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Impact of antipsychotic medication on family burden in schizophrenia: Longitudinal results of CATIE trial

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ABSTRACT

Background: This study evaluated the effectiveness of first- and second-generation antipsychotics in reducing family burden associated with schizophrenia.
Methods: The family caregivers of 623 SCID-diagnosed patients enrolled in the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) randomly assigned to a first-generation antipsychotic (perphenazine) or one of four second-generation drugs (olanzapine, quetiapine, risperidone or ziprasidone) were interviewed about resources provided and stresses experienced at baseline and followed for 18 months. Patient symptoms, side effects and service use were assessed as well. Hierarchical regression analyses evaluated the effect of treatment assignment on four burden factors: problem behavior, resource demands and disruption, impairment in activities of daily living and patient helpfulness. Intention-to-treat analyses with all available observations classified based on initial treatment assignment, including observations after medications changed were followed by secondary analyses excluding observations after the first medication change, i.e. only considering initial medication.
Results: Despite significant reductions on the problem behavior and resource demands/disruption factors, there were no significant differences between perphenazine and any of the second-generation medications. When only initial treatment period observations were included, patients were perceived as more helpful when medicated with perphenazine as compared to risperidone. In comparisons between second-generation drugs, patients on quetiapine were perceived as more helpful than those on risperidone ($p = 0.004$).
Conclusion: In this 18-month randomized trial, there was no evidence of superiority of second-generation antipsychotics in relieving family burden.

1. Introduction

Recent studies of treatment effectiveness of antipsychotic medications for patients with schizophrenia have focused on evaluating an expanded range of outcomes beyond the clinical symptoms of the illness. For example, several studies have evaluated the effect of different pharmacotherapies on

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the patient's neurocognitive status (Keefe et al., 1999; Keefe et al., 2004; Rosenheck et al., 2003) and on psychosocial functioning (Rosenheck et al., 2000; Rosenheck et al., 2003; Swartz et al., 2007). Despite recognition of psychosocial functioning as an important outcome domain, few studies have focused on patients' relationships with their families. Higher levels of caregiver strain reported by family members are associated with poorer clinical outcome over time (Perlick et al., 2001), and family members may influence their relative's adherence with medication and other treatment regimens (Cochran and Gitlin, 1988; Perlick et al., 2004), underscoring the importance of family burden as a treatment outcome domain, in its own right and as a mediator of patient outcomes.

Previous studies have compared the effectiveness of clozapine vs. haloperidol in reducing the burden experienced by family members of veterans with treatment-resistant schizophrenia and found a reduction in some but not all burden factors with treatment with clozapine over 12 months (Rosenheck et al., 2000). No additional studies, to our knowledge, have investigated the effects of treatment with different antipsychotics on caregiver burden in schizophrenia. The present study investigated the impact of random assignment to the first-generation antipsychotic, perphenazine and four second-generation drugs (olanzapine, quetiapine, risperidone or ziprasidone) on family burden as measured by four factors: *problem behavior*, *resource demands and disruption*, *impairment in activities of daily living* and *patient helpfulness* over an 18-month of study period. Consistent with the results of prior studies (Rosenheck et al., 2000), we hypothesized that the family caregivers of patients assigned to second-generation antipsychotics would report less burden overall over 18 months than the caregivers of patients assigned to perphenazine.

2. Methods

CATIE was conducted between January 2001 and December 2004 at 57 U.S. sites. Participants in the present study were 42.7% of the 1460 patients enrolled in CATIE with a diagnosis of schizophrenia who identified caregivers who agreed to be interviewed about their life situation and experiences with the patient ($N=623$). Patients were excluded if they had a diagnosis of schizoaffective disorder, mental retardation or other cognitive disorders; an unstable serious medical condition; past adverse reactions to a proposed treatment; treatment-resistant schizophrenia; or if they were in their first episode of schizophrenia, pregnant, or breast-feeding. Caregivers were identified by the patient as the family member or friend most directly involved in his/her care. All patients and caregivers gave written informed consent to participate in protocols approved by local IRBs.

Patients were initially randomized to olanzapine, perphenazine, quetiapine, risperidone, or ziprasidone under double-blind conditions. Identical capsules contained olanzapine (7.5 mg), quetiapine (200 mg), risperidone (1.5 mg), perphenazine (8 mg) or ziprasidone (40 mg). However, patients with TD (15% of the sample) were excluded from the randomization that included perphenazine, limiting comparisons with perphenazine to patients without pre-existing TD. In addition, ziprasidone only became available in the study after 40% of patients had been enrolled. Medications were flexibly dosed with one to four capsules daily, according to clinical need judged by the study doctor. Concomitant medications were permitted, except for additional antipsychotic agents. Further details about blinding, later phases of treatment, and modal dosing have been presented elsewhere (Lieberman et al., 2005; Stroup et al., 2003).

Patients who discontinued their first treatment were invited to receive other second-generation antipsychotics, including clozapine if they desired, with random assignment to specific agents (Phase 2). Open treatment was also offered to patients who refused or whose treatment failed after further randomization (Phase 3), but only a small number chose first-generation antipsychotics (FGAs).

2.1. Measures

2.1.1. Patient measures

The SCID (First et al., 1996) confirmed the diagnosis of schizophrenia and symptom severity and type were assessed using the Positive and Negative Symptom Scale (PANSS) (Kay et al., 1987). Depression was measured with the Calgary Depression Rating Scale (Addington et al., 1990). Comorbid use of drugs and alcohol over the past 3 months was evaluated on a 5-point scale (with 1 = abstinent and 5 = dependence) using the clinician-rated Alcohol Use and Drug Use Scale (AUS/DUS) (Drake et al., 1996). Severity of antisocial behavior prior to age 15 was assessed using the sum of 6 items taken from the SCID including violation of rules (e.g., school truancy or expulsion), running away from home, destruction of property, aggression (initiation of physical fights), and trouble with the law (e.g., getting arrested).

Questions from the Lehman Quality of Life Interview (QOLI) (Lehman, 1988), were used to evaluate the adequacy of the patient's finances over the past six months and the total number of hours of employment per week.

Medication side effects were evaluated using the Barnes scale for akathisia (range 0–14) (Barnes, 1989), the Abnormal Involuntary Movement Scale (AIMS for tardive dyskinesia (range 0–40) (Guy, 1976) and the Simpson–Angus scale for extrapyramical side effects (EPS) (range 0–40) (Simpson and Angus, 1970).

Service use variables included use of mental health outpatient services and/or residential treatment in the past month, occurrence of an exacerbation of mental symptoms requiring psychiatric hospitalization or crisis stabilization during the past three months, use of any type of hospitalization for any reason in the past month (all coded as yes/no), total number of years in mental health treatment, and the patient's subjective response to medications, evaluated by the Drug Attitude Inventory (DAI) (Sheehan and Nuttall, 1988), a 10-item “true”/“false” scale, where higher numbers indicate more positive views towards medication.

2.1.2. Caregiver characteristics and burden

Family burden was evaluated using an adapted version of the Family Experience Interview Schedule (FEIS) (Tessler and Gamache, 1995) which evaluates patient problem behavior, activities of daily living, role functioning, disruption of household routine, caregiver contributions in time and