Challenges in preventing schizophrenia

A major hurdle is identifying those at risk for developing psychosis in the future.

One of the reasons schizophrenia is so disabling is that obvious psychotic symptoms—which are what usually prompt treatment—occur relatively late in the disease process. By then, cognitive function, as measured by various neuropsychological tests, is already lower on average than in healthy individuals.

Neuroimaging studies have revealed that patients in this earlier "prodromal" phase have lost gray matter (neurons and other brain cells) when compared with controls—indicating that some underlying brain damage has occurred. And a preliminary study suggests that patterns of brain activation are already abnormal in those who may be at risk.

For the past 15 years, researchers around the world have been evaluating ways to prevent psychosis in patients most at risk for developing schizophrenia. The hope is that early intervention efforts might alter the disease course in a way that would improve outcomes and prevent disability.

A key obstacle is better identifying the young people most at risk for developing psychosis. Many investigators are therefore advocating for targeted interventions based on a more precise estimation of disease stage.

Aiming for early detection

Heart disease provides a dramatic example of the benefits of early detection, with blood pressure medication and cholesterol-lowering drugs literally saving the lives of many people who are deemed at risk on the basis of clinical tests. But the earliest warning signs of schizophrenia are more subtle and less specific than those for heart disease. Nonetheless, researchers agree that vulnerability to schizophrenia begins in the womb, and that the disease progresses through five stages.

• ***Premorbid.*** Subtle cognitive and social difficulties—such as a child who is a slow learner or has trouble playing with others—are the earliest signs of schizophrenia, but also may suggest other developmental problems.

• ***Prodromal.*** This phase involves an intensification of social difficulties and muted or fleeting psychotic symptoms, such as strange thoughts, odd perceptions, or hearing or seeing something that is not there. In the prodromal stage, an individual understands that these perceptions are not real.

• ***Psychotic.*** The onset of frank psychosis is often dramatic and sudden. It is characterized by florid hallucinations and delusions, the "positive" symptoms of schizophrenia. Moreover, the individual now believes his or her perceptions to be real ("the television is talking to me"). At this phase the goal is to begin antipsychotic treatment as soon as possible (see *Harvard Mental Health Letter*, November 2008).

• ***Transitional.*** In this phase, the patient may recover from the first psychotic episode, but is prone to relapse. This is also a time when other disorders, such as anxiety or depression, may develop in conjunction with schizophrenia.

• ***Chronic.*** In this final phase, the patient becomes more stable, but is likely to suffer persistent cognitive and social deficits—the "negative" symptoms that contribute to disability.

Schizophrenia prevention studies attempt to intervene at the prodromal stage. But only some people who develop prodromal symptoms later experience a psychotic episode—a transition known as "conversion." The results of early prevention studies have reported conversion rates ranging widely from 9% to 76% of participants, with a mean of about 30%. Researchers have therefore been trying to find ways to improve detection of those likely to convert to psychosis—which would reduce the number of people being treated for a problem they would never develop.

KEY POINTS

- Schizophrenia prevention seeks to alter the disease course in a way that would improve outcomes and prevent disability.
- Researchers are testing drugs, omega-3 supplements, and psychotherapy—with mixed results.
- A major challenge remains accurately identifying individuals most at risk for developing schizophrenia.

This was the initial goal of the North American Prodrome Longitudinal Study (NAPLS), funded by the National Institute of Mental Health (NIMH), which pooled the results of eight participating sites. All the investigators used the same detailed questionnaire, the Structured Interview for Prodromal Symptoms (SIPS), to identify participants at increased risk for schizophrenia.

The NAPLS investigators found that, after two and a half years of follow-up, 35% of participants deemed at high risk using the SIPS results had actually developed psychosis. However, the investigators found they could significantly increase predictive power by combining several features assessed at the start of the study into a mathematical formula to assess risk: family history of schizophrenia, recent decline in functioning, higher levels of unusual or paranoid thoughts, and degree of social impairment. When all of these variables were taken into account, the accuracy of predicting the conversion rate was 74% to 81%. However, the NAPLS researchers caution that these improved results were shown in a subset of people who sought help; the method may not apply to the general population.

Interventions tested

The early studies of ways to prevent schizophrenia examined antipsychotics, alone or in combination with psycho-

therapy. More recently, investigators have tested antidepressants, dietary supplements, and targeted psychotherapy.

• ***Antipsychotics.*** Because antipsychotic medications can help subdue psychosis in many patients, the hope was that using them in the prodromal phase might prevent full-blown psychosis later on. But so far the few controlled studies evaluating antipsychotics alone or in combination with psychotherapy have proved disappointing.

In one study, Australian researchers found that the combination of cognitive behavioral therapy (CBT) and low-dose risperidone (Risperdal) was no better than a control intervention at preventing the transition to psychosis. Likewise, researchers at Yale University concluded that low-dose olanzapine (Zyprexa) was no better than placebo.

Most recently, the Australian researchers conducted a double-blind, placebo-controlled trial in which 43 patients with prodromal symptoms were randomized to risperidone and CBT; 44 to placebo and CBT; and 28 to placebo and supportive therapy. After six months, there was no significant difference in the conversion rates in the three groups.

• ***CBT.*** Because cognitive techniques can help improve attention, memory, and social skills in patients who have already developed schizophrenia, researchers have hoped that CBT during the prodromal phase might instill coping skills that could prevent transition to psychosis. The results of small studies are encouraging.

Researchers in England analyzed results for 58 young people at risk for developing psychosis who were randomly assigned to six months of either CBT or monthly monitoring. After another six months in which all were monitored, 6% of those receiving CBT (two of 35) had developed a psychotic disorder, compared with 26% of those in the monitoring group (six of 23). At a three-year follow-up, researchers found that patients who had received CBT were significantly less likely to develop psychosis or to receive antipsychotic medications.

Another study evaluated an intervention that consisted of intensive case management, family involvement, social skills training, and psychoeducation delivered within the framework of CBT. The study enrolled patients diagnosed with schizotypal personality disorder, a condition that increases risk for developing a psychotic disorder.

After two years of treatment, 25% of patients (nine of 36) randomized to the integrated treatment were diagnosed with a psychotic disorder, compared with 48% of patients (14 of 29) assigned to standard treatment.

• ***Antidepressants.*** Researchers hoped that antidepressants might prevent schizophrenia, perhaps by improving mood and thinking ability so that individuals in the prodromal phase could better tolerate odd experiences or cope with environmental stresses that would otherwise trigger psychosis. The results are inconclusive.

One two-year study that tracked outcomes of young people in the prodromal phase found that 43% of participants who took second-generation antipsychotics (12 of 28) developed psychosis, but none of the 20 subjects taking antidepressants did. Because the study was not randomized, however, it's possible that the young people taking antidepressants had less severe symptoms and were at lower risk of conversion to psychosis.

• ***Omega-3 supplements.*** Research suggests that patients with schizophrenia have lower-than-normal levels of two types of polyunsaturated fats. Preliminary research suggests that omega-3 dietary supplements, which can help restore levels of essential fatty acids, might prevent schizophrenia.

A 12-week, double-blind, controlled trial randomized participants to receive daily 1.5-gram omega-3 supplements (slightly more than the 1 gram per day recommended for patients with heart disease) or a placebo pill. At an assessment 12 months later, 5% of participants (two of 41) who took daily omega-3 supplements developed psychosis, compared with 28% (11 of 40) who took a placebo.

Future directions for research

Preventing schizophrenia is still more dream than reality. A major hurdle remains finding ways to better identify those prodromal individuals who are most likely to convert to active psychosis.

The research continues. The Robert Wood Johnson Foundation is funding the Portland Identification and Early Referral program, which is testing antipsychotics, antidepressants, and psychosocial interventions to prevent onset of psychosis. Investigators have not yet published results.

The NIMH-sponsored consortium recently launched a second phase of NAPLS to determine what factors might influence the progression to psychosis. Another NIMH-funded study, Vulnerability to Progression in Schizophrenia, is currently recruiting patients. But results of these studies will not be available for years.

Until more is known about how to best target interventions to those most at risk, the investigators advise a conservative approach—using psychotherapy or drugs with the least distressing side effects first before prescribing antipsychotics. Even so, the goal of preventing schizophrenia is an important one to reduce the enormous suffering and disability caused by this disease.

Keshavan MS, et al. "Early Intervention in Schizophrenia: Current and Future Perspectives," *Current Psychiatry Reports* (Aug. 2007): Vol. 9, No. 4, pp. 325–28.

McGorry PD, et al. "Intervention in Individuals at Ultra-High Risk for Psychosis: A Review and Future Directions," *Journal of Clinical Psychiatry* (Sept. 2009): Vol. 70, No. 9, pp. 1206–12.

For more references, please see www.health.harvard.edu/mentalextra.