Exploration of the associations between neurocognitive function and neuroleptics side effects

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ABSTRACT

The etiology of side effects of antipsychotic medications can be conceptualized as involving both specific pharmacological actions of a drug and any mental and physical states attributed by the patient. Both factors are likely to be linked with neurocognitive functioning which may largely affect the subjective experience of side effects in patients with schizophrenia. In this study, we examined whether baseline neurocognitive functions, such as IQ, attention, executive functioning, and short-term memory, are associated with baseline and 6-month follow-up measures of self-reported Liverpool University Neuroleptics Side Effects Scale (LUNSERS) and clinician-rated Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS). At the baseline, anxiety and depression were significantly associated with LUNSERS red herring (RH) and total side effects (SE) but not with DIEPSS. There was no association between LUNSERS and DIEPSS. Controlling for anxiety and depression, IQ was significantly correlated with DIEPSS, while choice reaction time (CRT) and stop signal task (SST) direction errors correlated with RH, and intra−extradimensional set-shifting (IED) total errors and pre-extradimensional set-shifting (pre-EDs) errors correlated with SE. The baseline SST direction errors further correlated significantly with RH and SE and DIEPSS total score of 6-month follow-up, and CRT mean and SD correct latency also correlated with DIEPSS. The correlations between the 6-month changes (Δ) in the same side effects measures and baseline neurocognitive measures were also significant, except that between RH and SST direction errors. Such evidences supported association between both self-rated and clinician-rated side effects and selective impairments in attention and executive functioning.

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1. Introduction

Favorable outcome of antipsychotics treatment in patients with schizophrenia is largely dependent on good compliance, which is required for better assessment of efficacy and formulation of new treatment strategy. However, one of the major causes of noncompliance and treatment discontinuation has been found to be side effects of antipsychotic medication (Vorunganti et al., 2008; Kahn et al., 2008). Side effects can be largely conceptualized as comprising effects accountable by the specific pharmacological actions of a drug and by any mental and physical states attributed by the patient. As self-reported or subjective side effects arguably reflect more of the latter component compared to clinician-

assessed measures, they have proven to not only predict treatment compliance (Hogan et al., 1983; Kampman et al., 2002) but correlate significantly with other self-reported measures, such as quality of life (Hwang et al., 2009; Wolters et al., 2009). By the same token, self-reports of side effects have been found to be adversely affected by psychopathology, such as severity of positive and depressive/anxiety symptoms (Hwang et al., 2010), and to be associated with poor overall executive functioning (Hwang et al., 2009; Kim et al., 2002).

In most clinical studies, self-reported measures of side effects are accepted as outcome measures without an extensive examination of its validity. However, patients with schizophrenia in particular have been found to report side effects more frequently than the clinicians (Lindström et al., 2001). In addition, significant variability is present in how patients perceive their state of illness and side effects relative to clinical evaluation which may result in the lack of association between patient-rated and clinician-rated

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measures. For example, our recent study (Jung et al., 2010) demonstrated that patients with schizophrenia who show relatively low correspondence between subjective quality of life and the clinician-rated functioning also show weak or no association between subjective quality of life and clinician-rated side effects. Those with high correspondence, in contrast, showed stronger associations between self-report and clinician-rated measures, including side effects. From the etiological viewpoint, it may be important to examine whether such correspondence may be associated with the presence and severity of impairments in neurocognitive function in patients with schizophrenia, particularly in terms of self-reported and clinician-rated side effects. To date, however, no study has investigated how neurocognitive functions may be directly associated with cross-sectional and long-term ratings of side effects by patients and clinicians. In the present study, we therefore examined how neurocognitive functions at baseline are related to the self-reported and clinician-rated side effects of the baseline and 6-month follow-up and the changes (Δ) therein.

2. Methods

2.1. Participants

Fifty-four Korean outpatients were followed for 6-months post baseline assessment with lost-to-follow-up of only 3 female patients. These patients were also included in a recently published study by Yun et al. (2011), which cross-sectionally compared the executive functions of remitted and non-remitted patients of schizophrenia and healthy control. These patients were recruited from the psychiatric outpatient clinic of the Boramae Medical Center of Seoul, Korea, and have been diagnosed by two experienced psychiatrists (YK and HYJ) according the DSM-IV diagnostic criteria. The patients were further assessed with the Structured Clinical Interview for DSM-IV (SCID) by a trained clinical psychologist to exclude other Axis I diagnoses such as schizoaffective disorder and substance abuse. The age, years of education, and duration of illness of all patients at the baseline were 34.2 (SD = 10.4), 13.2 (SD = 2.4), and 8.7 (SD = 8.0), respectively, and 25 (46%) were males. Interested readers may refer to the study by Yun et al. (2011) for more detailed information on patient recruitment and diagnoses.

2.2. Procedure

At the time of initial clinical assessment, the Korean versions of the Liverpool University Neuroleptics Side Effects Scale (LUNSERS: Day et al., 1995; Lambert et al., 2003; Jung et al., 2005), the Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS: Inada, 1996; Kim et al., 2002), the Beck Anxiety Inventory (BAI: Beck et al., 1988; Kwon, 1997), and Hamilton Depression Rating Scale (HDRS: Hamilton, 1960; Yi et al., 2005) were completed. Then, within 10 days of clinical assessment, neuropsychological assessment that included the short form of the Korean version of the Wechsler Adult Intelligence Scale (K-WAIS: Wechsler, 1981; Yeom et al., 1992) and subtests of the CANTAB (CANTAB eclipse, 2006), a series of computerized tests using a touch-sensitive screen on an IBM-compatible PC, were completed. The patients were followed up 6 months post the baseline assessment, and they once again completed both side effects measures. Written informed consent was obtained from all patients prior to the initiation of study procedures whose protocol had been approved by the Institutional Review Board of Boramae Medical Center and carried out in accordance with the latest version of the Declaration of Helsinki. Detailed descriptions of the procedure and neurocognitive

measures used in this study are provided in the previous study by Yun et al. (2011).

2.3. Measures

2.3.1. Clinical measures

To assess the overall level of depression, the HDRS which includes items such as overall depression, guilt, suicide, insomnia, problems related to work, psychomotor retardation, agitation, anxiety, loss of weight, and loss of insight (Hamilton, 1960; Yi et al., 2005) was completed. As an interviewer-administered and rated measuring scale, a higher score signifies more severe levels of depression. The level of subjective anxiety of the patients was assessed with the BAI, a 21-item self-reported measure containing items such as numbness or tingling, feeling hot, wobbliness in legs, and inability to relax (Beck et al., 1988; Kwon, 1997).

2.3.2. Side-effects measures

All patients completed Korean version of the LUNSERS, a self-reported measure which consists of 41 items pertaining to various subscales of neuroleptics-related side effects (SE: psychic, extrapyramidal, anticholinergic, other autonomic, allergic, and hormonal) and 10 red herring (RH) items not directly related to known antipsychotic side effects. The RH subscale, which includes items such as runny nose, chilblains, hair loss, and urine darker than usual, has shown to be useful for detecting over-reporting patients (Lambert et al., 2003). Two experienced psychiatrists (YK and HYJ) assessed the severity of side effects with the Korean version of the DIEPSS. It contains 8 individual items, i.e., gait, bradykinesia, sialorrhea, rigidity, tremor, akathisia, dystonia, and dyskinesia, and one global item which considers the overall severity and frequency of the individual items and their negative influence on subjective distress and daily activity (Inada, 1996; Kim et al., 2002).

2.3.3. Neurocognitive measures

The short form of the K-WAIS is the Korean version of the WAIS-Revised (Wechsler, 1981). The composite score was derived from the four subtests from the K-WAIS (Vocabulary, Arithmetic, Picture Arrangement, and Block Design) to estimate current intellectual functioning. The correlation between the estimated IQ scores derived from the K-WAIS-short form and the full battery of the K-WAIS was reported to be 0.95 (Kim and Lee, 1995). Also, the Vocabulary subtest was additionally used as the estimation of premorbid IQ.

The subtests of the CANTAB were used to assess the domains of attentional ability, as reflected by processing speed and accuracy, executive function, including set-shifting and response inhibition, and spatial short-term memory. Specifically, Choice Reaction Time (CRT), a 2-choice reaction-time task, provided the measures of processing accuracy (no. of correct trials based on two assessment sets of 50 trials each following 24 practice trials), and motor speed (mean correct latency) and its variability (SD correct latency). Intradimensional/Extradimensional Shift (IED), a computer touch-screen adaptation of the Wisconsin Card Sorting Test (WCST), tested the ability to maintain attention on a reinforced stimulus (intradimensional shift, IDS) and then to shift attention to the previously irrelevant stimulus (extradimensional shift, EDS) through 9 stages of increasing complexity. Its outcome variables were the number of stages completed, total errors, pre-extradimensional shift errors (pre-ED errors), and errors at the extradimensional shift (EDS errors). Stop Signal Task (SST) measured an individual's ability to inhibit a prepotent response. We obtained direction errors, proportion of successful stops, reaction time on GO trials, and the processing time required to inhibit a prepotent motor