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The predictive value of early treatment response in antipsychotic-naive patients with first-episode psychosis: Haloperidol versus olanzapine

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ABSTRACT

Early antipsychotic response predicts outcomes for psychotic patients, but recent evidence suggests that this may not be true for patients treated with olanzapine. In this study, we assessed the predictive value of early response to olanzapine or haloperidol in 75 antipsychotic-naive, first-episode psychosis inpatients. Patients were assessed weekly using the Brief Psychiatric Rating Scale (BPRS), Hamilton Depression Rating Scale (HAM-D), Hamilton Anxiety Rating Scale (HAM-A), and Young Mania Rating Scale (YMRS). Regression analyses were used to determine whether improvement at week 2 or week 3 predicted improvement at hospital discharge. The majority of patients in both groups experienced a decrease in symptom severity of $\geq 50\%$ at week 2. In the haloperidol group, week 2 improvement predicted improvement at discharge for all measures except the HAM-A. In the olanzapine group, week 2 improvement only predicted improvement at discharge for HAM-D scores. However, week 3 improvement in the olanzapine group predicted improvement at discharge for all measures except the HAM-A. Olanzapine non-responders at week 3 (but not week 2) benefited from having olanzapine switched to another antipsychotic. These results suggest that a 2 week trial of haloperidol is sufficient to predict treatment outcomes, while a 3 week trial is required for olanzapine.

1. Introduction

Antipsychotic drugs are the mainstay of treatment for psychosis, but their mechanism of action is still incompletely understood. Early theories suggested that there was a “delayed onset” of antipsychotic action, whereby the therapeutic effect would not become apparent for several weeks after initiation of treatment. As a result, antipsychotic trials of at least 6 weeks were suggested before efficacy of the drug could be properly evaluated (Lehman and Steinwachs, 1998). In the last decade, however, it has become increasingly apparent that the therapeutic action of antipsychotics actually begins much earlier in the course of treatment, with the greatest improvement occurring in the first 2 weeks (Agid et al., 2003, 2006). This suggests that antipsychotic effectiveness could be assessed soon after treatment initiation, without the need for extended 6-week trials. Multiple studies have found that early response can be used to accurately predict which patients will eventually achieve adequate symptom improvement (Agid et al., 2013; Ascher-Svanum et al., 2008; Correll et al., 2003; Kinon et al., 2008; Samara et al., 2015; Schennach-Wolff et al., 2011). Although the clinical utility of this information has not yet been extensively tested, there is some evidence that identifying patients with a poor 2-week response and immediately switching them to another antipsychotic may improve treatment outcome (Kinon et al., 2010). The predictive value of early antipsychotic response has not been thoroughly studied in an antipsychotic-naive sample. Since patients with no prior antipsychotic exposure are more responsive to antipsychotic treatment (Emsley et al., 2006; McEvoy et al., 1991), the assessment of early response may be even more useful in this population.

Recent studies have reported that the predictive value of early response may not be equally applicable to all antipsychotic drugs. Hatta et al. (2011) found that early non-response at 2 weeks robustly predicted non-response at 4 weeks for patients treated with risperidone, but not for those receiving olanzapine. Similarly, Leucht and Zhao (2014) found that early response at 2 weeks predicted response at 6 weeks for patients treated with asenapine, risperidone, haloperidol, or placebo, but not with olanzapine. These studies suggest that olanzapine response at 2 weeks may not reliably predict response at later time points. It is not known whether olanzapine response at 3 weeks (or later) would provide

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sufficient predictive value. It is also unclear why olanzapine might perform differently than other antipsychotics. Furthermore, interpretation of these results is complicated by the fact that most of the patients studied were not antipsychotic-naive. An investigation of exclusively antipsychotic-naive patients might provide clearer information about early olanzapine response.

Another area of uncertainty is the role of affective symptomatology in early antipsychotic response. Depression and anxiety are associated with positive symptoms in schizophrenia and schizophreniform disorder (Emsley et al., 1999; Naidu et al., 2014), and depressive symptoms at baseline may predict a poorer treatment response (Naber et al., 2013; Riedel et al., 2012; Schennach et al., 2012). Moreover, early improvement in depressive symptoms has been reported to predict eventual remission in patients with schizophrenia (Chou et al., 2013). Additionally, in patients with bipolar I disorder receiving antipsychotic treatment, early improvement in psychotic or manic symptoms predicts eventual manic episode remission (Ketter et al., 2010; Szegedi et al., 2013). These studies suggest that early changes in affective symptomatology may predict treatment outcome in patients undergoing antipsychotic treatment, but these relationships have not yet been fully explored. Again, it is difficult to interpret the results of many of these studies because of the lack of antipsychotic-naive patients. Without assessing patients prior to any antipsychotic exposure, it is unclear whether the initial assessment represents a true "baseline." As a result, early improvements from baseline may not accurately represent initial responses to antipsychotic treatment. Unfortunately, antipsychotic-naive populations are rare; even in major randomized controlled trials of first-episode psychosis patients, a large majority of patients typically have some prior antipsychotic exposure (Kahn et al., 2008; Schooler et al., 2005).

While early antipsychotic response has emerged as a powerful predictor of treatment outcome, several uncertainties remain. In particular, it is important to clarify the predictive value of early response to olanzapine at multiple time points. Additionally, it is unclear whether improvement on concurrent symptoms of depression, anxiety, or mania can be predicted to the same extent based on early response. We investigated these issues in a sample of antipsychotic-naive patients admitted to hospital for first-episode psychosis.

2. Methods

2.1. Study design

All patients admitted to the inpatient psychiatry service at one hospital in Hamilton, Ontario over a three-year period were assessed for eligibility. To be considered eligible, patients had to be experiencing their first episode of psychosis and must have had no prior antipsychotic exposure. Patients were not excluded based on age, DSM diagnosis, or other criteria. Eligible patients received a complete description of the study before they or their substitute decision-makers were given the opportunity to provide written informed consent. All study protocols were approved by the McMaster University Research Ethics Board.

Patients entering the study were assessed at admission before any treatment was initiated. They were subsequently blindly randomized to receive either haloperidol or olanzapine. Olanzapine treatment began at 5 mg/day. The daily dose was adjusted in 2.5 mg increments/decrements as clinically indicated by clinicians blinded to the treatment assignment. Haloperidol treatment began at 2 mg/day, and the dose was adjusted in 1 mg increments/decrements. Supplementary medications (for example, benzodiazepines or anticholinergic medications) were permitted in accordance with usual clinical care. In cases where a changing of antipsychotic medication was deemed necessary due to intolerable side-effects or perceived treatment ineffectiveness, both the patient and physician were unblinded to the treatment condition, but patients continued to be assessed until the study endpoint. These patients were excluded from the main analysis.

2.2. Assessments

Upon admission, demographic information was collected along with each patient's psychiatric and medical history. Complete assessments were conducted at baseline and twice a week thereafter until discharge from hospital. The lowest scores recorded during each week were used for the analysis. Hospital discharge was used as the study endpoint.

Overall illness severity was assessed using the Brief Psychiatric Rating Scale (BPRS). Affective symptoms were assessed using the Hamilton Depression Rating Scale (HAM-D), Hamilton Anxiety Rating Scale (HAM-A), and the Young Mania Rating Scale (YMRS). To specifically evaluate psychosis, a BPRS psychotic symptom subscale was calculated from the sum of scores on conceptual disorganization, suspiciousness, hallucinations, and unusual thought content. Since akathisia may influence anxiety scores, akathisia was also assessed using the Barnes Akathisia Rating Scale (BARS). Assessments were conducted by physicians or a research nurse blinded to the treatment condition.

2.3. Statistical analysis

Along with total scores for each psychiatric measure at each time point, percent improvement from baseline was calculated. Since BPRS items are scored from 1 to 7, the minimum score (18) was subtracted from the total score to calculate percentages. Linear regression accounting for age and sex was used to determine whether improvement at week 2 or week 3 predicted improvement at discharge. This analysis was conducted separately for each psychiatric measure of interest. Percent improvement on the BPRS total score at hospital discharge was used as the primary outcome measure. This analysis was conducted on a per-protocol basis, including only those patients with complete information who did not switch antipsychotic drugs during their hospitalization.

Akathisia was determined to be present if patients scored at least "mild" (2) on the BARS global assessment item. In a secondary analysis, the presence of akathisia at hospital discharge was included in regression models assessing the predictive value of early improvement on the HAM-A. Since akathisia is often interpreted as anxiety, this analysis was intended to determine the extent to which akathisia influenced the final assessment of HAM-A improvement.

To directly compare treatment groups, independent *t*-tests were used for continuous variables and Fisher's exact test was used for categorical variables.

In previous studies, early improvement and eventual treatment response have been dichotomized using thresholds of 20% and 50% BPRS improvement respectively (Samara et al., 2015). We applied these thresholds to patients in our sample in order to calculate the sensitivity (probability that a non-responder at discharge was a non-responder at week 2), specificity (probability that a responder at discharge was a responder at week 2), positive predictive value (PPV, probability that a non-responder at week 2 was a non-responder at discharge) and negative predictive value (NPV, probability that a responder at week 2 was a responder at discharge). Following the example of Samara et al. (2015), this analysis emphasizes the identification of non-responders, since these are the patients who may benefit from a change of treatment.

Given the large number of patients who switched from