Prophylactic Antipsychotics: Do They Keep You From Catching Schizophrenia?

Stephen M. Stahl, M.D., Ph.D.

Issue: *Early studies suggest that atypical antipsychotics may prevent the progression of high-risk individuals to schizophrenia.*

Earlier, we reviewed the concept that treatments that reduce symptoms in psychiatry could also be disease modifying.[1] Now comes further evidence that this pretreatment may be possible in schizophrenia,[2–7] where it is already known that atypical antipsychotics not only get you better by treating acute symptoms, but also keep you better by preventing relapse.[2,8] Is it possible that giving these agents to high-risk individuals with prodromal symptoms could prevent or delay progression to schizophrenia?

Proven Versus Experimental Uses of Atypical Antipsychotics in Schizophrenia

The use of atypical antipsychotics to reduce symptoms in acute psychotic episodes and to prevent relapses in schizophrenia is not only proven but also FDA approved.[8] Accumulated evidence from first-episode studies also suggests that early intervention with atypical antipsychotics—as soon as possible after the onset of first psychotic symptoms—can improve outcomes.[2]

These treatment concepts are based on the idea that schizophrenia progresses first from a state of high risk without symptoms, then to a prodrome with cognitive and negative but not psychotic symptoms, and ultimately to first-episode schizophrenia with psychotic symptoms.[9] Once the illness can be diagnosed—after the onset of the first episode of psychotic symptoms—the long-term course of schizophrenia for many patients is then characterized as waxing and waning positive symptoms with ever-worsening cognitive symptoms.[9,10] Functional outcomes are thought be more closely linked to cognitive symptoms than to positive symptoms.[9]

Early treatment of first-episode patients is now generally considered to be the "best practice" in managing schizophrenia, even though early treatment has not been proved definitively to improve outcomes.[2] Once the first episode of psychosis has occurred, current state of the art for treatment of schizophrenia with atypical antipsychotics is to reduce cognitive and affective symptoms as well as positive symptoms in an attempt to improve functional recovery over the long term, even if this is unable to completely arrest declining function over time.[2,8–10] Using atypical antipsychotics to reduce both cognitive and affective symptoms of schizophrenia is a reasonable and neurobiologically informed approach to the treatment of schizophrenia based on current knowledge.[11] However, it is not yet known to what extent atypical antipsychotics can modify functional outcomes by improving cognitive and affective symptoms as well as positive symptoms over the long run.

Treatment of Prodromal Symptoms

Observations of improved outcomes with early intervention in first-episode cases have tempted investigators to theorize that initiating atypical antipsychotic treatment even before the onset of psychotic symptoms might also prevent or delay disease progression prior to the onset of significant functional decline.[3–7] A "prodrome" of depression, decreased concentration and attention span, lack of motivation, apathy, and social withdrawal can precede the first psychotic symptoms in schizophrenia by as

BRAINSTORMS is a monthly section of The Journal of Clinical Psychiatry *aimed at providing updates of novel concepts emerging from the neurosciences that have relevance to the practicing psychiatrist.*

From the Neuroscience Education Institute in Carlsbad, Calif., and the Department of Psychiatry at the University of California San Diego.

Reprint requests to: Stephen M. Stahl, M.D., Ph.D., Editor, BRAINSTORMS, Neuroscience Education Institute, 5857 Owens Street, Ste. 102, Carlsbad, CA 92009.

much as 4 or 5 years.[2,9,10] Some patients never progress beyond this phase of the illness. An open study of adults between 33 and 43 years of age with this prodrome who also had a first-degree relative with schizophrenia reports that the atypical antipsychotic risperidone reduced negative symptoms and improved working memory.[3]

In another open study, younger patients aged 15 to 20 years with a prodrome defined as a schizotypal, paranoid, or schizoid personality disorder, and who were presumably on a high-risk pathway to develop schizophrenia, were reportedly improved by risperidone in terms of their thought disorder and attention but not their social withdrawal.[4] Interestingly, a different open study of antidepressants either alone or in combination with mood stabilizers or anxiolytics in prodromal adolescents aged 14 to 22 years also seemed to improve symptoms over a period of 3 years.[5]

A controlled trial of prodromal individuals defined as having attenuated positive psychotic symptoms, brief intermittent psychotic symptoms, or genetic risk with recent functional decline reported that olanzapine improved prodromal symptoms better than placebo over 8 weeks.[6] Another controlled study examined the effects of risperidone treatment on the progression of "ultra high risk" individuals defined as those with nonspecific symptoms, impaired functioning, and a first-degree relative with psychosis; attenuated positive psychotic symptoms lasting at least a week; or brief episodes of psychotic symptoms not sustained beyond a week.[7] Significantly fewer individuals went on to develop a first-episode psychosis in the group treated with risperidone.

Summary of the State of the Art

Currently, the data only suggest but do not yet prove that atypical antipsychotics are effective for preventing progression of high-risk prodromal individuals to first-episode psychosis of schizophrenia. The symptoms implicated in the possible treatment effect include negative symptoms, affect, and cognitive difficulties as well as thought disorder. Atypical antipsychotics, particularly at low doses, as well as other psychotropic drugs and nonpharmacologic interventions may all contribute to the effects on symptomatic progression reported in the trials published to date.[3–7]

At this point, much more information will be required before presymptomatic or prodromal treatment can be recommended as part of current practice guidelines, including more controlled trials, consensus on definitions of the prodrome and functional outcomes, testing of additional atypical antipsychotics, and controlling for other psychotropic medications as well as nonpharmacologic interventions. The well-informed clinician can currently only determine the risks—which are relatively well known—versus the benefits—which are not well known—for each individual patient before deciding to embark on this treatment strategy.

Take-Home Points

- Individuals at high risk for developing schizophrenia include those who have prodromal symptoms such as cognitive difficulties, depression, and social withdrawal but not necessarily psychosis.
- Current neurodevelopmental and neurodegenerative theories of schizophrenia predict that reducing prodromal symptoms could prevent or delay their evolution to schizophrenia.
- Early studies suggest but do not yet prove that atypical antipsychotics reduce prodromal symptoms and may delay or prevent progression to schizophrenia.

REFERENCES

1. Stahl SM. Can psychopharmacologic treatments that relieve symptoms also prevent disease progression? [BRAINSTORMS] J Clin Psychiatry 2002;63:961–962
2. Remington G, Shammi C. The use of pharmacotherapy in the prodrome of schizophrenia. CNS Spectrums 2004;9:579–586
3. Tsuang MT, Stone WS, Seidman LJ, et al. Treatment of nonpsychotic relatives of patients with schizophrenia: four case studies. Biol Psychiatry 1999;45:1412–1418
4. Cannon TD, Huttunen MO, Dahlstrom M, et al. Antipsychotic drug treatment in the prodromal phase of schizophrenia. Am J Psychiatry 2002; 159:1230–1232
5. Cornblatt B, Lencz T, Correll C, et al. Treating the prodrome: naturalistic findings from the RAP program. Acta Psychiatr Scand 2002;106 (suppl):44
6. Woods SW, Breier A, Zipursky RB, et al. Randomized trial of olanzapine vs placebo in the symptomatic acute treatment of patients meeting criteria for the schizophrenia prodrome. Biol Psychiatry 2003;54:453–464
7. McGorry PD, Yung AR, Phillips LJ, et al. Randomized controlled trial of interventions designed to reduce the risk of progression to first-episode psychosis in a clinical sample with subthreshold symptoms. Arch Gen Psychiatry 2002;59:921–928
8. Stahl SM. Essential Psychopharmacology: The Prescribers Guide. New York, NY: Cambridge University Press; 2004
9. Lieberman JA, Perkins D, Belger A, et al. The early stages of schizophrenia: speculations on pathogenesis, pathophysiology, and therapeutic approaches. Biol Psychiatry 2001;50:884–897
10. Stahl SM. Essential Psychopharmacology. 2nd ed. New York, NY: Cambridge University Press; 2000
11. Stahl SM. Symptoms and circuits, pt 3: schizophrenia [BRAINSTORMS]. J Clin Psychiatry 2004: 65:8–9