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Optimal thresholds of early response to atypical antipsychotics: Application of signal detection methods

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ABSTRACT

Objective: Identify the optimal magnitude of response to antipsychotic medication at various early time points that best predicts subsequent non-response at 8 weeks.
Methods: Data were pooled from 5 randomized, double-blind clinical trials of atypical antipsychotics in the treatment of schizophrenia and related disorders ($n = 1137$ moderately-to-severely ill; $n = 300$ less than moderately ill). Signal detection methods (receiver-operating characteristic curves) were used to identify the optimal response threshold based on percent change from baseline on the PANSS total score at different early time points (Weeks 1–4) to predict subsequent 'non-response' at 8 weeks (i.e., not 'minimally improved', 'much improved' or 'remitted') while holding the false positive rate to a level of 30% or less. Analyses were implemented separately for patients with schizophrenia who differed on baseline illness severity.
Results: Using Area Under the Curve (AUC) ≥ 0.8 to define optimal discriminative ability at the earliest time point, the early response threshold in moderately-to-severely ill patients for predicting not 'minimally improved' was <15% reduction in PANSS total at Week 2, not 'much improved' was <23% at Week 2, and not 'remitted' was <26% at Week 4. Similarly, in less than moderately ill patients, the optimal early response threshold for predicting not 'minimally improved' was <12% reduction in PANSS total at Week 2, and not 'much improved' was <14% at Week 1.
Conclusion: Specific thresholds of response were identified at early time points for predicting subsequent non-response. Not attaining these early response thresholds may serve as important clinical markers of subsequent non-response to antipsychotic therapy.

1. Introduction

Prompted by the mounting evidence of early-onset of antipsychotic action in the treatment of schizophrenia (Agid et al., 2003, 2006; Leucht et al., 2005a), there is a growing interest in examining early clinical markers as predictors of later treatment outcome. In usual practice, clinical markers may be used for early identification of patients who are not responding to their current antipsychotic medication and who may require a change in their treatment regimen.

Previous research has used various symptom improvement thresholds to define early response/non-response, including an absolute lack of symptom improvement (0%) on the BPRS (Leucht et al., 2007, 2008) to 20% symptom improvement from baseline on the BPRS or PANSS (Correll et al., 2003; Ascher-Svanum et al., 2008; Kinon et al., 2008a). The time point at which early response/non-response was

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assessed in previous studies has also varied, but to a lesser extent, often focusing on the first or second week of treatment. Similarly, the criterion of subsequent response and time point at which subsequent treatment outcomes were assessed have also differed (i.e., 4 weeks to 6 months) (Correll et al., 2003; Ascher-Svanum et al., 2008; Kinon et al., 2008a; Leucht et al., 2008).

Although the same threshold has been used to assess both early response/non-response and subsequent response (Correll et al., 2003), recent studies (Leucht et al., 2005a, 2008; Kinon et al., 2008a) indicate greater overall predictive accuracy when higher thresholds are used to assess subsequent treatment outcomes. The research by Leucht et al. (2005b) helped clarify the clinical meaning of the PANSS total score and cut-offs used to define treatment response, indicating that being 'minimally improved' on the Clinical Global Impressions (CGI-I) scale was commensurate with a mean percentage PANSS reduction of 19%, 23%, 26% and 28% at Weeks 1, 2, 4, and 6, respectively. The corresponding values for 'much improved' were 40%, 45%, 51% and 53%.

In this study, we used pooled data ($n = 1437$) from 5 randomized, double-blind studies in the treatment of schizophrenia with atypical antipsychotics. Signal detection methods were used to identify – via percent change on PANSS total scores – the optimal magnitude of response to antipsychotic medication at various early time points (Weeks 1–4) that best predict subsequent non-response at 8 weeks. Subsequent non-response was defined in 3 different ways: not 'minimally improved', not 'much improved', and not 'remitted'. This analysis, which limited the false positive rate (false non-responder rate) to 30%, was implemented separately for schizophrenia patients who were considered to be either moderately-to-severely ill or less than moderately ill at baseline. We also validated the findings using data from another clinical trial.

2. Methods

2.1. Participants

The data used in the current *post-hoc* analyses were drawn from 5 randomized, double-blind, published trials (Breier et al., 2005; Keefe et al., 2006; Kinon et al., 2006a,b; Tran et al., 1997) comparing olanzapine with other atypical antipsychotics (risperidone, quetiapine and ziprasidone). The studies enrolled patients diagnosed with schizophrenia, schizophreniform, or schizoaffective disorder that were chronically ill but not treatment refractory.

The analytical sample included patients who were treated with any of the studied atypical antipsychotics, had both baseline and postbaseline Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1986) total scores available, and met the following illness severity grouping criteria:

A. Moderately-to-severely ill patients: baseline PANSS total score ≥75 (Leucht et al., 2005b), with at least "moderate" level of severity (score ≥4) on at least 2 of the 4 Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962) psychotic cluster items (i.e. conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content).
B. Less than moderately ill patients: baseline PANSS total score <75 and not meeting modified remission criteria defined as mild symptomatology [i.e. a score of 3 or less on 8 PANSS items: delusions (P1); conceptual disorganization (P2); hallucinatory behavior (P3); unusual thought content (G9); mannerisms and posturing (G5); blunted affect (N1); passive/apathetic social withdrawal (N4); and lack of spontaneity and flow of conversation (N6)], without the requirement that mild scores be maintained for at least 6 months given that the endpoint response was defined as 8 weeks in this analysis [Schizophrenia Working Group Expert Consensus Criteria; (Andreasen et al., 2005)].

Data from another olanzapine trial in the treatment of schizophrenia and related disorders (Kinon et al., 2008b) were used to validate the findings from the 5 pooled studies. Subjects from the validation trial had to meet the same inclusion and illness severity grouping criteria.

2.2. Definition of subsequent non-response

The guidelines for the treatment of schizophrenia have suggested a duration of antipsychotic drug therapy for 4 to 8 weeks prior to switching to another antipsychotic agent (Falkai et al., 2006; Kaplan and Sadock, 2005; Lehman et al., 2004; Miller et al., 2004). To give sufficient time to observe treatment responses, we defined the time of subsequent non-response as Week 8.

Subsequent non-response was defined in 3 different ways to reflect variations in level of response to medication: not 'minimally improved', not 'much improved', and not 'remitted'. The operational definitions of these 3 non-response levels differed between the 2 baseline severity groups given that the moderately-to-severely ill patients have more room for improvement, while the less than moderately ill patients will have less room for relative improvement.

For moderately-to-severely ill patients:

A. not 'minimally improved': <28% reduction in PANSS total scores (Leucht et al., 2005b),
B. not 'much improved': <53% reduction in PANSS total score (Leucht et al., 2005b), and
C. not 'remitted': not achieving a mild score or better (score ≤3) on at least one of the 8 PANSS items (Andreasen et al., 2005).

For the less than moderately ill patients:

A. not 'minimally improved': <20% reduction in PANSS total score,
B. not 'much improved': <40% reduction in PANSS total score, and
C. not 'remitted': not achieving a mild score or better (score ≤3) on at least one of the 8 PANSS items (Andreasen et al., 2005).

2.3. Statistical methodology

Baseline demographics, patient characteristics, psychiatric history and disease severity were reported for the moderately-to-severely ill and less than moderately ill patient groups using descriptive statistics. Proportions of subsequent