European Psychiatry 30 (2015) 277–283

Contents lists available at ScienceDirect

European Psychiatry

journal homepage: http://www.europsy-journal.com

Original article

Changes in body mass and metabolic profiles in patients with first-episode schizophrenia treated for 12 months with a first-generation antipsychotic

B. Chiliza [a,*], L. Asmal [a], P. Oosthuizen [a], E. van Niekerk [b], R. Erasmus [c], M. Kidd [d], A. Malhotra [e], R. Emsley [a]

[a] Department of Psychiatry, Faculty of Medicine and Health Sciences, Stellenbosch University, Tygerberg, South Africa
[b] Division of Human Nutrition, Faculty of Medicine and Health Sciences, Stellenbosch University, Tygerberg, South Africa
[c] Division of Chemical Pathology, Faculty of Medicine and Health Sciences, Tygerberg, South Africa
[d] Centre for Statistical Consultation, Stellenbosch University, Stellenbosch, South Africa
[e] Division of Psychiatry Research, The Zucker Hillside Hospital, Glen Oaks, New York, USA

ARTICLE INFO

Article history:
Received 24 May 2014
Received in revised form 26 November 2014
Accepted 27 November 2014
Available online 7 January 2015

Keywords:
First-episode schizophrenia
Flupenthixol
Weight gain
Metabolic syndrome
Developing countries

ABSTRACT

Objectives: To assess changes in body mass and metabolic profiles in patients with first-episode schizophrenia receiving standardised, assured treatment and to identify predictors and moderators of the effects.
Methods: We investigated the changes in body mass, fasting blood glucose and lipids in 107 largely antipsychotic naïve, first-episode schizophrenia patients who were treated according to a standard algorithm with long-acting injectable flupenthixol decanoate over 12 months.
Results: Eighty-three (78%) participants completed the 12 months of treatment, and 104 (97%) received 100% of the prescribed injections during their participation. There were significant increases in BMI ($P < .0001$), waist circumference ($P = 0.0006$) and triglycerides ($P = 0.03$) and decrease in HDL ($P = 0.005$), while systolic ($P = 0.7$) and diastolic blood pressure ($P = 0.8$), LDL ($P = 0.1$), cholesterol ($P = 0.3$), and glucose ($P = 0.9$) values did not change over time. The triglyceride: HDL ratio increased by 91%. Change in BMI was only correlated with change in triglycerides ($P = .008$). The only significant predictor of BMI increase was non-substance abuse ($P = .002$).
Conclusions: The risks of weight gain and metabolic syndrome associated with antipsychotic treatment in first-episode schizophrenia are not restricted to second generation antipsychotics. This is a global problem, and developing communities may be particularly susceptible.
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1. Introduction

Patients with schizophrenia are at increased risk of weight gain, metabolic syndrome (MetS), cardiovascular disease and mortality [29]. While factors such as sedentary lifestyle [6], smoking and poor diet play a role [41], it is now recognised that antipsychotics, via their adipogenic and dysmetabolic effects, are major contributors [10,15]. Young people experiencing a first-episode of psychosis with no or limited previous antipsychotic exposure are most susceptible [4,9,17,35,48]. The risk of weight gain varies amongst individuals and this may be genetically determined [27]. Also, the risk varies between individual antipsychotics. While most attention has focused on second-generation antipsychotics (SGAs), low potency first-generation antipsychotics (FGAs) are reported to carry a similar risk [26]. Other FGAs have not been associated with weight gain and, apart from haloperidol, have not generally been studied–despite the fact that they continue to be extensively used, particularly in lower-income countries. Considerable attempts have been made to identify clinical and laboratory predictors of weight gain. Predicting patients at risk for weight gain would be beneficial as interventions could then be tailored specifically to those patients who are at highest risk of weight gain. Previously identified predictors of weight gain have included sex, age, ethnicity and low BMI [48], however there have been conflicting results. Advances in pharmacogenomics have yielded the most promising results in predicting severe weight gain in some individuals [8].

* Corresponding author. Department of Psychiatry, Faculty of Medicine and Health Sciences, Stellenbosch University, Tygerberg 7505, Cape Town, South Africa Tel.: +27 21 938 9227; fax: +27 21 938 9738.
E-mail address: bonga@sun.ac.za (B. Chiliza).

http://dx.doi.org/10.1016/j.eurpsy.2014.11.013
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Estimates of the effects of antipsychotics on body mass and metabolic profiles are confounded by many factors, thereby making it impossible to draw firm conclusions from much of the published literature [18]. Many studies are limited by factors such as small sample sizes, brief evaluation periods, poorly characterised patient samples, non-standardisation of treatment and failure to assess the effects of dosage and non-adherence. Furthermore, interpretation of study results is often complicated by the use of inappropriate statistical analyses. For example, last-observation carried forward (LOCF) analyses are likely to underestimate drug effects [18,21,48], as longitudinal studies frequently have high rates of discontinuation. Similarly, observed cases, or per protocol samples may be biased as reasons for study discontinuation may not be random. Non-adherence is also likely to be a major cause of underreporting of effects of antipsychotics on body mass and metabolic profiles, with most studies either not assessing adherence, or utilising methods with inherent inaccuracies [46]. Non-adherence may be particularly relevant in early psychosis, given the very high rates reported in early phases of treatment of schizophrenia [18,45]. Finally, notwithstanding the fact that comorbid substance abuse is very common in schizophrenia, many studies either excluded these patients from their samples, or failed to assess their effects on body mass and metabolic changes. The above limitations have been highlighted and additional recommendations made, including the testing for dosage effects, controlling for age and sex and adoption of Consolidated Standards of Reporting Trials (CONSORT) [38] or Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) [47] guidelines to increase accuracy of reporting and of interpreting [18].

We conducted a study that was able to address several of these potential confounders. We selected first-episode, largely treatment-naïve patients and conducted regular, standardised assessments of body mass and metabolic profile during the course of treatment according to a standard protocol, with a single long-acting injectable antipsychotic which provided assured medication adherence. Also, we excluded comorbid medical conditions and carefully assessed the role of substance abuse. Studies to date have involved predominantly Caucasian and Chinese patient samples [44]. As far as we are aware, this is the first longitudinal study assessing weight-gain and its metabolic concomitants in an African sample, and the cohort, comprising largely individuals of mixed ancestry from the greater Cape Town region, may represent an economically emerging, particularly at-risk community for metabolic syndrome [14]. Finally, to the best of our knowledge this is the first study prospectively assessing the effects of flupenthixol on body mass and metabolic profiles.

Our study aimed to assess changes in body mass and metabolic profiles in patients with first-episode schizophrenia receiving standardised, assured treatment over 12 months, and to identify predictors and moderators of these effects. We hypothesised that there would be substantial weight gain which would be significantly correlated with changes in lipid and glucose profiles, and emergent cases of MetS.

2. Methods

This was a single-site cohort study. Approval was obtained from the Human Research Ethics Committee of Stellenbosch University Faculty of Medicine and Health Sciences. The study was conducted in accordance with the International Conference on Harmonization guidelines on good clinical practice (GCP) [23] and was registered at the South African National Clinical Trials Register (DOH-27-0710-1957), URL: www.sanctr.gov.za/SAClinicalTrials/tabid/169/Default.aspx.

3. Participants

Subjects were recruited from first-admissions to psychiatric hospitals and community clinics within our catchment areas in Cape Town between April 2007 and March 2011. Patients and/or their legal guardians provided written, informed consent. Eligible participants were men and women, in- or outpatients, aged 16 to 45 years, meeting Diagnostic and Statistical Manual of Mental Diseases, Fourth Edition (DSM-IV) [5] diagnostic criteria for schizophreniform disorder, schizophrenia or schizo-affective disorder. Patients were excluded if they had, during their lifetime, been exposed to >4 weeks of antipsychotic medication, been treated with a long-acting depot antipsychotic, had a serious or unstable medical condition, mental retardation or overt substance abuse.

4. Assessments

A physical examination was conducted at the start and completion of the study. For anthropometric measurements patients removed all surplus clothing including shoes and socks and were weighed on a regularly calibrated electronic scale. Waist circumference (WC) was measured between the lowest rib and the iliac crest with patients standing upright and breathing normally. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of height in meters. Weight was assessed at baseline, week 6, and months 3, 6, 9 and 12. Laboratory tests were conducted at baseline, 3, 6 and 12 months. Laboratory tests comprised fasting glucose, high density lipoprotein cholesterol (HDL), low density lipoprotein cholesterol (LDL), triglycerides and total cholesterol, as well as urine toxicology for cannabis, methaphetamines and methaqualone. For these tests patients fasted for at least 8 hours overnight and rested for 10 min prior to venipuncture. We used the Adult Treatment Panel (ATP III-A) criteria proposed by the American Heart Association for MetS [2]. MetS criteria comprise raised blood pressure, raised triglycerides, lowered high-density lipoprotein cholesterol, raised fasting blood glucose, and central obesity according to WC. Cut-off values for WC (≥ 90 cm men, ≥ 80 cm women) were adapted to our specific population norms [28]. Abnormal values for any 3 of the 5 criteria would qualify an individual for MetS.

Patients were assessed with the Structured Clinical Interview for DSM-IV (SCID) [16] and psychopathology was assessed by the Positive and Negative Syndrome Scale (PANSS) [24] and the Calgary Depression Scale for Schizophrenia (CDSS) [1]. Clinical outcomes will be reported separately.

5. Treatment

There was a one week lead-in period of oral flupenthixol 1 to 3 mg/day followed by long acting flupenthixol decanoate injections every two weeks for the duration of the study. The initiation dose was 10 mg 2-weekly. Additional oral flupenthixol was prescribed at the discretion of the investigator. Permitted concomitant treatment included medication for general medical conditions, lorazepam for sedation, orphenadrine or biperiden for extrapyramidal symptoms and propranolol for akathisia. No benzodiazepines, propranolol or anticholinergics were permitted in the 12 hours prior to assessments. Medications not permitted included other antipsychotics, mood stabilizers and psychostimulants.

6. Statistical methods

Analyses were performed on a modified intent-to-treat basis, meaning that all patients were included in the analysis if they had a

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