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Weight gain and metabolic change as predictors of symptom improvement in first-episode schizophrenia spectrum disorder patients treated over 12 months

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ABSTRACT

Background: Treatment-emergent weight gain is associated with antipsychotic efficacy in schizophrenia patients treated with clozapine and olanzapine. However, few studies have investigated this relationship in first-episode patients treated with other antipsychotics, in particular those with a lower obesogenic potential.

Aim

To investigate the relationships between weight gain and associated metabolic changes with psychopathology improvement in relation to age, sex, ethnicity, substance use, treatment duration and antipsychotic dose in first-episode schizophrenia spectrum disorder patients.

Methods: This single site cohort study included 106 minimally treated or antipsychotic-naive patients treated with flupenthixol decanoate over 12 months. Psychopathology was evaluated using the Positive and Negative Syndrome Scale (PANSS) and BMI, fasting blood lipids and glucose were assessed at regular intervals. Linear regression models were constructed to determine the effects of socio-demographic, clinical and metabolic factors as predictors of change in total PANSS score and factor-derived domains.

Results: BMI change scores were inversely correlated with change in PANSS total ($R = -0.25$; $p = 0.011$), positive ($R = -0.23$; $p = 0.019$), depressive anxiety ($R = -0.21$; $p = 0.031$) and disorganized symptoms ($R = -0.32$; $p < 0.001$). Linear regression analysis showed that increased BMI and treatment duration both predicted improvement in global psychopathology and disorganized symptoms independent of age, sex, ethnicity, substance use, co-medication with antidepressants and/or anticholinergics, as well as the dose and duration of antipsychotic exposure.

Conclusions: Our findings suggest that the relationship between treatment-emergent weight gain and psychopathology improvement is not limited to patients treated with antipsychotics most associated with weight gain, and is not confounded by treatment duration and dose.

1. Introduction

An increased prevalence of weight gain and metabolic syndrome in schizophrenia spectrum disorders contributes to elevated risk for cardiovascular disease (CVD) which is associated with excess morbidity and mortality (Riordan et al., 2011). In addition to diet, lifestyle and genetic factors, antipsychotic use has emerged as a major contributor to the higher risk for treatment-emergent metabolic syndrome evident for schizophrenia (Saha et al., 2007; Emul and Kalelioglu, 2015) even in first-episode cases (Tek et al., 2016). The high obesogenic potential of several second-generation antipsychotics is well known, with these drugs also posing an independent risk for metabolic changes associated with obesity (Falissard et al., 2011; Leucht et al., 2013). A recent meta-analysis (Bak et al., 2014) confirms that these changes are not limited to the second-generation antipsychotics and that almost all antipsychotics are associated with weight gain given sufficient treatment exposure. Indeed, certain metabolic abnormalities including hypertension may be more pronounced in patients treated with first-generation antipsychotics (Falissard et al., 2011), underscoring the need for early assessment and monitoring of cardio-metabolic risk in first-episode schizophrenia irrespective of antipsychotic type.

Several early studies dated prior to the introduction of second-generation antipsychotics (Planansky, 1958; Klett and Caffey Jr, 1960) suggested the prognostic importance of weight gain as a marker of favourable treatment outcome. Multiple subsequent studies have also reported that weight gain is associated with decreased global and

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general psychopathology in adult schizophrenia spectrum disorder patients, particularly those treated with clozapine and olanzapine (Sharma et al., 2014). Elevated serum lipids associated with antipsychotic use may also predict psychopathology improvement in acute and long-term settings (Lally et al., 2013; Solberg et al., 2015, 2016). Finally, greater reduction in global psychopathology has been correlated with weight gain (Kemp et al., 2013) and metabolic syndrome (Grover et al., 2016) in adolescent schizophrenia patients. A recent systematic review reported a link between antipsychotic-induced weight gain and therapeutic benefit in 22 (71%) of the 31 independent studies investigated, which collectively included 6063 patients with schizophrenia and related severe mental illnesses (Raben et al., 2018). These findings are in accordance with those reported in a previous review by Sharma et al. (2014) which reported an association between treatment-emergent metabolic changes and antipsychotic efficacy in 14 of the 15 studies evaluated. These systematic review findings support a relationship between weight gain and psychopathology improvement in schizophrenia patients independent of age, sex, ethnicity and prior antipsychotic use. The findings also raise the possibility of a potential shared mechanistic pathway between metabolic changes induced by weight gain and antipsychotic efficacy (Venkatasubramanian et al., 2013).

However, the relationship of metabolic syndrome to disease severity and clinical outcome remains incompletely described (Blin and Micallef, 2001). Several studies have failed to replicate a correlation between antipsychotic-induced weight gain and psychopathology improvement (Umbricht et al., 1994; Hummer et al., 1995). Further, the majority of reported associations of weight gain to date have been with global and general psychopathology, while mixed results were reported for positive and negative symptoms (Czobor et al., 2002; Procyshyn et al., 2007), and the illness-specificity of these findings has been questioned. In addition, the causal basis for such a relationship remains unclear, as reports of an association between weight loss and exacerbation of psychosis are conflicting (Chen et al., 2014; Chukhin et al., 2016). In addition, it remains unclear whether switching to antipsychotics with a lower obesogenic potential influences the effect of weight gain on treatment outcomes. Outcome studies to date are further limited by important confounders including variable treatment end-points and inconsistent approaches to dealing with dropouts, non-standardised antipsychotic treatment of patients, not assessing the role of adherence, and including chronic schizophrenia samples where previous medication and illness chronicity may affect outcome (Raben et al., 2018). Lastly, the potential modulating effects of add-on treatment such as antidepressants (Terevnikov et al., 2013; Lu et al., 2017) have not been extensively considered.

There is a critical lack of evidence from prospective longitudinal studies assessing the relationships between treatment-emergent weight gain/metabolic changes and treatment response in patients treated with antipsychotics other than the more commonly studied second generation drugs clozapine and olanzapine represented in most investigations to date. Importantly, most studies to date have also failed to control for adherence and compliance in a systematic fashion, in addition to limiting investigation to the acute stage of treatment, typically less than six months duration (Raben et al., 2018). It is also not always clear whether duration of treatment exposure has been considered. However, it stands to reason that patients with greater antipsychotic exposure are likely to gain more weight, and at the same time show greater reduction of symptoms. In addition, with the exception of limited early studies of schizophrenia patients treated with haloperidol (Bustillo et al., 1996), no studies have explored the link between weight gain and psychopathology improvement in first-episode patients treated with relatively "weight-neutral" (e.g. aripiprazole, ziprasidone) or depot (e.g. flupenthixol decanoate) antipsychotics. To the best of our knowledge, no outcome studies have further sought to evaluate the relationships with particular symptom domains consistently identified using factor analyses (Emsley et al., 2003; Jerrell and Hrisko, 2013).

In a previous study (Chiliza et al., 2015), we used linear mixed effects for continuous repeated measures (MMRM) to demonstrate a significant visit-wise increase in body mass index (BMI) in antipsychotic-naïve or minimally treated first-episode schizophrenia patients (n = 107) over 12 months of standardised treatment with flupenthixol decanoate, independent of age, sex, and end-point antipsychotic dose. In the present study, we sought to build on these existing findings by evaluating the relationships between treatment-emergent weight gain, metabolic changes and psychopathology improvement, drawing from the abovementioned patient cohort. In this context, we focused on linear regression analysis selected as the most appropriate statistical approach to establishing the effects of metabolic change scores as predictors of change in psychopathology over the course of antipsychotic treatment in relation to socio-demographic, clinical and treatment-related covariates.

2. Materials and methods

2.1. Study design and ethics approval

This was a single-site longitudinal study which recruited antipsychotic-naïve or minimally treated patients with first-episode schizophrenia spectrum disorders (schizophrenia, schizophreniform or schizoaffective disorder). Ethical approval was obtained from the Health and Research Ethics Committee (HREC) at Stellenbosch University (SU) (N06/08/148). Written, informed consent was obtained from participants and where appropriate, from a legal guardian. Our study was conducted in accordance with the International Conference on Harmonization Good Clinical Practice guidelines (International Conference on Harmonization, 1996).

2.2. Selection of study participants

Study participants were selected, as part of an ongoing study, from first admissions to hospitals and community clinics in the metro and rural areas of North Eastern Cape Town, the Winelands and the West Coast over a four year period (2007–2011). Inclusion criteria were men and women, in- or out- patients, aged 18 to 45 years, with a first psychotic episode meeting Diagnostic and Statistical Manual of Mental Diseases, Fourth Edition, Text Revisions (DSM-IV TR) (American Psychiatric Association, 1994) criteria for schizophrenia, schizophreniform or schizoaffective disorder. Exclusion criteria were: lifetime exposure to >4 weeks of antipsychotic medication, serious or unstable medical condition, psychosis arising from acute substance intoxication, and intellectual disability.

2.3. Antipsychotic treatment

Patients were treated according to a fixed protocol with flupenthixol decanoate. First-choice treatment with a depot antipsychotic was based on evidence that their greatest benefits may be observed early in the illness by improving adherence and preventing accruing morbidity, as well as their demonstrated efficacy and tolerability in this population (Chue and Emsley, 2007). We chose flupenthixol decanoate as the best-tolerated depot that was available in the public sector in South Africa. There was a seven-day lead-in with oral flupenthixol 1–3 mg/day followed by flexible doses of flupenthixol decanoate. The starting dose was 10 mg IM 2-weekly. The lowest possible dose was maintained, and only increased when an insufficient response persisted. Additional oral flupenthixol was permitted, but seldom prescribed. Permitted concomitant medications included lorazepam, biperidin, orphenadrine, propranolol and antidepressants. In order to minimize the potential effects of additional treatment on metabolic status, benzodiazepines, anticholinergics and propranolol were not allowed within 12 h of the time of assessment. Prohibited medications included other antipsychotics, mood stabilizers and psychostimulants.

2.3.1. Clinical assessments

Patients were assessed with the Structured Clinical Interview for DSM-IV (SCID) (First et al., 1994) and psychopathology was assessed by the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Evaluation of psychopathology symptom categories was performed by calculating PANSS factor analysis-derived domains (i.e. positive, negative, depressive-anxiety, disorganized and exhibition-hostility symptoms) (Emsley et al., 2003). Remission status was also assessed using the Remission in Schizophrenia Working Group (RSWG) consensus criteria proposed by Andreasen et al. (2005).

2.3.2. Metabolic assessments

A physical examination was performed at baseline and study completion. Body weight was measured at baseline, week 6, and months 3, 6, 9 and 12. Patients removed all surplus clothing including their socks and shoes and were weighed on an electronic scale that was regularly calibrated throughout the study. Height was measured with a pre-fixed wall-mounted measuring tape. Body mass index (BMI) was also calculated as the patient's body weight in kilograms (kg) divided by their height in meters squared (m^2). While we also measured waist circumference, we did not use this in the analyses, due to a large number of missing values (n = 26, 25%). Systolic (SBP) and diastolic (DBP) blood pressures were assessed at baseline and at months 3, 6 and 12. A peripheral venous blood sample was collected from participants following an eight hour fasting period and ten minute rest prior to venepuncture. Biochemical testing was performed at baseline and again at months 3, 6, 9 and 12, and included assessment of the fasting lipid profile (triglycerides, total, LDL and HDL cholesterol) and glucose levels.

2.3.3. Urine toxicology

Urine toxicology was performed at baseline and again at months 3, 6 and 12 to assess use of cannabis, methaqualone and methamphetamine over the course of the study. Patients who tested positive on any occasion were classified as substance use positive.

2.4. Statistical analysis

Statistical analyses were performed using the R Studio software package. All participants with at least one baseline and one follow-up measure were included for analysis. End-point scores were calculated by last observation carried forward. Clinical and metabolic change scores were calculated by subtracting the baseline score from the end-point score. Descriptive statistics and graphical summaries were used to assess whether the key variables meet standard assumptions for the planned analyses and to identify outliers. Non-normal data was log-transformed prior to analysis. Categorical variables were described using cross-tabulation and frequency tables and compared between study groups using the Pearson's Chi-Squared or Fisher's exact tests. Normality of distribution for numerical variables was established using the Shapiro-Wilk test. For normally distributed data, quantitative phenotypes were described as the means along with standard deviation (SD) and compared between study groups using a Student's *t*-test. Linear correlations were described using the Pearson's correlation or Spearman's rank correlation as applicable. Post-hoc Bonferroni corrections were performed where applicable to correct for multiple comparisons across the six psychopathology domains of interest (i.e. PANSS total score as well as positive, negative, disorganized, depressive-anxiety and excitement-hostility domains). Linear regression models were constructed to evaluate the role of metabolic change scores as predictors of psychopathology improvement in relation to socio-demographic (age, sex, ethnicity), clinical (substance use) and treatment-related (antipsychotic dose, treatment duration, antidepressant and/or anticholinergic co-medication)variables.

3. Results

3.1. Baseline characteristics of study population

Our study included 106 antipsychotic-naïve or minimally treated first-episode schizophrenia spectrum disorder patients (77 males, 29 females; mean age = 24.2 years). In total, 79 patients had a DSM-IV diagnosis of schizophrenia, while 26 patients were diagnosed with schizophreniform disorder, and one patient with schizoaffective disorder. Forty-one (39%) patients had a family history of schizophrenia. Mean duration of untreated psychosis (DUP) for the total sample was 34 weeks. Our sample consisted of self-reported Mixed Ancestry (n = 81, 76%), as well as Caucasian (n = 15, 14%) and Black African (n = 10, 9%) patients. The distribution of male to female patients was representative of that observed in our larger study sample (Chiliza et al., 2015) and reflects the sex distribution of patients presenting to the health care services in our catchment area. The 2-weeklymean modal dose of depot flupenthixol decanoate was 10 mg in the majority (n = 67; 63%) of patients, 15 mg in 15 (14%) patients, 20 mg in 12 (11%) patients, 5 mg in five (5%)patients, and 20 mg in one (1%) patient. In addition, 29 (27%) patients used benzodiazepines and three (3%) propranolol as needed over the course of the study, while 17 (16%) were prescribed anticholinergic drugs, and nine (8%) antidepressants. In total, 22 (21%) patients received antidepressant and/or anticholinergic co-medication, which were considered of interest as a treatment-related confounder due to their known association with weight gain and associated metabolic syndrome changes. A total of 64 (60%) patients completed the month 12 assessment; 98 (92%) patients had a treatment period of at least six months necessary to assess symptomatic remission status according to the RSWG criteria, with 63 (64%) attaining symptomatic remission.

A comparison of the baseline and end-point values for clinical and metabolic parameters is presented in Table 1. There was a significant decrease in PANSS total score as well as all factor-derived domains (i.e. positive, negative, disorganized, depressive-anxiety and excitement-hostility symptoms) from baseline to end-point (all $p < 0.001$). Mean BMI ($p < 0.001$) and triglycerides ($p < 0.001$) significantly increased, while HDL cholesterol significantly decreased ($p = 0.001$) from baseline to end-point. SBP, DBP and glucose did not change significantly from baseline to end-point. Visit-wise changes in BMI over the course of antipsychotic treatment in relation age, sex and end-point

Table 1
Comparison of baseline and end-point scores for clinical and metabolic characteristics of total study group.

Characteristic	Baseline scores Mean (SD)	End-point scores Mean (SD)	Unadjusted p-value
Clinical			
PANSS total score	94.64 (15.90)	48.16 (13.48)	<0.001
PANSS positive symptoms	17.36 (3.26)	6.06 (3.10)	<0.001
PANSS negative symptoms	20.14 (5.41)	11.52 (4.62)	<0.001
PANSS disorganized symptoms	11.98 (2.90)	6.48 (2.39)	<0.001
PANSS depressive-Anxiety symptoms	9.08 (4.25)	5.39 (2.48)	<0.001
PANSS excitement-hostility symptoms	8.29 (3.84)	4.71 (1.64)	<0.001
Metabolic			
Body mass index (kg/m2)	21.68 (3.87)	24.38 (4.97)	<0.001
Systolic BP (mmHg)	121.19 (13.66)	123.24 (12.49)	0.256
Diastolic BP (mmHg)	79.54 (10.34)	79.91 (10.18)	0.794
Glucose (mmol/L)	4.78 (0.71)	4.97 (1.37)	0.205
HDL cholesterol (mmol/L)	1.17 (0.55)	0.98 (0.26)	0.001
Triglycerides (mmol/L)	0.88 (0.52)	1.22 (0.85)	<0.001

PANSS = Positive and Negative Symptom Scale; BP = blood pressure; HDL = high-density lipoprotein.

flupenthixol dose were previously described in our study cohort (see Chiliza et al., 2015).

3.2. Relationship between weight loss and psychopathology change scores

A total of 20 (19%) patients lost weight over the course of our study; no significant differences in clinical change scores were noted between this subgroup and the rest of the study population ($p > 0.05$).

3.3. Relationship between metabolic change scores and treatment characteristics

DUP, modal antipsychotic dose and treatment duration were not significantly associated with any of the metabolic change scores of interest ($p > 0.05$). Weight gain and associated metabolic change scores were compared between remitters ($n = 63$) and non-remitters ($n = 35$) in a subgroup of 98 patients for whom sustained symptomatic remission could be assessed. No significant differences in change scores for BMI, SBP, DBP, glucose, triglycerides or HDL cholesterol were noted between remitters and non-remitters.

3.4. Correlation between baseline psychopathology and metabolic characteristics

In the total study group, triglyceride levels were negatively correlated with disorganized symptom severity at baseline ($r = -0.29$, $p = 0.002$). This correlation retained significance following post-hoc Bonferroni correction (0.008). A trend was also noted for an inverse association between triglycerides and total PANSS score at baseline ($r = -0.16$, $p = 0.065$). BMI, glucose and HDL cholesterol were not significantly correlated with total PANSS score or any specific symptom domain at baseline (Table 2).

3.5. Correlations between psychopathology improvement and metabolic change scores

BMI change scores were inversely correlated with change in PANSS total ($r = -0.25$; $p = 0.011$) as well as positive ($r = -0.23$; $p = 0.019$), depressive-anxiety ($r = -0.21$; $p = 0.031$) and disorganized symptoms ($r = -0.32$; $p < 0.001$) but not negative or excitement-hostility symptoms ($p > 0.05$). The inverse correlation between BMI and disorganized symptom change scores (Fig. 1) survived Bonferroni correction (0.008). Change in fasting glucose was inversely correlated with change in positive symptoms ($r = -0.21$; $p = 0.034$), while change in triglycerides was inversely associated with change in disorganized symptoms ($r = -0.20$; $p = 0.040$). SBP, DBP and HDL change scores were not significantly related to improvement in global psychopathology or factor-derived symptom domains (Table 3).

3.6. Metabolic factors as predictors of psychopathology improvement

Separate linear regression models were constructed with change scores for global psychopathology (model 1) and the domains of disorganized (model 2), positive (model 3) and depressive-anxiety (model 4) symptoms as dependent variables, selected based on their significant correlations with metabolic parameter change scores on initial analysis. We entered BMI and metabolic change scores as predictors and socio-demographic (age, sex, ethnicity), clinical (substance use) as well as treatment-related (antipsychotic dose, treatment duration, co-medication with antidepressants and/or anticholinergics) factors as covariates. In model 1 ($R^2 = 0.26$, $F(14,89) = 2.29$, $p = 0.010$), BMI change scores ($\beta = -1.25$, $p = 0.061$) and treatment duration ($\beta = -0.72$, $p < 0.001$) were independent predictors of the variance in PANSS total symptoms. In model 2 ($R^2 = 0.28$, $F(14,89) = 2.50$, $p = 0.005$), BMI change scores ($\beta = -0.29$, $p = 0.004$) and treatment duration ($\beta = -0.09$, $p = 0.002$) were also significant predictors of the variance in PANSS disorganized symptoms. In model 3, ($R^2 = 0.30$, $F(14,89) = 2.73$, $p = 0.002$), only treatment duration ($\beta = -0.16$, $p < 0.001$) was a significant predictor of the variance in positive symptoms. Model 4 was not significant for improvement in depressive-anxiety symptoms ($R^2 = 0.17$, $F(14,89) = 1.27$, $p = 0.241$).

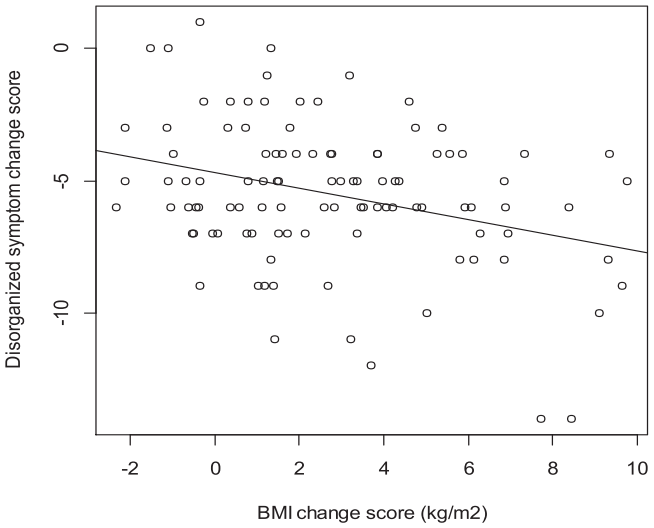

Fig. 1. Scatterplot diagram illustrating a significant inverse association between change scores for body mass index (BMI) and the disorganized symptom domain.

4. Discussion

The main finding from the present study was that increased BMI significantly correlated with improved global psychopathology and the disorganized symptoms of schizophrenia over the first 12 months of antipsychotic treatment. This association remained significant after controlling for the effects of age, sex, ethnicity, substance use, co-medication with antidepressants and/or anticholinergics, as well as the dose and duration of antipsychotic exposure. These findings are in accordance with those reported in previous studies suggesting a link

Table 2
Results from correlation analysis evaluating the linear relationship between clinical symptoms and metabolic parameters at baseline, presented as the R-value and corresponding unadjusted p-values.

	PANSS total baseline	Positive baseline	Negative baseline	Disorganized baseline	Depressive-anxiety baseline	Excitement-hostility baseline
BMI (kg/m2) baseline	−0.11; 0.265	0.04; 0.650	−0.07; 0.487	−0.12; 0.219	−0.05; 0.646	−0.03; 0.778
SBP (mmHg) baseline	−0.04; 0.659	−0.10; 0.305	0.04; 0.661	0.06; 0.565	−0.07; 0.474	−0.11; 0.253
DBP (mmHg) baseline	−0.04; 0.685	−0.04; 0.719	0.07; 0.464	−0.09; 0.381	0.04; 0.713	−0.10; 0.291
Glucose (mmol/L) baseline	−0.04; 0.648	0.01; 0.916	−0.02; 0.869	−0.13; 0.182	−0.08; 0.410	0.05; 0.609
HDL cholesterol (mmol/L) baseline	−0.01; 0.936	0.05; 0.633	0.06; 0.523	−0.06; 0.565	0.04; 0.710	−0.14; 0.157
Triglycerides (mmol/L) baseline	−0.16, 0.065	−0.01; 0.912	−0.14; 0.153	−0.29; 0.002	0.01; 0.903	−0.09; 0.375

PANSS = Positive and Negative Symptom Scale; BP = blood pressure; HDL = high-density lipoprotein.

Table 3
Results from correlation analysis evaluating the linear relationship between clinical and metabolic change scores, presented as the R-value and corresponding unadjusted p-values.

	PANSS total change	Positive change	Negative change	Disorganized change	Depressive-anxiety change	Excitement-hostility change
BMI (kg/m2) change	−0,25; 0.011	−0.23; 0.019	−0.09; 0.364	−0.32; <0.001	−0.21; 0.031	−0.02; 0.866
SBP (mmHg) change	0.06; 0.524	<−0.01; 0.973	0.07; 0.507	0.05; 0.594	0.06; 0.538	−0.02; 0.868
DBP (mmHg) change	<−0.01; 0.925	<0.01; 0.926	0.06; 0.570	0.01; 0.934	0.06; 0.539	−0.12; 0.240
Glucose (mmol/L) change	−0.06; 0.513	−0.21; 0.034	0.11; 0.256	−0.01; 0.935	0.02; 0.874	−0.04; 0.717
HDL cholesterol (mmol/L) change	<0.01; 0.978	0.10; 0.308	0.02; 0.832	−0.04; 0.674	−0.06; 0.509	−0.11; 0.268
Triglycerides (mmol/L) change	−0.09; 0.341	−0.13; 0.168	−0.13; 0.176	−0.20; 0.040	0.02; 0.846	0.06; 0.550

PANSS = Positive and Negative Symptom Scale; BP = blood pressure; HDL = high-density lipoprotein.

between treatment-emergent weight gain and therapeutic response in schizophrenia spectrum disorder patients (Sharma et al., 2014; Raben et al., 2018).

Importantly, our results extend previous research insofar as we were able to exclude several important factors that may have confounded these findings. First, we were able to control precisely for dose and duration of antipsychotic exposure. Similarly, poor adherence is likely associated with both worse outcome and reduced obesogenic effect of antipsychotics. Our use of depot formulation antipsychotic provided assured delivery and removed the confounding effect of non-adherence. This may be important, given the very high rates non- and partial adherence reported in the early stages of illness (Coldham et al., 2002). Additionally, by including only first-episode and minimally treated or never treated patients, we removed the effects of illness chronicity and previous medication. Finally, by standardising treatment with a single antipsychotic we addressed the potential confound of differential treatment effects in terms of both efficacy and weight gain. To the best of our knowledge, this is the first study to report an independent effect of weight gain on improvement in disorganized symptoms in a sample treatment-naïve or minimally treated patients with schizophrenia spectrum disorder. Most previous studies reporting a relationship between metabolic side effects and clinical improvement were conducted in chronic samples. Also, most studies investigated patients treated with clozapine and olanzapine - the two antipsychotics associated with the greatest risk of weight gain - with other drugs being poorly represented (Sharma et al., 2014).

Our results suggest that the relationship is not restricted to these two drugs, and may be present even with antipsychotics less frequently associated with weight gain. Indeed, flupenthixol is considered to be relatively "weight neutral" (Messer et al., 2009), although first-episode patients are more susceptible and significant weight gain has been reported in these patients (Chiliza et al., 2015). Whether weight gain is a necessary concomitant of efficacy (Sharma et al., 2014) remains to be further elucidated, although our results suggest that this is not the case, as the 20 patients who lost weight in our study did not do significantly worse than the rest of the sample.

There are several possible explanations for the link between weight gain and favourable treatment response. Firstly, it may be that greater improvement in symptoms leads to better and more structured health-seeking behaviours, including proper self-care and healthier diet. In this respect, our finding of an association between weight gain and improvement in disorganized symptoms specifically, may be relevant. Disorganized symptoms are a major contributor to acute impairment in functioning (Ortiz et al., 2017), health and wellbeing (Javitt, 2015). A second possibility is that the effects of antipsychotics on neurotransmitters that are responsible for weight gain may, at least in part, also be responsible for the efficacy of these agents (Meltzer et al., 2003). In particular, serotonin signalling may play a role, given its involvement in the regulation of appetite and satiety, with 5HT2C receptor blockade being directly implicated in antipsychotic-associated weight gain (Reynolds et al., 2006; Panariello et al., 2011), as well as its association with clinical response in schizophrenia (Gressier et al., 2016). Unlike most conventional antipsychotics, flupenthixol is a 5HT2A and 5HT2C receptor blocker (Wiesbeck et al., 2003). The role of the orexin hypothalamic neuropeptides may also be relevant. Orexins play a role in appetite regulation and energy homeostasis (Panariello et al., 2011) and share interaction mechanisms with serotonin (Donovan and Tecott, 2013). In this context, and of relevance to our findings, Chien et al. (2015) recently reported a correlation between lower disorganized and negative symptom severity and higher orexin A levels in a study of 127 schizophrenia patients, implicating orexin in treatment response.

Several recent studies have reported that elevated lipids may predict clinical response in schizophrenia (Solberg et al., 2015, 2016). Our results in this regard were less clear-cut. Thus, while we found several significant correlations between treatment-emergent metabolic changes other than weight gain and a decrease in specific factor-derived domain scores in the bivariate correlational analyses, none of these associations remained significant in the regression models. Nevertheless, our finding of an association between baseline triglycerides and PANSS total symptom severity, and increased triglycerides and greater reductions in disorganized symptoms, is consistent with previous work reporting an association between elevated triglycerides and fewer negative symptoms (Procyshyn et al., 2007; Lally et al., 2013), which share a strong association with disorganized symptoms (Demjaha et al., 2012). An association between increased lipids and better treatment response could be explained by lipid partitioning and altered blood-brain barrier permeability affecting antipsychotic levels, although elevated triglycerides may also exert a favourable effect on central serotonin transmission (Dursun et al., 1999) and perhaps also reflect a favourable change in central lipid metabolism and myelination potential or efficacy (Chrast et al., 2011). Finally, the inverse correlation between glucose and positive symptom change scores that we found is consistent with the proposal that insulin signalling is the common pathway linking metabolic risk with therapeutic benefit (Girgis et al., 2008).

The strengths of this study lie in its longitudinal design and evaluation of a well-characterized cohort of first-episode, minimally treated patients. Also, regular clinical and laboratory assessments allowed for accurate evaluation of changes over time. In addition, standardised treatment with a single antipsychotic ruled out the differential effects of treatment. However, there are important limitations. First, a longer treatment period would have been preferable and may have more clearly identified relationships between lipid and glucose changes and treatment outcome. Second, our sample was drawn from a largely socio-economically deprived community with low baseline BMI. Thirdly, our study did not include the assessment of waist circumference as an indicator of central obesity, and dietary habits and physical activity as determinants of cardio-metabolic risk in schizophrenia spectrum disorder patients treated with antipsychotics were not examined. Finally, our study only included patients treated with flupenthixol decanoate. These limitations mean that our findings are not necessarily generalizable to other patient populations which may differ in terms of clinical profile, treatment approach and metabolic risk profile.

In conclusion, our study supports the notion that weight gain is related to antipsychotic efficacy, perhaps via shared mechanistic pathways. The possible clinical usefulness of assessment and monitoring of metabolic syndrome risk in predicting treatment outcome remains to be defined.

Conflict of interest statement

HL, LP, FS, LA and SK report no conflicts of interest. BC has received honoraria from Lundbeck, Mylan and Sandoz for speaking at educational meetings. RE has participated in speakers/advisory boards and received honoraria from Janssen, Lundbeck, Servier and Otsuka, and has received research funding from Janssen and Lundbeck.

Contributors

All authors contributed and have approved the final manuscript.

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None to declare.

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