



Determinants of work outcome in neuroleptic-resistant schizophrenia and schizoaffective disorder: Cognitive impairment and clozapine treatment

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ABSTRACT

There is considerable evidence that cognitive impairment is a better predictor of work and social function in schizophrenia than are positive and negative symptoms. Atypical antipsychotic drugs have been shown to improve cognitive function in schizophrenia patients, but it is unclear whether this improves patients' ability to gain employment. Data from a prospective longitudinal study was used to test the hypotheses that (1) clozapine treatment would improve employment outcome in treatment-resistant schizophrenia or schizoaffective disorder patients, and (2) specific cognitive functioning at baseline and after treatment would predict work status at baseline and change in work status. Employment status and cognitive assessment data were collected in 59 treatment-resistant schizophrenia or schizoaffective disorder patients. Forty-seven of 59 (79.7%) patients were unemployed at baseline. Over a 12-month period, 23 (48.9%) additional patients were able to gain paid or volunteer jobs, or attend school. As predicted, neurocognitive performance was a better predictor of employment status and ability to gain of employment than clinical symptoms. Improvement in verbal working memory was found to be a better predictor of employment outcome than other cognitive functions. Treatment that enhances cognitive function, especially verbal working memory, may lead to better employment outcomes in treatment-resistant schizophrenia or schizoaffective disorder patients.

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1. Introduction

Before the introduction and widespread use of atypical antipsychotic drugs such as aripiprazole, clozapine, olanzapine, quetiapine, risperidone and ziprasidone, no more than 15% of patients with schizophrenia in developed countries were reported able to obtain competitive employment (Mulkern and Manderscheid, 1989). In agreement with this, Mueser et al. (2001) reported that the competitive employment rates in patients with chronic schizophrenia were only 21–23%. There are few studies examining whether atypical antipsychotic drugs are helpful in increasing this low rate of employment. Factors influencing employment have a strong bearing on the societal costs of schizophrenia, due to lost income, lost productivity and disability income payments. Together these account for about US \$46 billion (nearly 70% of a total of almost US\$65 billion) of the total cost of schizophrenia in the United States (Anonymous, 1996).

There has been a considerable amount of research examining why people with schizophrenia are unable to obtain and keep competitive employment. Cognitive impairment, a core feature of schizophrenia (Saykin et al., 1994; Mohamed et al., 1999), has been reported to be the most important determinant of work and social function in schizo-

phrenia (Green, 1996; Meltzer et al., 1996; Meltzer and McGurk, 1999; Green et al., 2000; McGurk and Meltzer, 2000; Bell and Bryson, 2001; Goldberg et al., 2001; Gold et al., 2002; Bryson and Bell, 2003). Among several domains of cognitive function, verbal memory and executive function appear to be the cognitive functions which most affect work and social function (Jaeger and Douglas, 1992; Lysaker et al., 1995; Green, 1996; Meltzer et al., 1996; Bryson et al., 1998; Meltzer and McGurk, 1999; Green et al., 2000; McGurk and Meltzer, 2000; Bell and Bryson, 2001; Martinez-Aran et al., 2002; Smith et al., 2002; Bryson and Bell, 2003). In contrast, most studies have found that psychotic symptoms (Mueser et al., 2001) are not significantly associated with functional outcome (Green, 1996; Green et al., 2000). However, several recent studies have suggested that psychopathology may be equally or more important than cognitive dysfunction with regard to functional outcome (Norman et al., 1999; Ertugrul and Ulug, 2002; Mohamed et al., 2008).

Recent reports have suggested the potential value of atypical antipsychotic drugs for improving cognitive impairment in patients with schizophrenia (Keefe et al., 1999; Meltzer and McGurk, 1999; Harvey and Keefe, 2001; Percudani et al., 2004; Woodward et al., 2005). Although there have been some exceptions (e.g. the CATIE Trial; Keefe et al., 2007), atypical antipsychotic drugs may be expected to improve employment outcome. Among the atypical antipsychotic drugs, clozapine has been most studied. Clozapine has been reported to produce improvements in treatment-resistant patients in attention,

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verbal fluency and some types of verbal learning and memory and executive function, but not working memory (Hagger et al., 1993; Lee et al., 1994; Lee et al., 1999; Meltzer and McGurk, 1999).

The goal of this prospective study was to test the hypotheses that (1) the clozapine treatment would improve employment outcome in treatment-resistant patients with schizophrenia or schizoaffective disorder, and (2) specific types of cognitive impairment but not psychotic symptoms in patients with schizophrenia would predict work status and that improvement in verbal memory and executive function in particular would predict improvement in employment status. In this study, treatment-resistant patients were chosen because clozapine use has generally been restricted to treatment-resistant patients with schizophrenia or schizoaffective disorder due to its ability to cause agranulocytosis.

2. Methods

2.1. Subjects

This study was conducted at Vanderbilt University. Data available from a prior prospective longitudinal study was used to test our hypotheses. Fifty-nine patients who met Diagnostic and Statistical Manual of Mental Disorders, third edition, Text Revision (DSM-III-R) (American Psychiatric Association, 1987) criteria for schizophrenia or schizoaffective disorder were included in this study. History of patients' response to antipsychotic treatment was assessed at the outset through intensive interviewing of the probands, first-degree relatives and other informants, as well as a review of hospital records. Treatment-resistance status was determined according to the criteria of Kane et al. (1988). Patients with a significant current history of substance abuse/dependence, seizure or radiologically confirmed head injury/malformation were excluded from the study. The patients were interviewed with the Schedule for Affective Disorders and Schizophrenia Lifetime (SADS-L) and Change (SADS-C) versions (Endicott and Spitzer, 1978) to establish diagnoses. The Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962; 0–6 scales) was also employed to evaluate severity of psychopathology. Work status was defined as follows: 1. Employed = full-time (minimum of 30 h/week or full-time student status) or part-time (1–29 h/week or part-time student status); and 2. Unemployed = unemployed and not in school. Before admission to the study, informed written consent was obtained from all patients after the procedure had been fully explained. Demographic data are presented in Table 1.

Forty-eight (81.4%) patients were drug-free at least 5 days before baseline evaluation. Baseline assessments of the measures described above and cognitive function were performed. Patients were subsequently treated with clozapine. All patients were evaluated with the same measures after 12 months.

2.2. Treatment

2.2.1. Drug treatment

The drug treatment was carried out on an open basis because of the unreliability of maintaining masking during clozapine treatment. Thirty-one of 59 (52.5%) patients required concomitant medications; 10 (16.9%) patients received benztropine, 13 used lorazepam for psychomotor agitation, two received clonazepam and two received phenytoin for seizures, two required antihypertensive medications (atenolol and hydrochlorothiazide), one received chloral hydrate for insomnia, one received dicyclomine for irritable bowel syndrome and one patient received ranitidine for ulcers. Four patients received fluoxetine, two patients received divalproex, two patients received triptophan, one patient received sertraline and one patient received anaftranil in addition to antipsychotic agents. The dosages of clozapine at 12 months were 422.4 (SD = 190.4) mg/day.

2.2.2. Psychosocial treatment

Patients received an intensive psychosocial treatment programme, which included group and multifamily therapy on a weekly basis throughout the course of the study. The nurse therapist who led these groups also provided a work readiness-training programme on both an individual and group basis for the treatment-resistant subjects.

Table 1

Demographic information at baseline ($n = 59$).

	Mean (SD)
Age (yrs)	35.6 (8.9)
Gender (Female/male)	15/44
Race (African American/Caucasian/others)	8/50/1
Age of illness onset (yrs)	19.6 (4.7)
Duration of illness (yrs)	16.0 (7.8)
Years of education (yrs)	12.4 (2.3)
Number of times hospitalised	8.6 (6.4)
IQ	90.8 (15.8)

This included obtaining clerical tasks needed by the hospital and supervising the work of the patients in carrying out these jobs.

2.3. Cognitive tests

We used a cognitive test battery as described elsewhere (Kenny and Meltzer, 1991), consisting of the following measures: (1) a measure of psychomotor speed and attention (Wechsler Adult Intelligence Scale-Revised (WAIS-R) Digit Symbol Substitution Test (DSST; Wechsler, 1981)); (2) verbal working memory (Consonant Trigram Test (CTT; Peterson and Peterson, 1959)); (3) verbal fluency (Controlled Word Association Test (CWAT; Benton et al., 1983) and the Category Instance Generation Test (CIGT; Talland, 1965)); (4) verbal learning and memory (Verbal List Learning (VLL) Immediate Recall (VLL-IR) and Delayed Recall (VLL-DR; Buschke and Fuld, 1974)); and (5) executive function (Wisconsin Card Sorting Test (WCST) category (CAT) and perseveration (PP; Berg, 1948); Wechsler Intelligence Scale for Children-Revised (WISC-R) Maze (Wechsler, 1974)). The neuropsychological tests were factor analysed into three factors: memory (CTT, VLL-IR, VLL-DR and WISC-R Maze), attention (DSST, CWAT and CIGT) and executive function (WCST) (Meltzer et al., unpublished results). These tests were administered by a psychologist who was not blind to the nature of drug treatment. An estimated intelligence score was obtained using WAIS-R.

2.4. Statistical methods

Data analysis was conducted using the SAS (Version 8.2, SAS institute, 1999) software. The comparison of categorical responses to employment groups was carried out using chi-square tests. *T*-test analyses for independent group comparisons were used to compare differences in psychopathology and cognitive variables on employment status at baseline and at 12 months between two groups of patients (patients who remained unemployed and patients who gained employment). Moreover, the differences in psychopathology and cognition variables at 12 months between three groups of patients (patients that remained unemployed, patients that remained gained non-competitive employment and patients that gained competitive employment) were compared by analysis of variance (ANOVA), followed by *post hoc* comparisons. Improvement of psychopathology and cognition over time across groups was analysed using a repeated-measure ANOVA model. A logistic regression model with forward selection criteria was used to predict employment status and change in employment at different time points (dichotomous response) using demographic variables, improvement in psychopathology and cognitive measures. A *P*-value of less than 0.05 was considered significant, and the statistical tests were two-sided.

3. Results

3.1. Changes in employment status

After 12 months, employment outcome had significantly improved from 20.3% (12/59) at baseline to 50.8% (30/59) [$\chi^2 = 12.0$, $df = 1$, $P < 0.001$]. Out of 47 patients, 23 (48.9%) who were unemployed at baseline became employed during the 12 months period. One, eight and 12 patients gained paid full-time jobs, paid part-time jobs and unpaid volunteer work respectively. One patient went back to school as a part-time student, and one patient undertook a vocational education programme. When the patients with unpaid employment (i.e., volunteer) were excluded, 15 (25.4% vs. 16.9% at baseline) patients had become competitively employed. Meanwhile, five of 12 (41.7%) patients employed at baseline became unemployed during the 12-month period.

3.2. Differences in baseline variables between unemployed and employed patients at baseline

Patients who were unemployed at baseline were significantly older [$t = 2.64$, $df = 38$, $P = 0.01$] and showed a trend towards a longer duration of illness [$t = 1.99$, $df = 57$, $P = 0.05$] than those who were employed (Table 2). Comparisons of these two groups revealed significantly better baseline scores in the employed group for the BPRS total [$t = 2.02$, $df = 52$, $P = 0.04$] and positive scores [$t = 2.85$, $df = 52$, $P < 0.01$]. There was a trend towards a higher WISC-R Maze score in the employed group [$t = -1.65$, $df = 52$, $P = 0.10$].

3.3. Predictors of work status at baseline

The logistic regression analysis used a forward stepwise procedure to predict work status at baseline from variables including baseline

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