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Inverse association between negative symptoms and body mass index in chronic schizophrenia

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ABSTRACT

Background: We investigated whether negative symptoms, such as poor motivation or anhedonia, were associated with higher body mass index (BMI) in stable patients with schizophrenia chronically treated with antipsychotic medication.
Methods: 62 olanzapine- or clozapine-treated patients with illness duration of at least four years were selected from an international multicenter study on the characterization of negative symptoms. All participants completed the Brief Negative Symptom Scale (BNSS) and the Positive and Negative Syndrome Scale (PANSS). Bivariate correlations between BMI and negative symptoms (BNSS) were explored, as well as multiple regression analyses. We further explored the association of two principal component factors of the BNSS and BMI. Subsidiary analyses re-modeled the above using the negative symptoms subscale of the PANSS and the EMSLEY factor for negative symptoms for convergent validity.
Results: Lower negative symptoms (BNSS score) were associated with higher BMI ($r = -0.31$; $p = 0.015$). A multiple regression analysis showed that negative symptoms (BNSS score) and age were significant predictors of BMI ($p = 0.037$). This was mostly driven by the motivation/pleasure factor of the BNSS. Within this second factor, BMI was negatively associated with anhedonia ($r = -0.254$; $p = 0.046$) and asociality ($r = -0.253$; $p = 0.048$), but not avolition ($r = -0.169$; $p = 0.188$). EMSLEY score was positively associated with BNSS ($r = 0.873$, $p < 0.001$), but negatively associated with BMI ($r = -0.308$; $p = 0.015$). The association between PANSS and BMI did not reach significance ($r = -224$, $p = 0.080$).
Conclusions: We conclude that lower negative symptoms were associated with higher BMI (assessed using both the BNSS and EMSLEY) in chronic stable schizophrenia patients, mostly due to lower anhedonia and asociality levels.

1. Introduction

Strategies for preventing weight gain, one concern often reported by individuals receiving treatment in the early phases of psychosis, have been partially successful. However, weight loss interventions are more limited in chronic schizophrenia compared with other phases of the illness and in the general population, despite a higher prevalence of obesity (Royal College of Psychiatrists, 2014; Zimbron et al., 2016).

Increased incidence of obesity in schizophrenia has been grossly attributed to antipsychotic medication-induced appetite, although a dose-dependent relationship has not been supported (Simon et al., 2009). This view contrasts with the multi-factorial approach of obesity applied to non-psychiatric populations, which considers a variety of genetic, epigenetic and behavioural factors (Ziauddeen et al., 2015). Current models for predicting antipsychotic medication-induced weight gain are unreliable (Fernandez-Egea et al., 2011) and there remains a need for identifying additional factors that might play a significant role in

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the cause and maintenance of weight gain leading to obesity in chronic schizophrenia. Intra-uterine stress (Ziauddeen et al., 2016) and genetic factors (Reynolds, 2012), for example, have already been shown to have an influence. Furthermore, it is likely that obesity in chronic schizophrenia has different predictors compared to other phases of the illness, due in part to variations in medication side effects, more persistent symptomatology and social consequences of the illness.

Negative symptoms severity has been intuitively associated with greater weight gain (Koga and Nakayama, 2005), prompting speculation that problems with motivation underlie physical inactivity in patients with schizophrenia. However, evidence in support of this is scarce (Janney et al., 2013) and has only been provided by studies in populations with medication switching (Hermes et al., 2011) and during the onset of the illness (Pérez-Iglesias et al., 2014), when changes in psychopathology and body weight are more severe. Understating the role of persistent negative symptoms in *chronic* stable patients with schizophrenia may differ from those with a recent diagnosis, as antipsychotic medication-induced weight gain is known to plateau after three to five years of continuous treatment (Bushe et al., 2013). One study investigating weight gain in patients with chronic schizophrenia found that higher negative symptoms were associated with lower body mass index (Chen et al., 2014). If *more severe* negative symptoms predict obesity, then behavioural interventions for patients with chronic schizophrenia might be more successful if modules for reducing negative symptoms, such as motivation and anhedonia, are implemented (e.g. promoting physical exercise; increasing social interaction).

We aimed to test whether high levels of negative symptoms were associated with increased body mass index (BMI) in a multi-center international study on the characterization of negative symptoms in chronic schizophrenia. We included patients with at least four years of continuous prescribed antipsychotic treatment with clozapine or olanzapine, the two leading obesogenic antipsychotics (Leucht et al., 2013), in order to reduce medication heterogeneity after the peak risk of weight gain. For the assessment of negative symptoms, the Brief Negative Symptoms Scale (BNSS) and the Positive and Negative Syndrome Scale (PANSS) were used (both English (Kirkpatrick et al., 2011, Kay et al., 1987) and Spanish (Mané et al., 2014; Peralta and Cuesta, 1994) versions). As secondary aims, we explored whether subscales of the BNSS and the more traditionally used PANSS predicted BMI.

2. Material and method

2.1. Study sample

The present sample was selected from a multi-center cross sectional study of the characterization of negative symptoms in chronic schizophrenia, which had four primary aims, including investigation of the role of negative symptoms in metabolic disease.

The study recruitment dates were May 2015 to May 2016 across four centers, which included the Clozapine Clinic at the Cambridgeshire and Peterborough NHS Foundation Trust (Cambridge) and three in Spain: one in Oviedo (Oviedo) and two in Barcelona (Hospital del Mar (HMar) and Hospital Clinic (HClinic)). The present study is a continuation of a prior collaboration between sites for the translation and adaptation of the BNSS in Spanish (Mané et al., 2014), but all cases analyzed here have not been reported elsewhere. All procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

2.2. Inclusion and exclusion criteria

The multicenter study included patients with a diagnosis of schizophrenia (ICD-10 criteria) at any stage of illness. For this particular analysis, we included only those patients who were prescribed with clozapine or olanzapine, the two medications mostly associated with weight gain (Leucht et al., 2013). An additional inclusion criterion was at least four years of antipsychotic treatment. All augmentation strategies were allowed, except for clozapine-aripiprazole, as we previously reported that this combination is associated with weight loss (Zimbron et al., 2016). No other exclusion criteria were applied.

2.3. Assessments

All participants were evaluated with psychopathology scales as well as morphometric measures including a full medical and psychiatric history. The prescribed daily doses of antipsychotic medications were converted to an estimated equivalent amount of chlorpromazine in accordance with the international consensus (Gardner et al., 2010).

Morphometric evaluation included measurements of height, weight, diastolic and systolic blood pressure and heart rate during resting state. BMI was calculated using the standard formula (BMI = weight (kg) / height^2 (m^2)).

Psychopathology scales included the BNSS (Mané et al., 2014; Kirkpatrick et al., 2011) and PANSS (Kay et al., 1987; Peralta and Cuesta, 1994), the Calgary Depression Scale (CDS) (Addington et al., 1990) and cognitive scales, the latter not included in the present study. To ensure interrater reliability between centers, each clinician (a total of five psychiatrists and two clinical psychologists) attended a training workshop to learn the administration and scoring of all the clinical tools used in the study (BNSS, PANSS and CDS).

2.4. Use of psychopathology scales BNSS and PANSS

We used the total BNSS score calculated from all thirteen items (total BNSS). Two major components have been defined from this scale (Strauss et al., 2012): Factor 1 reflects an *Emotional expressivity* dimension (PC1 BNSS), consisting of the Blunted Affect, Alogia, and Lack of Normal Distress subscales (items 4, 9, 10, 11, 12, 13); and Factor 2 reflects a *Motivation and Pleasure* dimension (PC2 BNSS), consisting of the Anhedonia, Avolition, and Asociality subscales (items 1, 2, 3, 5, 6, 7, 8). Some authors have argued that the BNSS comprises three, instead of two components (Garcia-Portilla et al., 2015) and that the alogia subscales (items 12 and 13) should also be considered as an independent component. For the purposes of this study, we first used the more widely accepted two components, but also explored the three-component view for comprehensiveness.

We used items P1 to P7 for the positive symptoms of the PANSS (Pos_PANSS). For negative symptoms, we used two different measures: the classical approach (sum of items N1 to N7, termed Neg PANSS), and the EMSLEY factor for negative symptoms (sum of items N1, N2, N3, N4, N6, GP7 and GP13 and GP16, termed Emsley PANSS (Emsley et al., 2003)). We chose these two factors because the PANSS negative subscale (N1 to N7) also contains pure cognitive symptoms (i.e. N5 and N6) and is thus less specific to negative symptoms. In addition, the BNSS and Neg_PANSS are also different measures of negative symptoms. For example, Neg_PANSS is based mostly on observed behavior, whereas the BNSS includes internal experiences as a factor of negative symptoms severity.

Before the introduction of newer and more valid scales, such as the BNSS, a common practice was the use of derived factors, which more accurately captured negative symptoms. In this sense, the negative symptoms Emsley PANSS factor includes three items related to avolition and asociality experiences, and removes two items considered 'purely cognitive'.

2.5. Statistical analyses

Zero-order bivariate correlations between total BNSS scores and BMI were explored using Person's correlation. Multiple regression analyses were run with BMI as the dependent variable and five independent variables including the total BNSS score and four factors that might make

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