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Predictors of negative symptoms in the chronic phase of schizophrenia: A cross-sectional study

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ABSTRACT

This study was designed to investigate the relationship between negative symptoms and key indicators for long-term hospital stays among inpatients with schizophrenia. A further aim was to elucidate the clinical determinants of negative symptoms. The following were used as index factors: age, duration of illness, duration of hospitalization, age at onset, years of education, smoking status, body mass index, concentrations of serum triglycerides, total cholesterol, uric acid, QTc interval duration from electrocardiography, dose equivalents of antipsychotic and anticholinergic agents, neurocognitive function, drug-induced extrapyramidal symptoms, involuntary movements, and psychiatric symptoms. Spearman's rank correlation coefficients were calculated and regression analyses were performed to examine associations between these factors and negative symptoms. Positive symptoms correlated positively with negative symptoms as rated on the Brief Psychiatric Rating Scale. Age at onset correlated negatively with negative symptoms. Multiple regression analysis showed that dose equivalents of atypical antipsychotics and positive symptoms predicted negative symptoms. Increasing our understanding of these predictors as key indicators of the severity of negative symptoms may aid in the re-consideration of therapeutic programs for chronic schizophrenia.

1. Introduction

Negative symptoms have long been considered the core feature of schizophrenia (Bleuler, 1950; Kirkpatrick et al., 2001). The underlying mechanisms of negative symptoms remain poorly understood, impeding the search for a therapeutic arsenal based on known mechanisms of action. Negative symptoms have become a special research interest in the last decade, because atypical antipsychotic drugs are reported to offer improved therapeutic efficacy in schizophrenic patients compared with older typical agents (Akhondzadeh et al., 2006). Unlike positive symptoms, negative symptoms remain an unmet therapeutic need and are associated with poor functional outcomes (Sevy et al., 2001; Tandon and Jibson, 2002) and limited response to pharmacotherapy (Garcia-Cabeza et al., 2001). The competing hypotheses that the action onset for antipsychotic medication assumes a course of early or delayed response have finally been tested in negative symptoms. The current results have generally highlighted no significant differences between early- and delayed-response effects based on a reanalysis of three large clinical trials of negative symptoms in schizophrenia (Levine and Leucht, 2012).

The present study included only chronically ill inpatients. In addition, our study did not primarily involve observations of outpatients residing in community settings. Residual symptoms are mainly seen among long-term hospitalized Japanese patients with chronic schizophrenia, but not among those with violence or other behavioral dyscontrol (Okada et al., 1996). In Japan, the mental health care system remains primarily hospital-based (Oshima et al., 2005). Japan has the greatest number of psychiatric beds in the world, and the duration of hospitalization is approximately five-fold longer than that of other countries. In addition, > 70% of psychiatric inpatients remain in hospital for > 1 year, and quality of life is reportedly very poor (Matsushita et al., 2004; Ministry of Health, 2008). It is worth noting that few systematic efforts at deinstitutionalization have been made in Japan (Oshima et al., 2002). Furthermore, many patients are hospitalized for a long period because no support is available after hospital discharge even if symptoms have stabilized (Okada et al., 1996). Taking the

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environment around inpatients and the number of long-stay inpatients in Japan into consideration, we think that it is meaningful to examine factors predictive of the level of negative symptoms, on the understanding that inpatient wards are characterized by very restrictive environments (Oshima et al., 2002, 1996).

A previous study focused on the importance of the distinction between primary and secondary negative symptoms for pathophysiological research (Arango et al., 2004). The deficit form of schizophrenia refers to a subgroup of individuals who display negative symptoms that are primary, enduring or trait-like, and are idiopathic. Conversely, the non-deficit form refers to a subgroup of individuals who display negative symptoms that are secondary to other aspects of the illness, such as psychosis, depression, anxiety, medication effects, intellectual disability, environmental deprivation, or other illnesses (Ahmed et al., 2015). This study was designed to investigate the relationship between negative symptoms and key indicators for the chronic phase using schizophrenia symptom measures in patients not limited to the deficit form. In choosing indicators, we were concerned with clinical data that were commonly measured in the daily medical practice of a psychiatric hospital. We therefore extracted baseline characteristics, metabolic outcomes, cardiovascular outcomes, dose-equivalents of psychotropic drugs, neurocognitive function, drug-induced extrapyramidal symptoms (EPS) and psychiatric symptoms that are commonly assessed in daily practice.

Antipsychotics are among the most effective drugs used in psychiatry in maintenance therapy for schizophrenia, mania, and acute psychotic reactions (Aarsland et al., 1999). Patients with schizophrenia who are receiving antipsychotic drugs report a better quality of life, but have a higher incidence of weight gain, sedation, and movement disorders (Leucht et al., 2012). As such, all patients who report symptom relief while receiving medication should be offered maintenance therapy with antipsychotics (Kreyenbuhl et al., 2010). However, a previous study reported that the prevalence of negative symptoms in patients treated with antipsychotics in daily clinical practice is considerably high (Bobes et al., 2010), which might indicate that higher doses of selective D_2 antagonists may worsen or induce negative symptoms, which would be in agreement with the hypodopaminergic pathophysiology postulated as being responsible for negative symptoms (Lecrubier et al., 2006). Furthermore, the severity of negative symptomatology correlated with reductions in activity in the ventral striatum among patients treated using first-generation antipsychotics (Juckel, 2016). On this neurochemical basis, all antipsychotics are dopamine D_2 receptor antagonists. By blocking dopaminergic neurotransmission in subcortical areas, D_2 receptor antagonists are capable of producing extrapyramidal side effects occurring acutely or during chronic treatment, including parkinsonism (tremor, akinesia, and rigidity), akathisia, dystonia, and tardive dyskinesia (Miyamoto et al., 2008). A significant positive correlation has been reported between postural sway area and the severity of negative symptoms (Bernard et al., 2014).

The side effects of antipsychotics cannot be separated from negative symptoms in the chronic stage of schizophrenia. As a result, the present study selected side effects as candidates for indicators. Additionally, although antipsychotics are the mainstay of schizophrenia treatment, they can unfortunately cause a broad range of side effects, including sedation, hypotension, weight gain, sexual dysfunction, and neurologic symptoms (Leucht et al., 2013). High serum triglyceride levels have been reported in patients with early-onset schizophrenia (Saari et al., 2004). Other reports have shown that schizophrenics show lower total cholesterol levels than healthy individuals (Boston et al., 1996; Ryan et al., 2003). Furthermore, adverse effects such as metabolic changes, including weight gain, insulin resistance, hyperglycemia, and lipid abnormalities, are frequently associated with the use of second-generation antipsychotics (SGA) (American Diabetes Association, 2004; Lehman et al., 2004; Leucht et al., 2012; Rummel-Kluge et al., 2010). In addition, individuals with schizophrenia are vulnerable to developing physical illnesses such as diabetes, metabolic syndrome, cardiovascular diseases, respiratory diseases, and cancer (Brown et al., 2000). One report found that people with schizophrenia died 10 years earlier from cardiovascular diseases than people in the general population (Westman et al., 2017). Frequent monitoring of blood pressure, body mass index (BMI), fasting glucose level, fasting lipid level, and other such markers has been recommended for patients receiving SGA (De Hert et al., 2011; Rummel-Kluge et al., 2010). The prevalence of metabolic syndrome, abdominal obesity, and hyperuricemia, all of which are considerably under-diagnosed and undertreated, has been shown to be elevated in French patients with schizophrenia (Godin et al., 2015). On the other hand, further decreases in plasma uric acid levels were observed in patients after haloperidol withdrawal (Yao et al., 1998). For these reasons, in addition to QTc interval duration, concentrations of serum triglycerides, serum total cholesterol, and serum uric acid were assessed in the present study.

We selected smoking status as a candidate of indicators, because in a review of 42 studies across 20 nations, it was found that the current smoking rate among male schizophrenia patients was constantly higher than that in the general population (de Leon and Diaz, 2005). Furthermore, smoking is associated with improved negative symptoms, which could account for the heavier smoking pattern observed among schizophrenia patients (Jiang et al., 2013).

In terms of cognitive function, a meta-analysis indicated that negative and disorganized dimensions are conflated in the association with neurocognitive alterations, contrary to the positive and affective dimensions (Dominguez Mde et al., 2009). In a study using multiple regression analysis, negative symptoms were reported to be significantly related to all z scores of the Brief Assessment of Cognition in Schizophrenia subdomains, composite score, and intra-individual variability z-scores (Akiyama et al., 2016). Negative symptoms are more strongly associated with cognition in schizophrenia than positive or depressive symptoms, and a recent meta-analysis estimated that a small-to-moderate portion of the variance in cognitive performance can be attributed to negative symptoms (Ventura et al., 2009). A number of studies have reported a moderate correlation between the severity of negative symptoms and cognitive impairment (Konstantakopoulos et al., 2011; Lin et al., 2013; Tanaka et al., 2012; Ventura et al., 2009).

We selected age as a candidate of indicators. Previous studies have suggested that younger age predicts higher negative scores (Bijanki et al., 2015; Drake et al., 2016). Age has been shown to correlate significantly with cerebral fractional anisotropy (FA) in each major brain region (frontal, temporal, parietal, and occipital lobes) and global Scale for the Assessment of Negative Symptoms scores; that is, younger schizophrenia patients tend to have both a higher cerebral FA score and more negative symptoms (Bijanki et al., 2015).

With these concerns in mind, the present study was designed to investigate the relationships between negative symptoms and key indicators for the chronic phase assessing baseline characteristics, metabolic outcomes, cardiovascular outcomes, dose equivalents of psychotropic drugs, neurocognitive function, drug-induced EPS and psychiatric symptoms commonly assessed in daily practice. A further aim was to elucidate clinical determinants of negative symptoms among patients with chronic schizophrenia. The following questions were addressed:

1. Are negative symptoms associated with characteristics commonly assessed in daily practice?
2. Which indicators (age, duration of illness, duration of hospitalization, age at onset, years of education, number of cigarettes smoked per day, BMI, concentrations of serum triglycerides, serum total cholesterol, and serum uric acid, QTc interval duration from electrocardiography, dose-equivalents of antipsychotics, dose-equivalents of anticholinergic agents, neurocognitive function, drug-induced EPS, involuntary movements, and psychiatric symptoms) indicate negative symptoms?