

Early response or nonresponse of schizophrenia symptoms to antipsychotic medication is a predictor of long-term outcome

After prescribing antipsychotic medication, many clinicians will wait 4 to 8 weeks before deciding whether to maintain the current treatment or to change it if the patient displays a suboptimal clinical response. However, a recent meta-analysis of randomised clinical trials (RCTs) has demonstrated that this delay is unnecessary, because the greatest reduction of symptoms occurs during the first 2 weeks of therapy. Furthermore, post hoc analyses of RCTs have shown that nonresponse in the first 2 weeks after treatment initiation is a reliable predictor of subsequent nonresponse in patients with schizophrenia.

This evidence has important economic and clinical significance. Unnecessary delays in treatment evaluation exposes nonresponders to prolonged exposure to subtherapeutic or ineffective antipsychotic treatment regimens and unnecessary costs. In addition, changing to an effective treatment regimen is delayed. However, evidence gathered from RCTs has limitations, in that the patients from whom the data is gathered are not necessarily representative of the majority of patients with schizophrenia in routine care. Patients included in RCTs are often acutely ill hospital inpatients and those with comorbid substance abuse and medical disorders are typically excluded.

In order to examine whether the observations gathered from the RCTs may also be applicable to chronically ill outpatients who are more representative of those seen in everyday practice, Dr Ascher-Svanum and colleagues performed a post hoc analysis using data collected from a practical, randomized, open-label, multisite, naturalistic study of antipsychotics in the treatment of schizophrenia that had broad inclusion criteria and did not exclude patients with comorbid medical or psychiatric disorders. The study included 664 schizophrenic patients randomized to treatment with olanzapine, risperidone or typical antipsychotics and followed-up for 1 year. Ninety five percent were outpatients at the time of enrolment with approximately 17 years since the first psychiatric hospitalization. If the patient demonstrated a suboptimal clinical response after 8 weeks of the initial treatment, they could be switched to an alternative therapy. This post hoc analysis included 443 patients who had documented Positive and Negative Syndrome Scale (PANSS) scores at 2 and 8 weeks and who completed the first 8 weeks of treatment on the antipsychotic to which they were initially randomized. At baseline, the patients had at least moderate illness severity, with a mean baseline PANSS score of 86.9. Patients were defined as 'early responders' if they had a $\geq 20\%$ decrease in PANSS score from baseline at 2 weeks and 'responders' based on the same criteria at 8 weeks. Symptom remission was defined as a score of mild or better (3 or less) on 8 PANSS items (delusions, conceptual disorganization, hallucinations, unusual thought content, mannerisms and posturing, blunted affect, social withdrawal, lack of spontaneity and flow of conversation). Other outcomes that were assessed included levels of physical and mental functioning, the patient's attitude to their medication and perception of health benefit, and

total direct healthcare costs.

At 2 weeks, 98 patients (22.1%) were early responders and 345 (77.9%) were early nonresponders. Baseline characteristics were similar in these 2 groups with the exception of total PANSS score (89.8 vs. 84.4, respectively; $P=0.023$), impulsivity/hostility subscale score (9.7 vs. 8.6; $P=0.004$) and anxiety/depression subscale scores (13.6 vs. 12.3; $P=0.01$).

Response or nonresponse at 2 weeks predicted the outcome at 8 weeks. Seventy two percent of eventual responders and nonresponders at 8 weeks were correctly identified after 2 weeks of treatment with the same antipsychotic agent. Specificity, indicating a high probability of correctly identifying nonresponders, was high (88.7%), whereas sensitivity, indicating a high probability of correctly identifying responders, was moderate (41.5%). Results were similar when an absolute definition of response (mild or better score on 4 PANSS psychotic items) was substituted for the relative definition of response, and regardless of baseline illness severity or the assigned treatment.

Compared to early responders, at 8 weeks early nonresponders were less likely to have achieved remission (27.5% vs. 46.9%; $P<0.001$) and they had significantly lower levels of improvement on the mental composite score and on 5 of the 8 functional domain scores. At 8 weeks, early nonresponders also scored significantly worse on measures of perceived medication benefits, including perceived daily benefits, fear of relapse, side effects relief and fulfillment of life goals. The total direct healthcare cost was almost twice as high for early nonresponders after 8 weeks of treatment, compared to early responders, primarily as a result of higher nonmedication costs. Significant differences in costs were seen as early as 2 weeks after therapy initiation.

This study confirms that the observations from RCTs are also applicable to the larger schizophrenic community of outpatients. Poor response to treatment after 2 weeks predicts a poor outcome, worse functional outcomes, poor perception of treatment and higher costs. Perception of treatment is important, because dissatisfaction with treatment may be associated with a higher rate of treatment discontinuation, increasing the risk of relapse and hospitalization. Consequently, early evaluation of treatment is warranted after initiating antipsychotic medication and changing the treatment regimen may be considered in patients who have not responded adequately after two weeks of therapy.

It is important to note, however, that response at 2 weeks does not imply that the patient has reached their full potential outcome after that time. Most patients may take 8 to 12 weeks to reach stable symptom improvement.

Reference

Ascher-Svanum H, Nyhuis AW, Faries DE, et al. Clinical, Functional, and Economic Ramifications of early Nonresponse to Antipsychotics in the Naturalistic Treatment of Schizophrenia. *Schizophrenia Bulletin* 2008; 34(6): 1163-1171.