Mr. M, age 28, was given a diagnosis of schizophrenia 6 years ago after experiencing a psychotic break involving auditory hallucinations and paranoia. Olanzapine, 10 mg/d, relieved his symptoms, but he stopped taking the drug after gaining 40 pounds and developing diabetes mellitus. He had 2 other hospital admissions for acute psychosis and has taken at least 1 other medication, the name of which he can’t recall. Recently, Mr. M was involuntarily admitted to the psychiatric ward of his local hospital. His psychiatrist started aripiprazole, 10 mg/d, which was titrated to 30 mg/d. After 2 weeks he reports only a slight decrease in hallucinations. His mother is growing concerned about the effectiveness of this medication and wants to know if it’s time to consider another drug.

Time to onset of action of antipsychotic agents has been debated since at least 1970.\textsuperscript{1} Supporters of the delayed-onset hypothesis assert that antipsychotics take weeks or months to show significant improvement of symptoms because of the need for depolarization block for efficacy.\textsuperscript{2} Trials of 4 to 6 weeks often are recommended for patients before failure is declared.\textsuperscript{3,4} and trials of this length or longer have proved useful for first-episode patients.\textsuperscript{5,7} Recent studies suggest, however, that response is cumulative for chronically ill patients with most improvement occurring during weeks 1 and 2.\textsuperscript{1,8}

Two meta-analyses found the greatest rate of cumulative improvement in symptoms during the first 2 weeks.\textsuperscript{1,4} These analyses included chronically ill patients with mean duration of illness of 15.5 and 10.4 years, respectively. Patients reported 21.9% and 20.5% reductions in symptoms from baseline at 2 weeks, with total responses between 30% at 4 weeks and 40% at 1 year, respectively. These meta-analyses indicate that most of the benefit from antipsychotics in this patient population occurs in the first 2 weeks, which supports the early-response hypothesis.

These observations led to questions about the predictive value of early response and minimum time to determine treatment failure. This article discusses the significance of early response and non-
response to antipsychotics and their impact on treating patients with schizophrenia.

What are the predictive factors? How can they guide treatment?

Of the 8 studies in our literature review, only 2 reported early response rates >50%.9,10 (see this article at CurrentPsychiatry.com for a Box describing the literature review.) Positive predictive value (PPV) ranged from 0.51 to 0.81, meaning that 51% to 81% of early responders continued to respond. Six of the 8 studies reported PPV of 50% to 70%.9,11-15 This appears to be true for chronic and first-episode patients, suggesting that 30% to 50% of early responders will fail to have a sustained response (Table 1,9-16 Table 2, page 54,9-16 and Figure).

Compared with early response, early non-response is a more consistent predictor of final non-response. In every study of chronically ill patients, negative predictive value; PPV: positive predictive value
value (NPV) was greater than PPV (Table 1, page 53). NPVs in the literature suggest that 58% to 91% of early non-responders will continue to be non-responders. This seems to be true of chronically ill patients for whom NPVs consistently were between 75% and 85%. By comparison, in first-episode patients NPVs of 58% and 66% were calculated (Table 1, page 53 and Figure, page 53).

These observations suggest that reassessing drug therapy is indicated early in treatment for early non-responders, particularly in chronically ill patients. However, early non-response in a first-episode patient is not as strong a predictor of eventual treatment failure, supporting the idea that first-episode patients may experience a delayed response to therapy. Researchers studying onset of antipsychotic effect report that median time to response onset in first-episode patients may be ≥8 weeks.

Clinical Point

Reassessing drug therapy is indicated early in treatment for early non-responders, particularly in chronically ill patients.
early response, assess dose, adherence, substance abuse, and psychosocial stressors. For patients without dose, adherence, substance use, or stress issues, switching drug therapy in chronically ill early non-responders is reasonable because the probability of a late response is small.

Individual patient characteristics determine how much these data aid clinical decision-making. If a patient has a good response to an antipsychotic in the first 2 weeks, continue the drug, but observe the patient closely because response may not be sustained. In first-episode patients who fail to respond within 2 weeks of starting an antipsychotic, it is reasonable to continue the drug for several weeks because these patients may be more likely to respond later in therapy.

Clinicians treating chronically ill patients who have failed several antipsychotic-
ics and demonstrate a poor response after 2 weeks of an appropriate antipsychotic dose are justified in changing medications because later significant response is unlikely. If a patient has a poor early response but has failed several other antipsychotics with few remaining alternatives, it is reasonable to continue the maximum tolerable dose of the current therapy because the patient may be a late responder. However, early non-response predicts future non-response in many patients.

**CASE CONTINUED**

Mr. M is failing his current treatment regimen with a reasonable antipsychotic dose after 2 weeks. Because Mr. M has been on 2 antipsychotics and demonstrated a good response to olanzapine, changing medications should be considered.

**References**


In this article, positive predictive value (PPV) is the percentage of early responders who experienced a sustained response and met predetermined response criteria at the end of the study, typically measured at week 4 to 12. A high PPV indicates a high probability of sustained response to antipsychotics; low PPV indicates a lack of correlation between early and sustained response. Negative predictive value (NPV) is the proportion of early non-responders who continued as late non-responders. A high NPV indicates that early non-responders are likely to be late non-responders.

\[
\begin{align*}
PPV &= \frac{\text{early, sustained response}}{\text{all early responders}} \\
NPV &= \frac{\text{early, sustained non-response}}{\text{all early non-responders}}
\end{align*}
\]

We searched Google Scholar for the terms “antipsychotics schizophrenia onset of action (early OR delayed)” to identify potentially relevant articles. Author name and title words from articles that we deemed pertinent were entered in PubMed and the results were reviewed for relevant and related articles. MeSH terms used for separate searches included “antipsychotic agents,” “humans,” and “time factors.” No time limits were specified and studies were included regardless of illness chronicity of study populations. We conducted a manual search of the bibliographies of all articles obtained. Articles were excluded if they reported onset of effect without analysis of predictive value of early measures or if they did not report sensitivity, specificity, PPV, and NPV.

Our literature search returned 8 studies that evaluated the predictive value of early response to antipsychotic treatment in patients with psychotic disorders. Most of these studies followed similar methodology with most being post-hoc re-analyses of previously conducted studies in patients with schizophrenia, schizophreniform disorder, or schizoaffective disorder (Table 1).9-16 Patients were assigned randomly to antipsychotics to which they were naïve. Early response was measured at a predetermined point using a response threshold from a validated symptom rating scale. Late response was measured at another predetermined time using the same or higher response threshold.

The studies have several differences (Table 1).a-h Study authors included either chronic (6 studies)a-f or first-episode (2 studies)g,h patients. Most determined early response after 2 weeks with 1 measuring response at 4 weeks.a Late response was determined at several points between 3 and 62 weeks with most studies falling within a 4- to 12-week window. Most authors defined early response as a ≥20% reduction in symptom score and late response as a ≥40% reduction in symptom score at endpoint. Two studies were based on criteria other than a threshold symptom reduction. Studies had sample sizes of 67 to 522 patients; the 2 pooled analyses had populations of 7,979 and 1,002.

References