What is the relevance of a 2-week response to an antipsychotic?

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Series Editor

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.[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.[2] Trials of 4 to 6 weeks often are recommended for patients before failure is declared,[3,4] and trials of this length or longer have proved useful for first-episode patients.[5-7] Recent studies suggest, however, that response is cumulative for chronically ill patients with most improvement occurring during weeks 1 and 2.[1,8]

Two meta-analyses found the greatest rate of cumulative improvement in symptoms during the first 2 weeks.[1,8] 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-

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Practice Points

- Chronically ill and first-episode patients **may respond differently to antipsychotics**.
- In chronically ill patients with schizophrenia, **early non-response accurately predicts non-response at weeks 4 to 12** in 75% to 85% of patients. Early response accurately predicts sustained response at weeks 4 to 12 in approximately 50% to 70% of patients.
- In first-episode patients with schizophrenia, **early non-response predicts non-response at weeks 12 to 16** in approximately 60% to 65% of patients. Early response predicts response at weeks 12 to 16 in approximately 60% to 75% of patients.

Table 1

Predictive value of early response to an antipsychotic

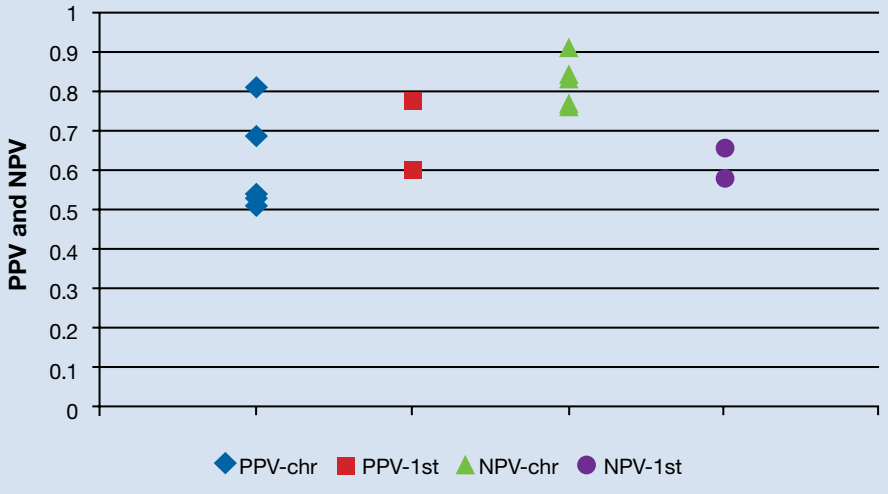
Study	Chronicity[a]	Early responders	PPV	NPV
Hatta et al, 2011[10]	Chronic	70%	0.81	0.91
Glick et al, 2009[11]	Chronic	36.2%	0.51	0.77
Jäger et al, 2009[13]	Chronic	40%	0.53	0.83
Kinon et al, 2008[12]	Chronic	31.2%	0.54	0.84
Kinon et al, 2010[9]	Chronic	52%	0.68	0.84
Kinon et al, 2010[14]	Chronic	28%	0.69	0.76
Stauffer et al, 2011[16]	First episode	43%	0.77	0.66
Gallego et al, 2011[15]	First episode	12.1%	0.60	0.58

[a]chronic for illness >10 years (average); first episode for illness for <2.2 years (average)

NPV: negative predictive value; PPV: positive predictive value

Figure

Positive and negative predictive values by illness chronicity



PPV for both chronically ill (blue diamonds) and first-episode patients (red squares) fall in the same range; NPV for chronically ill patients (green triangles) is greater than the corresponding PPV for the same patients (blue diamonds) and NPV for first episode patients (purple circles)

1st: first-episode patients; chr: chronically ill patients; NPV: negative predictive value; PPV: positive predictive value

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

Clinical Point

Compared with early response, early non-response is a more consistent predictor of final non-response

See this article at CurrentPsychiatry.com for a box describing the literature review methodology

Table 2

Characteristics of studies included in the literature review

Study	Design	Sample characteristics	Included conditions
Hatta, et al 2011[10]	Randomized prospective	N = 67 Chronically ill (duration of illness not reported)	Schizophrenia, schizophreniform disorder, schizoaffective disorder
Glick et al, 2009[11]	Re-analysis of 3 double-blind, placebo controlled trials	N = 797 Chronically ill (illness for ≥1 year, estimated average = 10 years)	Schizophrenia
Jäger et al, 2009[13]	Randomized naturalistic	N = 237 Chronically ill (average 10.3 years)	Schizophrenia, schizophreniform disorder
Kinon et al, 2008[12]	Re-analysis of 5 randomized, double-blind trials	N = 1002 Chronically ill (average 15 years)	Schizophrenia, schizophreniform disorder, schizoaffective disorder
Kinon et al, 2010[9]	Re-analysis of 2 randomized, double-blind, placebo-controlled trials	N = 252 Chronically ill (average 15 years)	Schizophrenia
Kinon et al, 2010[14]	Randomized, double-blind, prospective trial	N = 522 Chronically ill (average 18 years)	Schizophrenia, schizophreniform disorder, schizoaffective disorder
Stauffer et al, 2011[16]	Re-analysis of 1 randomized double-blind trial	N = 225 First-episode patients who had been ill 1.1 to 1.4 years	Schizophrenia, schizophreniform disorder, schizoaffective disorder
Gallego et al, 2011[15]	Re-analysis of one randomized, open-label trial	N = 112 First-episode patients who had been ill for an average 2.2 years and lifetime exposure to antipsychotics of <12 weeks	Schizophrenia, schizophreniform disorder, schizoaffective disorder

BPRS: Brief Psychiatric Rating Scale; CGI-I: Clinical Global Impressions – improvement scale; PANSS: Positive and Negative Syndrome Scale; SADS-C + PD: Schedule for Affective Disorders and Schizophrenia Change Version with Psychosis and Disorganization Items

Clinical Point

Reassessing drug therapy is indicated early in treatment for early non-responders, particularly in chronically ill patients

value (NPV) was greater than PPV (***Table 1, page 53***).[9-16] 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***[9-16] and ***Figure, page 53***).[14,15]

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.[6,8] In patients who do not achieve modest

Study medications	Response criteria
Risperidone, olanzapine	Early: CGI-I score ≤3 at treatment week 2 Late: ≥50% reduction on PANSS total score at week 4
Paliperidone	Early: ≥30% reduction on PANSS total score at week 2 Late: "persistence" of response for up to 6 weeks
First-generation and second-generation antipsychotics, tranquilizers, mood stabilizers, antidepressants	Early: ≥20% reduction in PANSS total score at week 2 Late: ≥40% reduction in PANSS total score at weeks 3 to 62
Olanzapine, risperidone, quetiapine, ziprasidone	Early: ≥20% reduction in PANSS total score at 2 weeks Late: ≥40% reduction in PANSS total score at 12 weeks
Olanzapine, haloperidol	Early: ≥25% reduction in BPRS total score at 2 weeks Late: ≥40% reduction in BPRS total score at 6 weeks
Risperidone, olanzapine	Early: ≥20% reduction in PANSS total score at 2 weeks Late: ≥30% reduction in PANSS total score at 1 2 weeks
Olanzapine, haloperidol	Early: ≥26.2% reduction in PANSS items 0 to 6 at 2 weeks Late: ≥40% reduction in PANSS total score at 12 weeks
Olanzapine, risperidone	Early: ≥20% reduction in SADS-C + PD at 4 weeks Late: Ratings of mild or better on 6 SADS-C + PD items

early response, assess dose, adherence, substance abuse, and psychosocial stressors.[3] For patients without dose, adherence, substance use, or stress issues, switching drug therapy in chronically ill early nonresponders 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 antipsychot-

Clinical Point

If a patient has a good response to an antipsychotic in the first 2 weeks, continue the drug, but observe the patient closely

Related Resource

- Correll CU, Hauser M. The year in psychosis and bipolar disorder: predicting response to schizophrenia treatment. www.medscape.com/viewarticle/735211_7.

Drug Brand Names

Aripiprazole • Abilify	Quetiapine • Seroquel
Haloperidol • Haldol	Risperidone • Risperdal
Olanzapine • Zyprexa	Ziprasidone • Geodon
Paliperidone • Invega	

Clinical Point

If a patient has a poor early response and has failed other antipsychotics, it is reasonable to continue the highest tolerated dose

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 tolerated 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

1. Agid O, Kapur S, Arenovich T, et al. Delayed-onset hypothesis of antipsychotic action: a hypothesis tested and rejected. Arch Gen Psychiatry. 2003;60(12):1228-1235.
2. Grace AA, Bunney BS, Moore H, et al. Dopamine-cell depolarization block as a model for the therapeutic actions of antipsychotic drugs. Trends Neurosci. 1997;20(1):31-37.
3. Lehman AF, Lieberman JA, Dixon LB, et al; American Psychiatric Association Steering Committee on Practice Guidelines et al. Practice guideline for the treatment of patients with schizophrenia, second edition. Am J Psychiatry. 2004;161(suppl 2):1-56.
4. Meltzer HY, Bobo WV, Heckers SH, et al. Chapter 16. Schizophrenia. In: Ebert MH, Loosen PT, Nurcombe B, Leckman JF, eds. CURRENT Diagnosis & Treatment: Psychiatry. 2nd ed. New York: McGraw-Hill; 2008. http://www.accessmedicine.com/content.aspx?aID=3284037. Accessed December 5, 2013.
5. Robinson DG, Woerner MG, Alvir JM, et al. Predictors of treatment response from a first episode of schizophrenia or schizoaffective disorder. Am J Psychiatry. 1999;156(4):544-549.
6. Emsley R, Rabinowitz J, Medori R. Time course for antipsychotic treatment response in first-episode schizophrenia. Am J Psychiatry. 2006;163(4):743-745.
7. Lieberman JA, Phillips M, Gu H, et al. Atypical and conventional antipsychotic drugs in treatment-naive first-episode schizophrenia: a 52-week randomized trial of clozapine vs chlorpromazine. Neuropsychopharmacology. 2003;28(5):995-1003.
8. Leucht S, Busch R, Hamann J, et al. Early-onset hypothesis of antipsychotic drug action: a hypothesis tested, confirmed and extended. Biol Psychiatry. 2005;57(12):1543-1549.
9. Kinon BJ, Chen L, Stauffer VL, et al. Early onset of antipsychotic action in schizophrenia: evaluating the possibility of shorter acute efficacy trials. J Clin Psychopharmacol. 2010;30(3):286-289.
10. Hatta K, Otachi T, Sudo Y, et al. Difference in early prediction of antipsychotic non-response between risperidone and olanzapine in the treatment of acute-phase schizophrenia. Schizophr Res. 2011;128(1-3):127-135.
11. Glick ID, Bossie CA, Alphs L, et al. Onset and persistence of antipsychotic response in patients with schizophrenia. J Clin Psychopharmacol. 2009;29(6):542-547.
12. Kinon BJ, Chen L, Ascher-Svanum H, et al. Predicting response to atypical antipsychotics based on early response in the treatment of schizophrenia. Schizophr Res. 2008;102(1-3):230-240.
13. Jäger M, Schmauss M, Laux G, et al. Early improvement as a predictor of remission and response in schizophrenia: results from a naturalistic study. Eur Psychiatry. 2009;24(8):501-506.
14. Kinon BJ, Chen L, Ascher-Svanum H, et al. Early response to antipsychotic drug therapy as a clinical marker of subsequent response in the treatment of schizophrenia. Neuropsychopharmacology. 2010;35(2):581-590.
15. Gallego JA, Robinson DG, Sevy SM, et al. Time to treatment response in first-episode schizophrenia: should acute treatment trials last several months? J Clin Psychiatry. 2011;72(12):1691-1696.
16. Stauffer VL, Case M, Kinon BJ, et al. Early response to antipsychotic therapy as a clinical marker of subsequent response in the treatment of patients with first-episode psychosis. Psychiatry Res. 2011;187(1-2):42-48.

Box

Literature review methodology

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.

$$PPV = \frac{\text{early, sustained response}}{\text{all early responders}} \qquad NPV = \frac{\text{early, sustained non-response}}{\text{all early non-responders}}$$

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.[h] 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.[b]

References

a. Glick ID, Bossie CA, Alphs L, et al. Onset and persistence of antipsychotic response in patients with schizophrenia. J Clin Psychopharmacol. 2009;29(6):542-547.
b. Kinon BJ, Chen L, Ascher-Svanum H, et al. Predicting response to atypical antipsychotics based on early response in the treatment of schizophrenia. Schizophr Res. 2008;102(1-3):230-240.
c. Kinon BJ, Chen L, Stauffer VL, et al. Early onset of antipsychotic action in schizophrenia: evaluating the possibility of shorter acute efficacy trials. J Clin Psychopharmacol. 2010;30(3):286-289.
d. Hatta K, Otachi T, Sudo Y, et al. Difference in early prediction of antipsychotic non-response between risperidone and olanzapine in the treatment of acute-phase schizophrenia. Schizophr Res. 2011;128(1-3):127-135.
e. Jäger M, Schmauss M, Laux G, et al. Early improvement as a predictor of remission and response in schizophrenia: results from a naturalistic study. Eur Psychiatry. 2009;24(8):501-506.
f. Kinon BJ, Chen L, Ascher-Svanum H, et al. Early response to antipsychotic drug therapy as a clinical marker of subsequent response in the treatment of schizophrenia. Neuropsychopharmacology. 2010;35(2):581-590.
g. Stauffer VL, Case M, Kinon BJ, et al. Early response to antipsychotic therapy as a clinical marker of subsequent response in the treatment of patients with first-episode psychosis. Psychiatry Res. 2011;187(1-2):42-48.
h. Gallego JA, Robinson DG, Sevy SM, et al. Time to treatment response in first-episode schizophrenia: should acute treatment trials last several months? J Clin Psychiatry. 2011;72(12):1691-1696.