Factors associated with non-completion in a double-blind randomized controlled trial of olanzapine plus sertraline versus olanzapine plus placebo for psychotic depression

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ABSTRACT

High rates of attrition have been reported in randomized controlled trials of patients with severe psychiatric illness, including psychotic depression (MDpsy). The purpose of this study is to examine factors associated with overall attrition and with subtypes of attrition in the Study of the Pharmacotherapy of Psychotic Depression (STOP-PD). Secondary analysis of data collected in a multi-site, randomized, placebo-controlled trial. Clinical services of academic hospitals. Participants comprised 259 persons with MDpsy, aged 18-93 years. The intervention consisted of the random allocation to 12 weeks of treatment of either olanzapine plus sertraline or olanzapine plus placebo. Demographic and clinical variables associated with overall non-completion and sub-types of non-completion of randomized treatment. One hundred and seventeen (45.2%) subjects did not complete 12 weeks of randomized treatment. In a logistic regression analysis, inpatient entry status, olanzapine monotherapy, and higher cumulative medical burden were statistically significant independent predictors of overall non-completion. In a multinomial logistic regression model that examined predictors of subtypes of non-completion, subjects who entered the study as an inpatient were less likely to complete because of inadequate efficacy as determined by the investigator, and older subjects were less likely to complete because of poorer tolerability. Subjects who were assigned to olanzapine monotherapy, younger subjects, and subjects who entered the study as inpatients were less likely to complete because of reasons other than efficacy or tolerability. Understanding factors that contribute to premature discontinuation in studies of MDpsy, and to the specific reasons for attrition, has the potential to improve the management of this disorder, as well as improve the design of future clinical trials of MDpsy.

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1. Introduction

High attrition rates have been reported in placebo-controlled trials of patients with severe psychiatric illnesses, and particularly in trials of schizophrenia (Labelle et al., 1999; Kemmler et al., 2005). Major Depression with psychotic features (MDpsy) is also a severe, disabling disorder. It has poorer outcomes than major depression without psychotic features (Rothschild, 2003). Evidence-based expert guidelines recommend either electroconvulsive therapy (ECT) or the combination of an antidepressant medication and an antipsychotic medication ('combination treatment') for the treatment of MDpsy (American Psychiatric Association, 2000). Nevertheless, there has been limited evidence for the efficacy of combination therapy in MDpsy (Andreescu et al., 2006; Wijkstra et al., 2006). We recently reported that the combination of olanzapine and sertraline had greater efficacy than olanzapine plus placebo in the treatment of MDpsy, with 41.2% of subjects randomized to combination treatment achieving remission within twelve weeks (Meyers et al., 2009). However, 45.2% of the randomized subjects failed to complete the trial, raising the question of causes of attrition in this study. This question

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is important not only to researchers but also to clinicians: identifying baseline demographic and clinical factors that predict a low probability of completing a medication trial could lead to selecting ECT as an alternative evidence-based first-line treatment for these patients with MDpsy.

Factors related to patient, illness, and treatment can affect adherence with pharmacologic treatment and participation in clinical trials. Little is known about factors that contribute to non-completion in clinical trials of MDpsy or to poor adherence with pharmacotherapy in MDpsy. Previous randomized clinical trials comparing combination treatment with either antidepressant monotherapy or antipsychotic monotherapy in the acute treatment of MDpsy have reported non-completion rates of 12-59% (Spiker et al., 1985; Anton and Burch, 1990; Rothschild et al., 2004; Wijkstra et al., 2010), with the highest rate of non-completion being reported in the single study that included a placebo-only arm (Rothschild et al., 2004). In these published trials, reasons for non-completion were primarily lack of efficacy and adverse events. However, with the exception of the study by Spiker et al. (1985), none of these studies examined patient, illness, or treatment characteristics that could have contributed to non-completion. Spiker et al. (1985) found no difference between completers and non-completers on selected sociodemographic or clinical variables, but this analysis was limited by the small number of non-completers (n = 7) and the relatively small sample size. Understanding factors that contribute to discontinuation in pharmacologic studies of MDpsy, and the specific reasons for attrition, has the potential to improve treatment adherence in clinical practice, aid decision making in when to select ECT as an alternative treatment, and improve the design of future clinical trials for this disorder.

The Study of the Pharmacotherapy of Psychotic Depression (STOP-PD) was a NIMH-funded, 12-week randomized controlled trial that compared the efficacy and tolerability of olanzapine plus sertraline ('combination treatment') with olanzapine plus placebo ('monotherapy') in the treatment of adults aged 18 years or older with MDpsy (Meyers et al., 2009). We have reported in our initial analysis that efficacy was significantly higher and attrition was significantly lower in subjects randomized to olanzapine plus sertraline than in subjects randomized to olanzapine plus placebo (Meyers et al., 2009). However, to date, we have not determined whether other variables predict overall attrition or examined the predictors of specific types of attrition. Thus, the current study seeks to determine which sociodemographic and/or clinical variables were independently associated with overall non-completion and with specific types of non-completion in STOP-PD.

2. Methods

2.1. Participants

This study was approved by the Institutional Review Boards of the four participating sites and was carried out in accordance with the latest version of the Declaration of Helsinki. Written informed consent was obtained from all participants, either directly or through IRB-approved surrogate consent procedures, after the study had been fully explained. Full details of the study's participants, design and methodology have been reported elsewhere (Meyers et al., 2009). To summarize, the study group consisted of inpatients and outpatients aged 18 years or older with MDpsy based on the Structured Clinical Interview for DSM-IV-TR (First et al., 2001). All subjects had to have a baseline 17-item Hamilton Depression Rating Scale (HAM-D; Hamilton, 1960) score of at least 21, a baseline Schedule for Affective Disorders and Schizophrenia (SADS; Spitzer and Endicott, 1979) delusion severity score of at least 3 ('delusion definitely present'), and a score of 2 or higher on at least one of the baseline conviction items of the Delusion Assessment Scale (DAS; Meyers et al., 2006). Patients with any of the following were excluded: currently meeting or had met DSM-IV criteria for bipolar disorder, schizoaffective disorder, schizophrenia or other psychotic disorders; currently meeting DSM-IV criteria for body dysmorphic disorder or obsessive compulsive disorder; a history of substance abuse or dependence, including alcohol, within the last three months; a diagnosis of dementia or history of ongoing significant cognitive impairment (from informant report) prior to the index episode; an unstable medical illness; medical conditions (such as hypothyroidism), metabolic abnormalities (such as B12 deficiency), or medication (such as carbidopa) that could contribute to

psychopathology, confound response to pharmacotherapy, or render participants unable to tolerate or complete the study; being pregnant, planning to get pregnant, or breast feeding; a documented history of being unable to tolerate either sertraline or olanzapine; failure to respond to olanzapine taken at a dose of 15 mg/day or greater for at least 4 weeks during the current depressive episode; or being sufficiently ill to require immediate open pharmacotherapy or ECT (e.g., due to imminent risk of suicide or refusal to eat).

2.2. Outcomes and measures

The main outcome in STOP-PD was remission, defined as a HAM-D score of 10 or lower at 2 consecutive assessments and the absence of delusions (SADS delusion item score of 1) at the second assessment. The protocol stipulated *a priori* that subjects would be discontinued from the study at the end of Week 5 if they had 'significant clinical worsening' (worsening depression or psychosis or increased suicidality) or 'insufficient clinical response', defined as having both a Clinical Global Impression (CGI; Guy, 1976)-improvement score of ≤2 ('no or minimal improvement') and a CGI-severity score of ≥4 ('moderately or more severely ill') after five weeks of randomized treatment. This protocol directive was made on clinical and ethical grounds, given the severity of the illness, the fact that half of the study group was not receiving antidepressant medication, and the availability of ECT as an alternative treatment for this severe illness. With the exception of this sub-group of patients, the goal was to have all other subjects complete 12 weeks of randomized treatment.

For this analysis, subjects were categorized as 'completers' of 12 weeks of randomized treatment or 'non-completers'. In order to examine the association between predictor variables and specific reasons for non-completion, the non-completers were further divided into four subgroups, based on the reason for discontinuation ascertained by the research psychiatrist at the time of the patient's discontinuation (i.e., before the blind was broken): (i) discontinued by the study investigator because of either 'significant clinical worsening' or 'insufficient clinical response' by the end of Week 5 (based on the aforementioned *a priori* criteria); (ii) discontinuation initiated by subjects, their families or their non-study physicians because of actual or perceived lack of efficacy; (iii) discontinuation because of poor tolerability (adverse effects or intercurrent medical events affecting tolerability); and (iv) discontinuation due to other reasons. Although non-completion described under categories (i) and (ii) both pertained to lack of treatment efficacy, we analyzed these categories separately, because they were intrinsically different: the first group was a 'forced' discontinuation by the study investigator based on protocol-defined *a priori* criteria, whereas the second group was an 'elective' discontinuation by the subject, surrogate, or non-study physician based on actual or perceived lack of efficacy. The fourth category, 'other reason', comprised a variety of reasons for discontinuation, other than overt efficacy or tolerability; the most frequent reasons being 'changed mind about participation in a research study', 'refused further study medication', 'lost to follow-up', and 'protocol violation'. Each of these reasons had too few subjects to be analyzed separately; therefore they were combined into a heterogeneous group. Analyses were based on all subjects randomized to treatment. The four non-completer subgroups were mutually exclusive.

The baseline sociodemographic and clinical measures examined for their association with outcome were age, gender, race, Hispanic ethnicity, marital status, living arrangements, number of years of education, single versus recurrent index episode of depression, duration of index episode of depression, randomized treatment assignment, inpatient versus outpatient status at the time of consent, consent status (subject consent versus surrogate consent), and baseline scores of the following rating scales: 17-item HAM-D, SADS delusion severity, Brief Psychiatric Rating Scale (BPRS; Overall and Gorham, 1962), the first 5 items of the Suicide Ideation Scale (Beck et al., 1979), Mini Mental State Examination (MMSE; Folstein et al., 1975) (a measure of global cognitive function), and Cumulative Illness Rating Scale-Geriatrics (CIRS-G; Miller et al., 1992) (a measure of cumulative medical burden).

2.3. Data analysis

Chi-square tests (for categorical variables) and analysis of variance (for continuous variables) were used to examine the relationship of each of independent variable with i) completion and overall non-completion, and ii) completion and the four subgroups of non-completion (Tables 1 and 2). Variables with a main effect p-value<0.1 were chosen for inclusion in the separate logistic regression models that examined the independent association of predictor variables with i) overall non-completion, and ii) the 4 sub-groups of non-completion, with the completer group serving as the reference. Variables with a p-value<0.05 were considered statistically significant independent predictors of non-completion and remained in the final model.

3. Results

The study group consisted of 259 subjects ($n = 117$ aged 18–59 and $n = 142$ aged 60 years or older), of whom 129 were randomized to combination treatment and 130 to monotherapy. Clinical and sociodemographic characteristics of this sample have been previously described (Meyers et al., 2009). Table 1 provides descriptive data for each of the independent variables in this study.