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Neurocognitive effects of atypical and conventional antipsychotic drugs in schizophrenia: A naturalistic 6-month follow-up study

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Abstract

The present study aimed to assess the neurocognitive effects of atypical and conventional antipsychotic drugs on neurocognition under naturalistic treatment conditions. Eighty-two patients with schizophrenia underwent a comprehensive neuropsychological assessment both at baseline during inpatient treatment and 6 months after discharge from hospital (follow-up). From this sample, we selected two subgroups of patients, which had either a continuous atypical ($n = 33$) or conventional ($n = 16$) antipsychotic medication. Twenty-seven out of 40 healthy controls were also retested to control for practice effects. Both patient groups showed a moderate and significant improvement in global cognitive functioning. The repeated measurement ANOVAs revealed no differential treatment effects for all neuropsychological domains. These results remained after controlling for potential confounders between groups. Administering antipsychotic medications in an individually optimized manner seems to have the potential to improve some aspects of neurocognition in schizophrenia, regardless of the kind of antipsychotic medication.

Keywords: Schizophrenia; Neurocognition; Drug effects; Non-randomized; Follow-up study

1. Introduction

Neurocognitive deficits are increasingly considered as essential in schizophrenia disorders. There is convincing evidence that verbal memory, executive functions, and attention are impaired in schizophrenia (Goldberg & Gold, 1995; Heinrichs & Zakzanis, 1998; Weickert et al., 2000). The neuropsychological test performance of schizophrenia patients has been reported to reach one and one half standard deviations below the mean for healthy comparison subjects (Heinrichs & Zakzanis, 1998). Comparable cognitive impairments also have been observed prior to the first manifestation of psychosis or in the first episode of psychosis and may be as severe as in chronic schizophrenia (Bilder et al., 2000; Hoff et al., 1992; Saykin et al., 1994). Certain neuropsychological deficits may even reflect a genetic vulnerability to schizophrenia (Kremen et al., 1994; Wittorf, Klingberg, & Wiedemann, 2004). These findings led to the assumption that cognitive deficits comprise a separate domain of the illness and not a secondary factor. The fact that cognitive deficits are more closely associated with functional outcome than are psychotic symptoms or any other symptom domain (Green, 1996; Green, Kern, Braff, & Mintz, 2000; Green, Kern, & Heaton, 2004; Green &

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Nuechterlein, 1999) as well as the possibly limited benefit from psychoeducational treatment due to reduced cognitive functions (Feldmann, Buchkremer, & Hornung, 2000) raises the strong interest to find ways to improve cognitive performance in schizophrenia.

The amount of studies which assess the influence of antipsychotic medication on cognitive performance increases steadily, especially since the atypical antipsychotic medication is available. Several earlier studies demonstrated only minimal positive effects of conventional antipsychotics on cognitive deficits (Blyler & Gold, 2000; Cassens, Inglis, Appelbaum, & Gutheil, 1990). A meta-analysis (Keefe, Silva, Perkins, & Lieberman, 1999) of 15 studies, which assessed the cognitive effects of clozapine und risperidone, suggested that significant improvement in cognitive functioning was found with the atypical antipsychotics. Later studies showed that olanzapine may have cognition-enhancing qualities that are at least as substantial as those reported for risperidone and clozapine (Bilder et al., 2002; Purdon et al., 2000).

However, recent considerations, such as the impact of the dose of the conventional antipsychotic comparator (Harvey & Keefe, 2001; Keefe et al., 1999), have called into question whether atypical antipsychotic drugs actually improve cognitive functioning or whether they simply afford a release from the detrimental effects, such as extrapyramidal symptoms, of inappropriately high doses of conventional antipsychotics and concomitant adjunctive agents such as anticholinergic substances (Carpenter & Gold, 2002; Keefe et al., 1999). The randomized, double-blind comparisons of the effects of olanzapine (Keefe, Goldberg, et al., 2004) and risperidone (Green et al., 2002) with low doses of haloperidol showed only small differences in cognitive benefit. Remillard, Pourcher, and Cohen (2005) found in their randomized, double blind study that risperidone and haloperidol did not differ in their effect on executive functioning as measured with the Wisconsin Card Sorting Test (WCST). Most recently, the randomized controlled CATIE trial (Keefe, Bilder, et al., 2007) found small but significant cognitive improvements for olanzapine, quetiapine, risperidone, ziprasidone, and perphenazine, with no significant differences between groups at 2 and 6 months. After 18 months of treatment, cognitive improvement was even greater in the perphenazine group than in the olanzapine and risperidone groups.

Putting together these heterogeneous findings, conventional antipsychotic drugs per se do not unavoidably seem to be the cognitive hindrances they have earlier thought to be. The main research question of this study is: Do the slightly superior effects of atypical antipsychotics on neurocognition, which have been demonstrated in some randomized trials, hold under conditions of clinical routine care? Non-randomized trials might be clinically more relevant than randomized ones as all patients get their individually optimized antipsychotic treatment.

Thus, the present exploratory study aims at examining the neurocognitive effects of atypical and conventional antipsychotic drugs in schizophrenia under naturalistic treatment conditions. An advantage to the non-random assignment of antipsychotics in our study is that if a medication is clinically more effective for certain subgroups of patients who are recognizable by health care professionals, the neurocognitive effectiveness of this treatment might be improved. The study takes into account several potential confounders for differential treatment effects like antipsychotic dose, medication side effects, compliance, and psychopathology. In order to not overestimate general effects of antipsychotic medications on neurocognition, the study also controls for practice effects.

2. Method

2.1. Patient selection

Between April 1998 and June 2001, 169 inpatients who met DSM-IV criteria for schizophrenia or schizoaffective disorder were consecutively recruited as part of a combined large-scale psychotherapy and neuropsychology study at the Tuebingen University Hospital, department of psychiatry and psychotherapy, and the Rottweil state hospital of psychiatry and psychotherapy (Germany). All patients were admitted to the hospital due to an acute episode of their psychosis. Diagnoses were determined by the German version of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I; Wittchen, Zaudig, & Fydrich, 1997). All patients gave written informed consent to participate in the study, which was approved positively by the local ethics committee. Patients were selected on the basis of the following inclusion criteria: (1) beginning stabilization phase of illness after an acute phase, and (2) ages between 18 and 60 years. We considered patients to be in the beginning stabilization phase if they showed a symptom reduction and voluntarily agreed to be treated at an open ward. Exclusion criteria for neuropsychological testing were: (1a) lifetime history of substance dependence (DSM-IV/SCID-I) or (1b) substance abuse (DSM-IV/SCID-I) during