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Psychopathology, coronary heart disease and metabolic syndrome in schizophrenia spectrum patients with *deficit* versus non-deficit schizophrenia: Findings from the CLAMORS study☆

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Abstract

The objective of this study was to compare coronary heart disease (CHD) risk and metabolic syndrome (MS) prevalence in patients with *deficit* (DS) and non-deficit schizophrenia treated with antipsychotics. A total of 1452 antipsychotic-treated outpatients meeting criteria for schizophrenia, schizophreniform or schizoaffective disorder were included in this cross-sectional multicentre study. CHD risk was assessed by SCORE (10-year cardiovascular death) risk score, and metabolic syndrome was assessed according to NCEP-ATP III criteria. A total of 1452 patients (863 men, 60.9%), 40.7±12.2 years (mean±SD) were included. DS was found in 404 patients (35.1%). Patients with DS were older, more frequently male and obese, more likely to be receiving sickness benefits, and had longer illness duration and fewer previous hospitalisations. Furthermore, DS patients had higher negative PANSS scores (56.3% vs. 40.6% of patients with PANSS-N>21). High/very high risk of fatal CHD according to SCORE function (≥3%) was

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significantly higher in DS [11.8% (95% CI: 8.8–15.5) vs. 6.0% (95% CI: 4.4–8.1), ($p<0.05$)]. Schizophrenia spectrum patients with DS were more obese and had a higher CHD risk than non-deficit patients.

1. Introduction

The identification of different symptoms or diagnoses as predictors of side effects to antipsychotics has rarely been studied (Moreno et al., 2010; Bobes et al., 2010). Along the same lines, the differential risk of antipsychotic side effects based on the severity and quality of negative symptoms has rarely been assessed. When assessing negative symptoms in relationship to different clinical variables, it seems that the identification of deficit symptoms as opposed to negative symptoms has produced more consistent results (Kirkpatrick et al., 2001). The term 'deficit symptoms' should be used to refer specifically to those negative symptoms that are present as primary and enduring traits (Carpenter et al., 1988). Deficit symptoms may be present during and between episodes of exacerbation of positive symptoms. These deficit symptoms occur regardless of the patient's medication status and are not specifically responsive to anticholinergic or antipsychotic drug withdrawal.

The current study was designed to compare the degree of cardiovascular risk and the prevalence of metabolic syndrome in *deficit* versus non-deficit schizophrenia, in the context of the Cardiovascular, Lipid and Metabolic Outcomes Research in Schizophrenia Study — the CLAMORS study (Bobes et al., 2007), which in turn was designed to ascertain the prevalence of cardiovascular risk factors (CVRFs), cardiovascular mortality (CVM) risk, and the prevalence of metabolic syndrome (MS) in patients with schizophrenia, or schizophreniform or schizoaffective disorders treated with the antipsychotics most commonly used in routine practice.

2. Experimental procedures

2.1. Investigators, patients and study design

The CLAMORS study methods have been published in detail elsewhere (Bobes et al., 2007). In brief, this cross-sectional, multicentre study enrolled consecutive outpatients, both male and female, 18–74 years of age, with a diagnosis of schizophrenia, or schizophreniform or schizoaffective disorder according to the DSM-IV classification, who had been receiving oral antipsychotic monotherapy for at least 12 weeks. An accredited independent ethics committee approved the study protocol. Written informed consent was obtained prior to participation in all cases. The first two patients receiving treatment with each of the most commonly-used antipsychotic drugs in our health care setting (risperidone, olanzapine, quetiapine, ziprasidone, amisulpiride, and haloperidol) were recruited consecutively.

A total of 1704 patients were recruited by 117 psychiatrists from 91 different outpatient centres. Of these, 252 (14.8%) who failed to meet the study selection criteria were excluded. The main reason for exclusion (202 patients, 11.9%) was current treatment with an antipsychotic for less than 12 weeks. Thus, 1452 patients were considered eligible for inclusion in analysis.

2.2. Variables and measurement instruments

2.2.1. Remission and deficit/non-deficit definitions

Clinical severity, and particularly the severity of psychotic symptoms, was assessed upon entry into the study using the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987; Peralta and Cuesta, 1994). Patients were categorised as in remission (n=449) or not in remission (n=981) according to previously published criteria (Andreasen et al., 2005; Van Os et al., 2006).

Patients were categorised into *deficit* and non-deficit schizophrenia groups using the Proxy for the Deficit Syndrome (PDS) (Kirkpatrick et al., 1993; Kirkpatrick et al., 1996). As ratings were likely to differ for those in remission versus those in an exacerbation of their illness, the two groups were categorised into *deficit* and non-deficit groups separately. For all subjects, a PDS score was calculated by combining PANSS item scores as follows: PDS = (blunted affect + poverty of speech) − (hostility + anxiety + guilt + depression). A high score quantifies the combination of a high number of negative symptoms and an absence of dysphoria that is a characteristic of deficit patients (Kirkpatrick et al., 1989; Kirkpatrick et al., 1994), while low scores are consistent with an absence of this clinical profile. Based on data on the prevalence of *deficit* and non-deficit schizophrenia and performance on the PDS versus the standard Schedule for the Deficit Syndrome (Kirkpatrick et al., 1989; Kirkpatrick et al., 1993), cut-off points were chosen to define putative *deficit* and non-deficit groups separately for the remission and non-remission groups. We then categorised the 25% (approximately) of patients with the highest PDS scores into the *deficit* category, those with the lowest 50% (approximately) of PDS scores into a non-deficit group, and the remaining 25% into an ambiguous group, which was not included in further analyses. These percentages were approximate as the categorisations were limited by the precise distribution of PDS scores. For patients considered to be in remission, those with a score of −11 to −3 were categorised as non-deficit, those with scores from −1 to 2 were categorised as *deficit*, and those with a score of −2 were considered ambiguous. For patients who were not considered to be in remission, the cut-off points for categorisation were −15 to −3 for non-deficit, 0 to 8 for *deficit*, and −2 to −1 for the ambiguous group.

2.2.2. Prevalence of cardiovascular risk factors

The prevalence of CVRFs was estimated using the criteria (SEA, 2003) of age ≥ 40 (males) or ≥ 45 (females) years, presence of diabetes (diagnosed or receiving treatment with oral antidiabetic drugs or insulin), total cholesterol ≥ 200 mg/dl, HDL cholesterol < 45 mg/dl (males) or < 50 mg/dl (females), systolic blood pressure ≥ 140 mmHg (or ≥ 130 mmHg in patients with prior cardiovascular disease, renal disease and diabetes), and diastolic blood pressure ≥ 90 mmHg (or ≥ 80 mmHg in patients with prior cardiovascular disease, renal disease and diabetes). For determination of these risk factors, blood clinical chemistry testing performed no more than 3 months before the start of the study was required. Cardiovascular (CV) risk was estimated using the SCORE (Systematic Coronary Risk Evaluation) function for fatal CV risk (Conroy et al., 2003) (including coronary death, sudden death, stroke, aortic aneurysm and heart failure), and the Framingham function to estimate the overall risk of any fatal or nonfatal CHD (Wilson et al., 1988) (including, in addition to the fatal CHD events mentioned above, any type of angina, myocardial infarction, other type of coronary ischaemia, congestive heart failure, intermittent claudication or peripheral arterial ischaemia) within 10 years. In this study, patients were classified according to the probability of presenting "very high/high" risk for fatal