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Challenging the assumption that improvement in functional outcomes is delayed relative to improvement in symptoms in the treatment of schizophrenia

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ABSTRACT

Objectives: Functional improvement is generally thought to be distal to improvement in psychiatric symptoms in patients with schizophrenia. In this study, we assessed the effects of early response/non-response to an atypical antipsychotic across multiple outcome measures.
Methods: This was a randomized, double-blind, flexible-dose, 12-week study that enrolled chronically-ill patients ($n=628$) diagnosed with schizophrenia or schizoaffective disorder who were experiencing acute symptom exacerbation. Patients were initially assigned to risperidone drug therapy (2–6 mg/day), and their response status at 2 weeks was determined. Early responders (ERs) continued with risperidone therapy, whereas early non-responders (ENRs) were randomized (1:1) in a double-blind manner to either continue on risperidone or switch to another atypical antipsychotic for 10 additional weeks of therapy. Subsequent treatment outcomes were measured by the Quality of Life Scale (QLS), Schizophrenia Objective Functioning Instrument (SOFI), and Subjective Well-being under Neuroleptics (SWN-K) scale.
Results: Compared to ENRs, ERs to risperidone showed significantly more improvement from baseline to endpoint on the QLS total score and all 4 categories ($p<.01$), the SOFI overall global score and all 4 domains ($p<.001$), and the SWN-K total score and all 5 subscales ($p<.05$). Among ERs, the majority of improvement had already been attained by Week 2. There was concordance among clinician- and patient-rated scales across outcomes.
Conclusion: Improvement across multiple outcome dimensions was not delayed relative to improvement in psychiatric symptoms. Rather, patients who showed an early response to antipsychotic treatment as defined by improvement in psychiatric symptoms also showed early and consistent improvement in functioning, quality of life, and subjective well-being.

1. Introduction

An important goal in the treatment of patients with schizophrenia and related psychotic disorders is enabling each patient to re-engage in "meaningful life experiences" — active involvement in psychosocial and occupational activities, satisfaction with life, and subjective well-being. Lehman (1999) provided a framework for conceptualizing the multiple dimensions of outcomes. His model proposed that

Abbreviations: ANOVA, analysis of variance; ANCOVA, analysis of covariance; mg, milligram; MADRS, Montgomery–Asberg Depression Rating Scale; MMRM, Mixed Effects Model Repeated Measure; *n*, number; PANSS, Positive and Negative Syndrome Scale; QLS, Quality of Life Scale; SD, standard deviation; SOFI, Schizophrenia Objective Functioning Instrument; SWN-K, Subjective Well-being on Neuroleptics Scale.

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most of the "proximal" outcomes of antipsychotic medications occur in the clinical domain and involve the reduction of psychotic and other psychiatric symptoms as well as the occurrence of medication-related side effects, while "distal" outcomes occur in the rehabilitative, humanitarian and public welfare domains and involve improvement in patient's functional status, quality of life, and family and community welfare. The terms "proximal" and "distal" refer not only to *causal immediacy* of the outcome to the action of the antipsychotic drug treatment, but also imply a *temporal cascade* in which improvement in proximal outcomes may lead to success in more distal outcomes. The effects of treatment are thought to be stronger and more immediate on "proximal" rather than on "distal" outcomes.

Recent data have demonstrated that a patient's likelihood to "respond" to a given antipsychotic medication (i.e., symptom reduction) is evident within the first 2 weeks of starting an antipsychotic medication (Ascher-Svanum et al., 2008; Correll et al., 2003; Kinon et al., 2008; Leucht et al., 2007, 2008). Early response to antipsychotic drug therapy has been associated subsequently (at 8 weeks) with an increased likelihood of achieving symptom remission, with greater improvement on functional outcomes, higher perception of medication as beneficial, and with lower health care costs (Ascher-Svanum et al., 2008). How does the concept of "early response" relate to changes in functioning? Is improvement in functioning delayed relative to improvement in symptoms?

In a 12-week, prospective, clinical trial, we demonstrated that compared to early non-responders (ENRs), early responders (ERs) to risperidone showed significantly greater improvement in psychopathology at 12-weeks (Kinon et al., 2009). In this analysis, we extend the concept of early response to multiple outcome dimensions by comparing ERs and ENRs to risperidone on the following endpoints: 1) the effect of early response/non-response on functioning, quality of life and subjective well-being assessed at the 12-week endpoint, 2) the relationship of change in these outcome domains at 2 weeks to the change observed at 12 weeks, and 3) the degree of similarity in outcomes observed between clinician- and patient-rated functional scales.

2. Patients and methods

2.1. Study design

This was a randomized, double-blind, flexible-dosed, parallel 12-week study enrolling 628 patients to explore the relationship between early response to an antipsychotic medication and subsequent improvement in psychopathology (primary outcome measure) using the oral atypical antipsychotic risperidone. Secondary outcome measures included comparisons between ER and ENR groups across additional efficacy measures and across multiple outcome dimensions. Patients met diagnostic criteria for schizophrenia, schizoaffective disorder or schizophreniform disorder according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). After complete description of the study was given to the patients, written informed consent was obtained. In addition, the study was approved by the Ethics Committee from each institution in which it was conducted, patient confidentiality was not breached, and the study was done in accordance to the Declaration of Helsinki.

The primary manuscript from this clinical trial describes in detail the overall study design, inclusion/exclusion criteria, and concomitant medications (Kinon et al., 2009). In brief, there were three study periods (SP): SPI, screening; SPII, study enrollment in which all patients were treated with risperidone for initial 2 weeks; and SPIII, early responder status was assessed, with ERs and a subset of ENRs continuing on risperidone for additional 10 weeks. A second subset of ENRs was switched to olanzapine for 10 additional weeks of treatment; these patients were not included in the current analysis given the focus on comparing ERs and ENRs on functioning and not on the potential benefits of switching. Patients had to be at least moderately-ill at the start of the study and experiencing an exacerbation of their illness within the 2 weeks preceding Visit 1 that led to an intensification of the level of psychiatric care.

2.2. Measures

The Positive and Negative Syndrome Scale ($PANSS_{1-7}$) (Kay et al., 1987) was used to assess psychopathology. The PANSS is a 30-item rating scale used by clinicians to evaluate the severity of positive and negative symptoms and general psychopathology of schizophrenia, with each item rated on a 7-point scale (1 = absent, 7 = extreme severity), with the total score ranging from 30 to 210. Higher scores indicate worse symptomatology. Patients were assigned into ER or ENR groups at 2 weeks based on *a priori* defined improvement in the $PANSS_{1-7}$ total score. ERs showed $\geq$20% improvement in PANSS total score from baseline. ENRs showed <20% improvement in PANSS total score from baseline.

The Montgomery–Asberg Depression Rating Scale (MADRS) (Montgomery and Asberg, 1979) is used by clinicians to measure the severity of depressive symptoms. The MADRS consists of 10 items, with each item being rated on a scale from 0 to 6. The MADRS total score is the sum of the 10 items, with the total score ranging from 0 to 60. Higher scores indicate worse depressive symptoms.

The Heinrich's Carpenter Quality of Life Scale (QLS) is a 21-item, clinician-rated scale based on a semi-structured interview designed to assess deficit symptoms in patients with schizophrenia (Heinrichs et al., 1984). Each item is rated on a 7-point scale (0–6). Total scores range from 0 to 126, with higher scores indicating better functioning (e.g., less functional impairment). There are four distinct categories including 1) Common Objects and Activities — possession of common objects and engagement in a range of regular activities, 2) Intrapsychic Foundation — clinical judgments of patient's sense of purpose, motivation, curiosity, empathy, ability to experience pleasure, and emotional interaction, 3) Interpersonal Relations — frequency of social contact and complex judgments of the capacity for intimacy, active versus passive participation, and avoidance and withdrawal tendencies; and 4) Instrumental Role — role of worker, student, or housekeeper/parent, and judgments about patient's level of accomplishment, degree of underemployment, and satisfaction derived.