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Impact of prior pharmacotherapy on remission of psychotic depression in a randomized controlled trial

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ABSTRACT

Having failed to respond to an adequate antidepressant treatment course predicts poorer treatment outcomes in patients with major depression. However, little is known about the impact of prior treatment on the outcome of major depression with psychotic features (MDpsy). We examined the effect of prior treatment history on the outcome of pharmacotherapy of MDpsy in patients who participated in the STOPD-PD study, a randomized, double-blind, clinical trial comparing a combination of olanzapine plus sertraline vs. olanzapine plus placebo. The strength of treatment courses received prior to randomization was classified using a validated method. A hierarchy of outcomes was hypothesized based on treatments received prior to randomization and randomized treatment. A high remission rate was observed in subjects with a history of no prior treatment or inadequate treatment who were treated with a combination of olanzapine and sertraline. A low remission rate was observed in subjects who had previously failed to respond to an antidepressant alone and who were treated with olanzapine monotherapy. A low remission rate was also observed in subjects who had previously failed to respond to a combination of an antipsychotic and an antidepressant. Similar to patients with major depression, these results emphasize the impact of prior pharmacotherapy on treatment outcomes in patients with MDpsy.

1. Introduction

Major Depressive Disorder (MDD) is a highly prevalent mental illness in North America (Kessler et al., 2003; Patten et al., 2006). Major depression with psychotic features (MDpsy) is a severe form of major depressive disorder (MDD) that carries significant morbidity and a poor prognosis (Coryell et al., 1996; Rothschild, 2003). Thus, clinicians require indicators of treatment response prior to initiating a management plan. Prior treatment has been shown to predict remission and response of MDD when patients receive electroconvulsive therapy (ECT) (Prudic et al., 1996) or psychopharmacological treatment (Dombrovski et al., 2005; Rasmussen et al., 2007; Tew et al., 2006). In particular, patients who fail to respond to a previous adequate course of pharmacotherapy are significantly less likely to respond to treatment than treatment naïve patients or than those who have been exposed to an inadequate course (Amsterdam et al., 2009; Hennings et al., 2009; Tew et al., 2006). Thus, accurate assessment of treatment resistance and differentiating it from inadequate treatment has clinical implications for the treatment of MDD. However, little is known about the impact of prior treatment on the outcome of MDpsy.

We conducted this analysis to examine the impact of prior treatment history on the outcome of pharmacotherapy of MDpsy in patients who participated in a randomized clinical trial comparing, under double-blind conditions, a combination of olanzapine plus sertraline vs. olanzapine plus placebo (Meyers et al., 2009), referred to in this manuscript as combination and monotherapy

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respectively. We used a validated and reliable method to classify the strength of treatment courses received prior to randomization (Andreescu et al., 2007; Oquendo et al., 2003; Oquendo et al., 1999). We hypothesized a hierarchy of outcomes based on the adequacy of treatments received during the index episode and treatment assignment during the study. Specifically, we hypothesized that patients who had not received any prior treatment and who were randomized to combination therapy would have a high rate of remission; those who had been treated with an adequate combination of an antidepressant and an antipsychotic and who were randomized to monotherapy would have a low rate of remission; and those who had failed to respond to an antidepressant or an antipsychotic but not both, would have an intermediate rate of remission.

2. Methods

2.1. Subjects

As described previously (Meyers et al., 2009), patients 18 years of age or older admitted to the inpatient or ambulatory services of four academic sites between December 2002 and June 2007 were eligible for participation in the study. The Institutional Review Boards of the four institutions and a Data Safety Monitoring Board at the National Institute of Mental Health approved study consent forms and monitored the study's progress. Informed consent was obtained from all subjects, either directly or through locally approved substitute decision makers.

Strategies to identify eligible patients included review of new admissions, advertisements, and direct referrals by community psychiatrists. Subjects were assessed with the Structured Interview for Clinical Diagnosis (SCID) (First et al., 2002) to assure that DSM-IV-TR criteria for unipolar MDpsy were met. Other inclusion criteria included: the presence of at least one delusional belief defined as a fixed idea that was held contrary to the laws of logic; a score of $\geq$3 on the delusion severity rating item of the Schedule of Affective Disorders and Schizophrenia (SADS) (Endicott and Spitzer, 1978) (meaning that subjects had no more than a transient ability to consider the implausibility of their irrational belief); a score of $\geq$2 on one of the conviction items of the Delusional Assessment Scale (DAS) (Meyers et al., 2006); and a score $\geq$21 on the 17-item Hamilton Depression Scale (Ham-D) (Hamilton, 1960), which was administered using the GRID-Ham-D method (Williams et al., 2008). Exclusion criteria included: immediate indication for ECT because of refusal to eat or drink or imminent risk for suicide (however, patients with current suicidal ideation without immediate intent and those who had made a suicide attempt during the current episode were allowed to begin the study on an inpatient basis); a dementia or a history of impaired cognition prior to the current depressive episode; meeting criteria for another Axis I psychotic or mood disorder, current body dysmorphic disorder or obsessive-compulsive disorder, or substance abuse during the preceding three months; the presence of an unstable medical condition that might interfere with completion of the twelve-week trial; a neurological disease, such as Parkinson's disease, that might affect neuromuscular functioning; ongoing need for medications known to cause depression or psychosis; having received olanzapine 15 mg/day or more for a minimum of four weeks during the current episode; and benefiting from one's current psychotropic medications. Patients with known hyperlipedemia or diabetes mellitus, including insulin-dependent diabetes, were allowed to enroll if their metabolic conditions were stable. Screening also involved baseline laboratory assessments, including TSH, folate and B12 levels, an electrocardiogram, and a toxicology screen to detect undisclosed illicit drug use.

2.2. Intervention

Eligible subjects were randomized using computer-generated lists with investigators and raters blind to treatment assignments. Randomization was stratified by site and age $\geq$60 with a block size of four. Subjects taking antidepressant or antipsychotic medications at entry had these tapered prior to randomization but a wash out period was not enforced because of the severity of illness anticipated in study participants. Subjects began 2.5–5 mg/day of olanzapine and 25–50 mg/day of sertraline or matching placebo, with dose increases permitted every three days as tolerated. Olanzapine was administered openly and sertraline or placebo under double-blind conditions. An attempt was made to reach minimum doses of 10 mg/day of olanzapine and 100 mg/day of sertraline or placebo before the end of week one. Doses were increased to 15 mg/day of olanzapine and 150 mg/day of sertraline or placebo during week two, with further increases allowed to a maximum of 20 mg/day of olanzapine or 200 mg/day of sertraline, as tolerated, beginning in week three. Slower titration or temporary dose reductions of one or both medications was allowed if side effects were suspected; however, subsequent attempts to achieve minimum daily target doses of 15 mg/day of olanzapine and 150 mg/day of sertraline or placebo were required. Adjunctive lorazepam up to 4 mg/day was allowed to control anxiety or agitation and benztropine up to 2 mg/day to control extrapyramidal symptoms. No other psychotropics were allowed.

2.3. Clinical assessments

Baseline assessments were completed within seven days of obtaining consent. Follow-up research assessments were conducted weekly for the first six weeks and then every other week until week twelve or termination. Research assessments included overall symptom severity using the Clinical Global Illness Scale for severity (CGI-S) (Guy, 1976), Ham-D, assessments for delusional ideation using the DAS and the SADS delusional item. At baseline, the Cumulative Illness Burden Scale (Miller et al., 1992) was used to assess general medical burden and the Mini-Mental-State-Examination (MMSE) (Folstein et al., 1975) was used to assess global cognitive functioning. Raters were trained to achieve adequate reliability prior to conducting study assessments and inter-rater reliability reassessed annually thereafter.

2.4. Assessment of strength of prior antidepressant treatment courses

The strength of each pharmacological course received by the subjects during their current episode prior to enrollment (i.e., under usual clinical conditions) was assessed with a modified version of the Antidepressant Treatment History Form (ATHF) as described previously (Andreescu et al., 2007). Information regarding previous medications was obtained from all available sources: patients' reports, family reports, treating physicians, medical records, and pharmacy records. We used the original ATHF to rate the strength of antidepressant courses (Oquendo et al., 2003): the ATHF scores each antidepressant course based on the dose and the duration of treatment as: 1 (definitely inadequate); 2 (probably inadequate); 3 (probably adequate); 4 (definitely adequate); or 5 (definitely adequate antidepressant with lithium augmentation). Thus, a score of 1 corresponds to an antidepressant course of less than four weeks or a course of more than four weeks with a very low dose (e.g., sertraline less than 25 mg/day). A score of 2 corresponds to a course of more than four weeks with probably inadequate doses (e.g., fluoxetine or paroxetine between 10 and 19 mg/day). A score of 3 corresponds to a course of more than four