover, the weight gain induced by previous treatments shows a significant negative association with the weight gain induced by the present treatment ($p = 0.03$), i.e. patients who had already experienced a strong weight increase during a previous treatment tended to gain less weight on their current medication, than those who experienced a weaker weight gain during

Table 3
Univariate analyses between weight gain and several covariables ($n = 126$).

Categorial covariables	p-values	
Male vs female	0.973	
Caucasian vs other ethnicities	0.786	
Smoker vs non-smoker	0.659	
Daily physical activity (more or less than 1H)	0.962	
MS vs SGA	0.617	
Medication grouped by their expected impact on weight gain	0.835	
One vs more than one studied drug	0.054	
Comedications potentially altering weight (weight loss, no change, weight gain)	0.221	
Continuous covariables	p-values	r_s
Treatment duration	0.071	0.16
Baseline age	0.195	−0.12
Current age	0.651	−0.04
Previous weight gain	0.030 *	−0.20
Baseline BMI	0.008 *	−0.24

r_s: spearman correlation.
*: significative results.

a previous treatment. Similarly, the BMI at the beginning of the treatment was significantly correlated with BMI change ($p = 0.008$). Finally, using weights recorded in the medical files or those self-reported, weight increase at 3 ($n = 44$, 8 recorded, $r_s = 0.61$, $p < 0.0001$) and 6 months of treatment ($n = 48$, 9 recorded, $r_s = 0.70$, $p < 0.0001$), but not at 1 month ($n = 42$, 1 recorded, $p = 0.27$) were found to be good predictor for long-term weight gain (>6 months), $p = 0.27$). Fig. 2 presents the median weight gains after 3 months and 6 months, and the weight gain at the time of inclusion, when grouping the weight gains after 3 months of treatment into 3 tertiles (low, intermediate and high increases of weight).

3.3.3. Risks for an important weight gain

An important weight gain (≥10% weight increase from the baseline to the time of inclusion) was found in 47% patients ($n = 67$, see Table 1). A logistic regression analysis showed that the type of medication and previous weight gain were significantly associated with important weight gain in the model, adjusted for age, sex and treatment duration (pseudo-R^2 of 15%). Compared to clozapine or olanzapine, both the prescription of risperidone or quetiapine ($p = 0.034$), and of lithium or valproate ($p = 0.008$) were found to be less likely to induce an important weight gain (odds ratio = 0.29 (CI: 0.09–0.91) and 0.17 (CI: 0.04–0.63), respectively). Moreover, the past weight gain showed to be a protective factor (odds ratio 0.93 (CI: 0.87–0.98), $p = 0.011$).

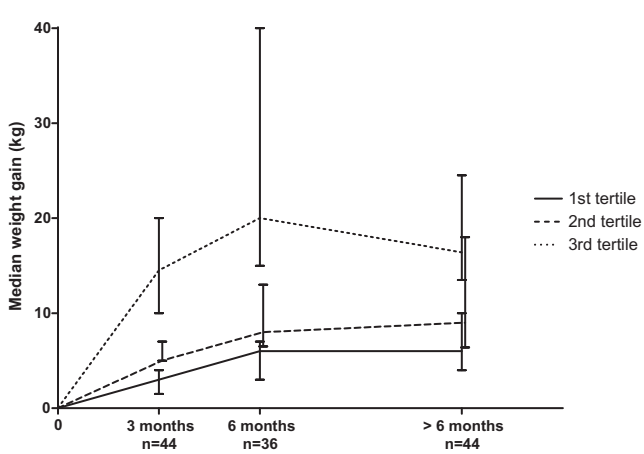

Fig. 2. Weight gains after 3 months, 6 months, and weight gain at the time of inclusion, when grouping the weight gains after 3 months of treatment into 3 tertiles (high, intermediate and low increases of weight for 3rd, 2nd and 1st tertile, respectively). Median weight gain and interquartile ranges are shown.

3.4. Appetite modification

More than half of 193 patients reported a change in their feelings of satiety following the introduction of their current treatment, with 48% having an increase and 5% a decrease of appetite; regardless of the medication. The weight gain was significantly associated with the appetite change, with weight change of 10 kg ($n = 68$, range: 6–18 kg), 4 kg ($n = 67$, range: 1–9 kg) and −2 kg ($n = 5$, range: −20 kg to +5 kg) for patients experiencing an increase of appetite, no change in appetite and a decrease of appetite ($p = 0.0001$). In the whole group, no difference of self-reported appetite was found when examining each drug ($p = 0.6$) or each class (i.e. SGA vs. MS, $p = 0.26$) separately. On the other hand, considering the subgroup of patient with one single drug potentially linked to weight gain, an increase of self-reported appetite was reported by 50% of patients treated with a SGA ($n = 111$) compared to only 21% patients treated with a MS ($n = 19$, $p = 0.025$).

3.5. Mixed-model approach

A mixed-model was used to investigate which clinical variables can influence BMI evolution under treatment. The effect of the studied medication (grouped according to their expected impact on weight), standardised doses, concomitant drugs potentially causing an increase in weight, age, gender, appetite change, physical activity, duration of treatment and the drug plasma level thresholds corresponding to 10% of the minimal therapeutic level were considered. The model allowed to take into account the whole cohort ($n = 196$). Based on the model, predicted BMIs after 24 months with the current treatment are shown in Table 4 for the different relevant categorised covariables. A significant association was found between BMI during treatment and the type of medication studied, with a significantly lower BMI with lithium or valproate ($p = 0.005$), and risperidone or quetiapine ($p = 0.032$) as compared to clozapine or olanzapine (Table 4). Moreover, gender ($p < 0.001$), appetite change ($p = 0.027$), standardised dose ($p < 0.001$), and drug plasma level thresholds ($p = 0.034$) were found to influence BMI evolution but not physical activity ($p = 0.22$) and concomitant drugs potentially causing an increase in weight ($p = 0.84$, Table 4, b–e). Evolution of BMI controlling for age over treatment duration for each gender regardless of the studied drugs is shown in Fig. 3 ($p = 0.008$). Since appetite was self-reported and

Table 4
Predicted BMI after 24 months with the current treatment for relevant covariables (according to the mixed-model). CI: 95% confidence intervals.

Covariables assessed		24 months of treatment		
		predicted BMI	Lower CI	Upper CI
a)	Clozapine or olanzapine	26.30	25.07	27.53
	Quetiapine or risperidone	25.63	24.42	26.83
	Lithium or valproate	24.45	23.01	25.89
b)	Men	28.09	26.84	29.33
	Women	26.30	25.07	27.53
c)	Increased appetite	27.27	25.95	28.59
	No change or decreased appetite	26.30	25.07	27.53
d)	Plasma threshold >10%	26.30	25.07	27.53
	plasma threshold <10%	24.49	22.70	26.29
e)	Daily physical activity <1H	26.30	25.07	27.53
	Daily physical activity >1H	25.59	24.17	27.01

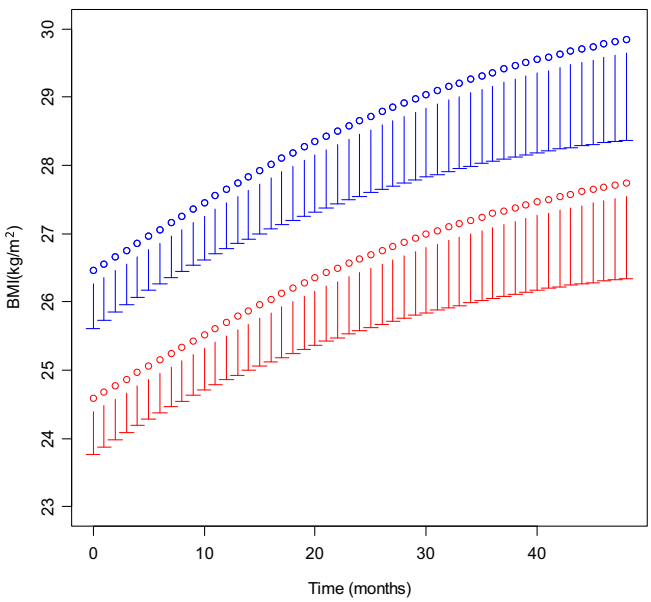

Fig. 3. Predicted evolution of BMI controlling for age over treatment duration for each gender regardless of the studied drugs (Top curve: men, bottom curve: women).

several factors might influence it, we performed the mixed-model analysis without this factor. Similar results were obtained (data not shown). Physical activity was significantly associated to BMI when the standardised dose is not taken into account ($p = 0.020$). All positive associations found in the present report for drug-induced weight gain were independent of the psychiatric diagnostic of the patients ($p > 0.2$) or the number of studied drugs ($p = 0.6$).

4. Discussion

The present results showed a median BMI of 28 kg/m^2, corresponding to an overweight status. In this Swiss psychiatric population recruited in a natural setting, a higher prevalence of CHOLtot levels (21%), dyslipidemia (47%), and smoking habits (60%) was found compared to a general Swiss population of the same average age, with obesity and smoking prevalence being about 1.5–2 times more frequent. This confirms the high prevalence of some cardiovascular risk factors found in other European psychiatric populations (Birkenaes et al., 2007; De Hert et al., 2011; De Hert et al., 2006; Garcia-Portilla et al., 2009; Salvi et al., 2008; Van Winkel et al., 2008a). Moreover, a strong correlation was found between self-reported appetite change and weight gain. Previous weight gain, baseline BMI, early weight gain (3 months) were all found to be a good predictor of weight gain in the subgroup of patients having had these data recorded. To allow the taking into account of the whole population, an extensive mixed-model analysis on BMI evolution was performed. BMI evolution was associated with gender, type of medication, standardised dose, appetite and higher blood levels.

Of note, a first relevant clinical point can be addressed. Only, 4% of the patients received a lipid lowering agent, while 21% of them had high CHOLtot levels (median CHOLtot: 7.1 (6.6–7.3) mmol/L for patients above the threshold). According to the cardiovascular risk management proposed by the European psychiatric, cardiology and diabetes societies (De Hert et al., 2009), statins may be required to achieve CHOLtot $\leq$5 mmol/L. This underlies the underestimated risk of somatic disease management in a psychiatric population and the usefulness of somatic analyses to detect potential metabolic complications.

A second relevant clinical point is that patients remain vulnerable to weight gain during their current treatment (median weight gain of 6 kg, range: 2–13 kg), although 66% of them were previously treated with other SGA (56%) and/or MS (26%).. Interestingly, past weight gain somehow masked the impact of current treatment as previous weight gain was negatively correlated with weight gain induced by the current drug. On the same line, as previously reported (Umbricht et al., 1994; Wetterling and Mussigbrodt, 1999), a low BMI at the initiation of the current psychiatric treatment was found to be a risk factor for a stronger subsequent weight gain,- Another study showed an association between premorbid BMI (before onset of psychiatric disease) and weight gain (Gebhardt et al., 2009). This information was not available in this study and was not assessed. In the present study, both the baseline BMI and the weight gain at 3 and 6 months of treatment were predictive for the long-term weight gain. The latter result is in agreement with reports showing that the weight change is mostly noticeable during the first year of treatment, the weight often reaching thereafter a plateau (Allison et al., 2001; Kinon et al., 2001; Wirshing et al., 1999; Zimmermann et al., 2003).

As mentioned, the mixed-model showed significant association between BMI evolution and clinical variables, and the predicted BMI for each significant covariable are reported in Table 4. Approximately, 2 more units of BMI were found in patient with clozapine or olanzapine than with lithium or valproate. Similarly, risk of important weight gain (>10%) adjusted by age, sex and treatment duration was found to be significantly different between medication with, in decreasing order of risks, clozapine, olanzapine > quetiapine, risperidone > lithium, valproate.

The model also showed that the strongest increase of appetite was constantly and significantly associated with the greatest weight gain with 1 more BMI unit in those with increased appetite. Therefore, self-reported increased appetite might be a predictor of weight gain which could be easily collected by a physician. Furthermore, patients with SGA were more likely to self-report an increase of appetite than patients with MS when they had been prescribed one single drug linked to weight gain, which is in agreement with previous reports on the effects of SGA on appetite change (Gebhardt et al., 2007; McIntyre et al., 2001; Theisen et al., 2003). In addition, patients appear to have a good awareness of their weights before treatment, as suggested by the strong correlation between self-reported and recorded baseline weight, and also a good knowledge of the potency of the drugs to induce weight gain.

The drug action on satiety feeling and the weight gain mechanisms are only partially understood (Stahl, 2008). Several studies suggest the involvement of hypothalamic receptors involved in the energy expenditure and satiety pathway, such as the histamine H_1 and serotoninergic $5HT_2$ receptors (Allison et al., 2001; Baptista, 1999; Basson et al., 2001; Chagnon, 2006; Stahl, 2008; Taylor and McAskill, 2000; Zimmermann et al., 2003). Clozapine and olanzapine, as strong antagonists of these receptors, are associated with the highest weight gain. Interestingly, physical activity is significantly and negatively correlated with drug-induced weight gain, although this association became no more significant when drug standardised doses were taken into account. To determine whether physical activity could reduce drug-induced weight gain, we calculated predicted BMI at 24 months for less or more than 1 h of daily physical activity (including sport but also softer activities such as walking). Although our results did not reach significance, a 0.7 kg/m^2 lower predicted BMI value was found for patient practising more than 1 h of daily physical activity. This is in line with reports recommending regular exercises as prevention and treatment of established obesity (Alvarez-Jimenez et al., 2008; De Hert et al., 2009).

Several studies found that weight gain is likely to be more frequent and pronounced in female than in male patients (Aichhorn et al., 2006; Covell et al., 2004; Homel et al., 2002; Russell and Mackell, 2001). No explanations can be given for the sex-difference in weight gain found in the present study, with male patients having more pronounced side-effects, although another study also found male gender to be predictive for weight gain (Basson et al., 2001). The apparent discrepancies on the influence of gender on BMIs obtained either by the marginal analyses or by the mixed-model can probably be explained by the fact that marginal tests are applied on observations from each time point separately and cannot be done on all observations simultaneously. In addition, the non-parametric tests used in marginal analyses are usually conservative and need a higher number of observations to identify a significant effect while the linear mixed-model is more flexible and more powerful in detecting differences. It also remains to be determined whether the heterogeneous drug prescription and/or the presence of MS drugs could contribute to the present results.

Finally, a positive association between higher blood levels and weight gain was previously reported for clozapine and olanzapine although no clear association was found with their daily dose and with the other atypical antipsychotics (Simon et al., 2009). We used the mathematical tool "standardisation" to allow comparison between the different drug doses. Our results suggested a positive association between BMI and increased standardised dose but this can, however, not be extrapolated to the daily dose for each specific treatment.

A strength of the present study is the natural clinical design involving a general psychiatric out-patient population and allowing to investigate different factors, such as different types of medication (especially antipsychotics and mood stabilizers. The limitations of the study must also be discussed. Firstly, the design of the study, with a cross-sectional analysis, heterogeneous treatment durations, and the absence of a control group implies that the different causes of weight gain could only be hypothesised but not be demonstrated with certainty. In addition, a median observation period of 2.3 years as calculated for the patients of the present study is short with respect to a life-long treatment. The present results are, however, generally in agreement with previously published studies. Secondly, weights before the inclusion in the study (i.e. weights at the beginning of the current treatment) were self-reported for the majority of the patients. Although a strong correlation was found between self-reported weights and weights found in the medical files, demonstrating a good awareness and reliability of patient self-declaration on their weight, other studies should be performed to confirm these findings. Thirdly, the patients were recruited in out-patient psychiatric centres from a single city and the results should be generalized with caution. Fourthly, the effect of weight gain could be masked and/or underestimated by previous treatment impact, years of previous treatment duration, and years of illness as suggested by our results. Thus, the majority of patients in our cohort are not drug naive. Some patients might have reached a weight plateau before initiation of the current studied psychotropic drugs, during which weight gain tends to gradually decelerate. Therefore, the impact of medication on weight might be more important than what was shown in the present study. The impact of previous treatments is also possibly contributing to the strong weight losses observed in some patients, probably when switching from a drug inducing a strong increase of weight to another with a more favourable profile concerning this side-effect. Finally, this cohort is only constituted of patients wishing to be enrolled in a study examining the prevalence of weight gain induced by drugs, which might introduce a bias towards increased reports and increased frequencies of such side-effects. On the other hand, patients who had previously presented severe side-effects in relation to the metabolic syndrome may have been switched to other drugs less likely to induce metabolic risks and might be therefore under-represented in this cohort.

In summary, increased mortality observed in psychiatric patients can be, in part, explained by the high prevalence of cardiovascular risk factors. Besides psychiatric illnesses and other environmental and lifestyle factors, prescription of psychotropic drugs might be an important modulator of cardiovascular risks. To our knowledge, this is the first study to examine the prevalence of weight gain and subsequent cardiovascular risk factors in a Swiss psychiatric population under long-term SGA and/or MS treatment. Metabolic risk factors in psychiatric populations were investigated in the US (American Diabetes Association, American Psyhiatric Association, American Association of Clinical Endocrinologists, North American Association for the Study of Obesity, 2004; McEvoy et al., 2005; Stroup et al., 2009) and Europe (Birkenaes et al., 2007; De Hert et al., 2011; Garcia-Portilla et al., 2009; Salvi et al., 2008; Van Winkel et al., 2008a) and high prevalence of metabolic syndrome (18–25%) were reported in psychiatric populations of other European countries (Birkenaes et al., 2007; De Hert et al., 2011; Garcia-Portilla et al., 2009; Salvi et al., 2008; Van Winkel et al., 2008a). This study proposes a snap shot of a cohort with psychiatric out-patients in Switzerland, with multiple treatment histories, taking into account the country's health care system, lifestyle, diet habit and aetiology. Given the high prevalence of some cardiovascular risk factors in this sensitive population, the importance of adequate somatic care and general health monitoring should be addressed. Several clinical covariables were linked to weight gain and BMI evolution. Of note, patients showed good awareness of their weight which underlies some treatment adherence issued in regards to weight gain-related side-effect with all the subsequent possible human, social, and financial consequences of relapse (Weiden et al., 2004).

5. Conclusion

The present study found several covariables linked to weight gain as well as high prevalence of cardiovascular risks factors in a Swiss psychiatric population treated with SGA and/or MS. The increased frequencies of obesity, dyslipidemia and smoking behaviour highlight the importance of an adequate somatic care and general health monitoring in this type of population.

Funding

This work was funded in part by the Swiss National Research Foundation (no 120686).

Contributors

Chin B. Eap obtained the funding, designed the study, wrote the protocol and revised the manuscript.

Eva Choong interpreted the data, performed the statistical analysis, and wrote the manuscript.

Mehdi Gholam-Rezaee performed the statistical analysis and revised the manuscript.

Guido Bondolfi, Manuela Etter, Françoise Jermann, Jean-Michel Aubry, Javier Bartolomei were involved in the recruitment of patients, in the acquisition of data, and revised the manuscript.

Author disclosure information

Dr Eap received research support from Eli Lily, Fujisawa, Janssen-Cilag, Novartis, and Bristol-Myers Squibb. He received honoraria for conferences or teaching CME courses from Astra Zeneca,

Bristol-Myers Squibb, Eli Lily, Essex Chemie, Glaxo-Smith Kline, Janssen-Cilag, Lundbeck, Novo Nordisk, Organon and Sandoz.

Dr Guido Bondolfi has received research funding from Bristol-Myers Squibb, Janssen-Cilag, Lundbeck, Sanofi-Synthelabo, Glaxo-Smith Kline and Wyeth. He received honoraria for conferences or teaching CME courses from Bristol-Myers Squibb, Eli Lily, Glaxo-Smith Kline, Janssen-Cilag, Lundbeck, and Servier.

Dr Jean-Michel Aubry has received research funding from Eli Lily, Wyeth, Lundbeck. He received honoraria for conferences or teaching CME courses from Astra Zeneca, Bristol-Myers Squibb, Eli Lily, Essex Chemie, Glaxo-Smith Kline, Janssen-Cilag, Lundbeck, Organon, Servier, and Vifor.

All other authors have no personal affiliations or financial relationships with any commercial interest to disclose relative to this article.

Acknowledgements

The authors thank Quteineh L., Crettol S. (scientific discussion), Brogli C. (logistical assistance), Ochsner A., Pion D, Manco A. (editorial assistance), Ponce E. (bibliographical help), Aubert A.C., Kottelat A., Brawand M., Powell Golay K., Hodel V., Jacquet S., Jonzier M., Brocard M., Cochard N., Delessert M. (sample analysis), Guarin A., Rethoret Y., Lufungula A., Amani S., Bonavitacola P., Glauser F., Vracar S., Rrustemi I., Michalopoulos G., Dudouit M., Gervasoni N., Charmillot A., Dallon C., Mehl P., Minem Ba G., Sanghvi S., Navarro R. (recruitment and clinical investigations), Monnier M.C., Durak M.J., Boguet R., Piccard C. (samples collection).

References

Aichhorn W, Whitworth AB, Weiss EM, Marksteiner J. Second-generation antipsychotics: is there evidence for sex differences in pharmacokinetic and adverse effect profiles? Drug Safety 2006;29:587–98.

Albrecht A, Morena PG, Baumann P, Eap CB. High dose of depot risperidone in a nonresponder schizophrenic patient. Journal of Clinical Psychopharmacology 2004;24:673–4.

Allison DB, Casey DE. Antipsychotic-induced weight gain: a review of the literature. Journal of Clinical Psychiatry 2001;62(Suppl. 7):22–31.

Alvarez-Jimenez M, Hetrick SE, Gonzalez-Blanch C, Gleeson JF, McGorry PD. Non-pharmacological management of antipsychotic-induced weight gain: systematic review and meta-analysis of randomised controlled trials. British Journal of Psychiatry 2008;193:101–7.

American Diabetes Association, American Psyhiatric Association, American Association of Clinical Endocrinologists, North American Association for the Study of Obesity. Consensus development conference on antipsychotic drugs and obesity and diabetes; 2004.

Angst F, Stassen HH, Clayton PJ, Angst J. Mortality of patients with mood disorders: follow-up over 34–38 years. Journal of Affective Disorders 2002; 68:167–81.

Baptista T. Body weight gain induced by antipsychotic drugs: mechanisms and management. Acta Psychiatrica Scandinavica 1999;100:3–16.

Basson BR, Kinon BJ, Taylor CC, Szymanski KA, Gilmore JA, Tollefson GD. Factors influencing acute weight change in patients with schizophrenia treated with olanzapine, haloperidol, or risperidone. Journal of Clinical Psychiatry 2001;62: 231–8.

Baumann P, Hiemke C, Ulrich S, Gaertner I, Rao ML, Eckermann G, et al. Therapeutic monitoring of psychotropic drugs – an outline of the AGNP-TDM expert group consensus guideline. Therapeutic Drug Monitoring 2004;26:167–70.

Birkenaes AB, Opjordsmoen S, Brunborg C, Engh JA, Jonsdottir H, Ringen PA, et al. The level of cardiovascular risk factors in bipolar disorder equals that of schizophrenia: a comparative study. Journal of Clinical Psychiatry 2007;68: 917–23.

Bobes J, Arango C, Aranda P, Carmena R, Garcia-Garcia M, Rejas J. Cardiovascular and metabolic risk in outpatients with schizophrenia treated with antipsychotics: results of the CLAMORS study. Schizophrenia Research 2007;90:162–73.

Chagnon YC. Susceptibility genes for the side effect of antipsychotics on body weight and obesity. Current Drug Targets 2006;7:1681–95.

Chiolero A, Prior J, Bovet P, Masson JC, Darioli R. Expectation to improve cardiovascular risk factors control in participants to a health promotion program. Journal of General Internal Medicine 2008;23:615–8.

Choong E, Rudaz S, Kottelat A, Guillarme D, Veuthey JL, Eap CB. Therapeutic drug monitoring of seven psychotropic drugs and four metabolites in human plasma by HPLC-MS. Journal of Pharmaceutical and Biomedical Analysis 2009;50: 1000–8.

Cohn TA, Remington G. Risk factors for coronary heart disease in longer term patients on antipsychotic medication: high prevalence of syndrome X. Schizophrenia Research 2003;60:353–4.

Correll CU, Frederickson AM, Kane JM, Manu P. Equally increased risk for metabolic syndrome in patients with bipolar disorder and schizophrenia treated with second-generation antipsychotics. Bipolar Disorders 2008;10:788–97.

Covell NH, Weissman EM, Essock SM. Weight gain with clozapine compared to first generation antipsychotic medications. Schizophrenia Bulletin 2004;30: 229–40.

De Hert M, Dekker JM, Wood D, Kahl KG, Holt RI, Moller HJ. Cardiovascular disease and diabetes in people with severe mental illness position statement from the European Psychiatric Association (EPA), supported by the European Association for the Study of Diabetes (EASD) and the European Society of Cardiology (ESC). European Psychiatry 2009;24:412–24.

De Hert M, Mittoux A, He Y, Peuskens J. Metabolic parameters in the short- and long-term treatment of schizophrenia with sertindole or risperidone. European Archives of Psychiatry and Clinical Neuroscience 2011;261:231–9.

De Hert M, Van Winkel R, Van Eyck D, Hanssens L, Wampers M, Scheen A, et al. Prevalence of diabetes, metabolic syndrome and metabolic abnormalities in schizophrenia over the course of the illness: a cross-sectional study. Clinical Practice and Epidemiology in Mental Health 2006;2:14.

Documed SA. In: Morant J, editor. Compendium Suisse de Médicaments®. Bâle (Suisse): Documed S.A; 2010.

Fiedorowicz JG, Palagummi NM, Forman-Hoffman VL, Miller DD, Haynes WG. Elevated prevalence of obesity, metabolic syndrome, and cardiovascular risk factors in bipolar disorder. Annals of Clinical Psychiatry 2008;20:131–7.

Firmann M, Mayor V, Vidal PM, Bochud M, Pecoud A, Hayoz D, et al. The CoLaus study: a population-based study to investigate the epidemiology and genetic determinants of cardiovascular risk factors and metabolic syndrome. BMC Cardiovascular Disorders 2008;8:6.

Fondation Suisse de Cardiologie. Chiffres et données sur les maladies cardiovasculaires en Suisse, www.swissheart.ch; 2002 (last access Nov 2011).

Garcia-Portilla MP, Saiz PA, Bascaran MT, Martinez AS, Benabarre A, Sierra P, et al. Cardiovascular risk in patients with bipolar disorder. Journal of Affective Disorders 2009;115:302–8.

Gebhardt S, Haberhausen M, Heinzel-Gutenbrunner M, Gebhardt N, Remschmidt H, Krieg JC, et al. Antipsychotic-induced body weight gain: predictors and a systematic categorization of the long-term weight course. Journal of Psychiatric Research 2009;43:620–6.

Gebhardt S, Haberhausen M, Krieg JC, Remschmidt H, Heinzel-Gutenbrunner M, Hebebrand J, et al. Clozapine/olanzapine-induced recurrence or deterioration of binge eating-related eating disorders. Journal of Neural Transmission 2007;114: 1091–5.

Hasnain M, Vieweg WV, Fredrickson SK, Beatty-Brooks M, Fernandez A, Pandurangi AK. Clinical monitoring and management of the metabolic syndrome in patients receiving atypical antipsychotic medications. Primary Care Diabetes 2009;3:5–15.

Heller S, Hiemke C, Stroba G, Rieger-Gies A, Daum-Kreysch E, Sachse J, et al. Assessment of storage and transport stability of new antidepressant and antipsychotic drugs for a nationwide TDM service. Therapeutic Drug Monitoring 2004;26:459–61.

Homel P, Casey D, Allison DB. Changes in body mass index for individuals with and without schizophrenia, 1987–1996. Schizophrenia Research 2002;55:277–84.

Isomaa B, Almgren P, Tuomi T, Forsen B, Lahti K, Nissen M, et al. Cardiovascular morbidity and mortality associated with the metabolic syndrome. Diabetes Care 2001;24:683–9.

Kinon BJ, Basson BR, Gilmore JA, Tollefson GD. Long-term olanzapine treatment: weight change and weight-related health factors in schizophrenia. Journal of Clinical Psychiatry 2001;62:92–100.

Komossa K, Rummel-Kluge C, Schmid F, Hunger H, Schwarz S, Srisurapanont M, et al. Quetiapine versus other atypical antipsychotics for schizophrenia. The Cochrane Collaboration; 2010.

Lakka HM, Laaksonen DE, Lakka TA, Niskanen LK, Kumpusalo E, Tuomilehto J, et al. The metabolic syndrome and total and cardiovascular disease mortality in middle-aged men. JAMA: Journal of the American Medical Association 2002; 288:2709–16.

Laursen TM, Munk-Olsen T, Nordentoft M, Mortensen PB. Increased mortality among patients admitted with major psychiatric disorders: a register-based study comparing mortality in unipolar depressive disorder, bipolar affective disorder, schizoaffective disorder, and schizophrenia. Journal of Clinical Psychiatry 2007;68:899–907.

Leucht S, Corves C, Arbter D, Engel RR, Li C, Davis JM. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. Lancet 2009;373:31–41.

McElroy SL, Frye MA, Suppes T, Dhavale D, Keck Jr PE, Leverich GS, et al. Correlates of overweight and obesity in 644 patients with bipolar disorder. Journal of Clinical Psychiatry 2002;63:207–13.

McEvoy JP, Meyer JM, Goff DC, Nasrallah HA, Davis SM, Sullivan L, et al. Prevalence of the metabolic syndrome in patients with schizophrenia: baseline results from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial and comparison with national estimates from NHANES III. Schizophrenia Research 2005;80:19–32.

McIntyre RS, Konarski JZ. Tolerability profiles of atypical antipsychotics in the treatment of bipolar disorder. Journal of Clinical Psychiatry 2005;66(Suppl. 3): 28–36.

McIntyre RS, Mancini DA, Basile VS. Mechanisms of antipsychotic-induced weight gain. Journal of Clinical Psychiatry 2001;62(Suppl. 23):23–9.
Meyer JM. Strategies for the long-term treatment of schizophrenia: real-world lessons from the CATIE trial. Journal of Clinical Psychiatry 2007;68(Suppl. 1): 28–33.
Musselman DL, Evans DL, Nemeroff CB. The relationship of depression to cardiovascular disease: epidemiology, biology, and treatment. Archives of General Psychiatry 1998;55:580–92.
National Institute of Health. Third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III); 2002. Final Report.
Newcomer JW. Second-generation (atypical) antipsychotics and metabolic effects: a comprehensive literature review. CNS Drugs 2005;19(Suppl. 1):1–93.
Newcomer JW, Haupt DW. The metabolic effects of antipsychotic medications. Canadian Journal of Psychiatry 2006;51:480–91.
Office fédéral de la statistique-Neuchâtel Suisse. Statistique de la santé, http://www.bfs.admin.ch/bfs/portal/fr/index.html; 2009 (last access Nov 2011).
Osby U, Correia N, Brandt L. Mortality and causes of death in schizophrenia on Stockholm County, Sweden. Schizophrenia Research 2000;45:21–8.
Pregibon D. Data analytic methods for generalized linear models. Toronto: University of Toronto; 1979.
Pregibon D. Goodness of link tests for generalized linear models. Applied Statistics 1980;29:15–24.
R Development Core Team. R: a language and environment for statistical computing. Vienna, Austria: R Fondation for Statistical Computing, http://www.R-project.org; 2010 (last access Nov 2011).
Russell JM, Mackell JA. Bodyweight gain associated with atypical antipsychotics: epidemiology and therapeutic implications. CNS Drugs 2001;15:537–51.
Salvi V, Albert U, Chiarle A, Soreca I, Bogetto F, Maina G. Metabolic syndrome in Italian patients with bipolar disorder. General Hospital Psychiatry 2008;30: 318–23.
Schokker DF, Visscher TL, Nooyens AC, Van Baak MA, Seidell JC. Prevalence of overweight and obesity in the Netherlands. Obesity Reviews 2007;8:101–8.
Sicras A, Rejas J, Navarro R, Serrat J, Blanca M. Metabolic syndrome in bipolar disorder: a cross-sectional assessment of a Health Management Organization database. Bipolar Disorders 2008;10:607–16.
Simon V, Van Winkel R, De Hert M. Are weight gain and metabolic side effects of atypical antipsychotics dose dependent? A literature review. Journal of Clinical Psychiatry 2009;70:1041–50.
Stahl SM. Stahl's essential psychopharmacology – neuroscientific basis and practical applications. New York: Cambridge University Press; 2008.
Stroup TS, Lieberman JA, McEvoy JP, Davis SM, Swartz MS, Keefe RS, et al. Results of phase 3 of the CATIE schizophrenia trial. Schizophrenia Research 2009;107:1–12.
Taylor DM, McAskill R. Atypical antipsychotics and weight gain – a systematic review. Acta Psychiatrica Scandinavica 2000;101:416–32.
Theisen FM, Linden A, Konig IR, Martin M, Remschmidt H, Hebebrand J. Spectrum of binge eating symptomatology in patients treated with clozapine and olanzapine. Journal of Neural Transmission 2003;110: 111–21.
Tschoner A, Engl J, Laimer M, Kaser S, Rettenbacher M, Fleischhacker WW, et al. Metabolic side effects of antipsychotic medication. International Journal of Clinical Practice 2007;61:1356–70.
Tukey JW. One degree of freedom for non-additivity. Biometrics 1949;5:232–42.
Umbricht DS, Pollack S, Kane JM. Clozapine and weight gain. Journal of Clinical Psychiatry 1994;55(Suppl. B):157–60.
Van der Kooy K, Van Hout H, Marwijk H, Marten H, Stehouwer C, Beekman A. Depression and the risk for cardiovascular diseases: systematic review and meta analysis. International Journal of Geriatric Psychiatry 2007;22: 613–26.
Van Winkel R, De Hert M, Van Eyck D, Hanssens L, Wampers M, Scheen A, et al. Prevalence of diabetes and the metabolic syndrome in a sample of patients with bipolar disorder. Bipolar Disorders 2008a;10:342–8.
Van Winkel R, Van Os J, Celic I, Van Eyck D, Wampers M, Scheen A, et al. Psychiatric diagnosis as an independent risk factor for metabolic disturbances: results from a comprehensive, naturalistic screening program. Journal of Clinical Psychiatry 2008b;69:1319–27.
Vieweg WVR, Levy JR, Fredrickson SK, Chipkin SR, Beatty-Brooks M, Fernandez A, et al. Psychotropic drug considerations in depressed patients with metabolic disturbances. American Journal of Medecine 2008;121:647–55.
Weiden PJ, Mackell JA, McDonnell DD. Obesity as a risk factor for antipsychotic noncompliance. Schizophrenia Research 2004;66:51–7.
Wetterling T, Mussigbrodt HE. Weight gain: side effect of atypical neuroleptics? Journal of Clinical Psychopharmacology 1999;19:316–21.
Wirshing DA, Wirshing WC, Kysar L, Berisford MA, Goldstein D, Pashdag J, et al. Novel antipsychotics: comparison of weight gain liabilities. Journal of Clinical Psychiatry 1999;60:358–63.
Wood SN. GAMMs with R. In: Carlin BP, Chatfield C, Tanner M, Zidek J, editors. Generalized additive models – an introduction with R. Broken. Chapman & Hall/CRC; 2006. p. 319–24.
Zheng L, Mack WJ, Dagerman KS, Hsiao JK, Lebowitz BD, Lyketsos CG, et al. Metabolic changes associated with second-generation antipsychotic use in Alzheimer's disease patients: the CATIE-AD study. American Journal of Psychiatry 2009;166:583–90.
Zimmermann U, Kraus T, Himmerich H, Schuld A, Pollmächer T. Epidemiology, implications and mechanisms underlying drug-induced weight gain in psychiatric patients. Journal of Psychiatric Research 2003;37:193–220.