The Prevention of Schizophrenia: What Interventions Are Safe and Effective?

by Richard Warner

Abstract

Obstetric complications appear to increase the risk of developing schizophrenia, and post–World War II improvements in obstetric care may have contributed to a decline in the incidence of the illness in the developed world. Educating providers and consumers of psychiatric and obstetric services about the risk of obstetric complications in increasing the risk of schizophrenia could bring about a further small decrease in the incidence of the illness, safely and at low cost. On the other hand, attempts to prevent the occurrence of schizophrenia by treating people who manifest high-risk indicators prior to the development of the illness have a low probability of success and a high probability of unintended negative consequences. Early intervention with people who have developed the full schizophrenia syndrome is likely to have few negative effects and may yield benefits, although it is not yet clear that it will.

Keywords: Schizophrenia, prevention, obstetric complications, early intervention, risk assessment.


Risk Assessment Measures

Prevention approaches must be based on an assessment of the risk posed by potentially harmful factors. Risk measures of illness may be based on either absolute differences between groups or relative differences between groups. Measures of absolute difference are preferred when preventive interventions are being considered because the goal is usually an absolute reduction in occurrence. Population attributable risk, an absolute risk measure, estimates the proportion of the disease risk in the total population associated with exposure to a risk factor by calculating the difference between risk in the total population and that in exposed subjects. Population attributable risk is usually expressed as a percentage—the incidence attributable to exposure to the risk factor as a percentage of the incidence in the total population (Szklo and Nieto 2000). Relative risk, the ratio of the risk of illness in exposed versus unexposed individuals, is more useful in the search for causes that precede a preventive intervention. Where the incidence of an illness is low, the odds ratio is very similar in value to the relative risk (Szklo and Nieto 2000).

The difference between these two methods of risk measurement is illustrated by a recent article assessing...
risk factors for schizophrenia in a Danish population sample (Mortensen et al. 1999). Although a history of schizophrenia in a parent or sibling was found to be associated with the greatest relative risk of developing schizophrenia, the population attributable risk for this factor was only 5.5 percent. The population attributable risk was 34.6 percent for urban (vs. rural) place of birth and 10.5 percent for season of birth, indicating that these two factors accounted for many more cases of illness on a population basis (Mortensen et al. 1999). The greater prominence of the latter two factors over family history of illness is the result of population attributable risk being highly influenced by the rate of exposure of the population to the risk factor (Szklo and Nieto 2000). Continuously distributed factors such as urban or rural living and season of birth will have a greater effect on occurrence of illness. Commonly occurring factors, such as obstetric complications, will exert a greater population effect than rare factors, such as family history of schizophrenia.

Primary Prevention

Obstetric Complications. Geddes and Lawrie (1995), in their meta-analysis of studies conducted before mid-1994 on the influence of obstetric complications, conclude that complications before and around the time of birth double the risk of developing schizophrenia—an odds ratio of 2.0. In a more recent meta-analysis of a different sample of studies, Geddes et al. (1999) found the relative risk to be lower, with an odds ratio of 1.38. Research published since these meta-analyses were conducted has shown variable results. Studies using data gathered at the time of birth from very large cohorts of children born in Finland and Sweden in different years in the 1960s and 1970s reveal that various obstetric complications double or triple the relative risk of developing schizophrenia (Jones et al. 1998; Dalman et al. 1999; Hultman et al. 1999). A recent Irish study indicates that the obstetric complications leading to Caesarean section are increased only in people who develop schizophrenia before age 30 (Byrne et al. 2000). Similarly, a recent study of a Philadelphia sample reveals that the odds of developing schizophrenia become progressively greater with increasing numbers of hypoxia-related obstetric complications but that this risk is specific for cases of early-onset schizophrenia (Cannon et al. 2000). A study of one Scottish sample failed to indicate an association between schizophrenia and obstetric complications, whereas a later Scottish sample revealed significant increases in emergency Caesarean section and prolonged labor (Kendell et al. 2000). The authors of this report suggest that the relative risk of obstetric complications in people with schizophrenia is likely to be less than the 2:1 excess computed by Geddes and Lawrie’s original meta-analysis (Kendell et al. 2000).

In the general population, obstetric complications occur in up to 40 percent of births (the precise rate of occurrence depends on how they are defined) (McNeil 1988; Geddes and Lawrie 1995). Because these complications are so common, they present a high population attributable risk in schizophrenia. In their meta-analysis, Geddes and Lawrie (1995) estimated that complications of pregnancy and delivery increase the prevalence of schizophrenia by 20 percent, but, based on the lower relative risk in the later meta-analysis by Geddes et al. (1999), this estimate would need to be reduced.

The obstetric complications most closely associated with the increased risk of developing schizophrenia are those that induce fetal oxygen deprivation (Lewis et al. 1989; Geddes et al. 1999), particularly prolonged labor (McNeil 1988) and placental complications (Jones et al. 1998; Dalman et al. 1999; Hultman et al. 1999). Premature delivery, often provoked by complications of pregnancy, is also more common for those who develop schizophrenia, and infants who suffer perinatal brain damage are at a much increased risk of subsequent schizophrenia (Jones et al. 1998; Geddes et al. 1999). Recent studies of a large California sample reveal maternal obesity before pregnancy (which is often associated with complications of pregnancy and delivery) (Schaefer et al. 2000) and maternal respiratory infections in the second trimester of pregnancy (Brown et al. 2000) to be associated with increased risk of schizophrenia in the offspring, whereas a population-based Finnish study indicates maternal undernutrition to be a risk factor (Wahlbeck et al. 2001). Several authors conclude that obstetric risk factors provide potential opportunities for prevention of some cases of schizophrenia (Geddes et al. 1999; Brown et al. 2000; Cannon et al. 2000; Schaefer et al. 2000; Warner 2000; Wyatt and Susser 2000).

Has there been a reduction in the incidence of schizophrenia associated with improvements in obstetric care? It is possible, but by no means certain, that there has been a decline in the incidence of schizophrenia since the end of World War II. About three-quarters of post-1960 studies of change in the incidence of schizophrenia reviewed by Warner and de Girolamo (1995) indicate a decrease in the incidence, and the remainder reveal no change or an increase. Several studies from Britain, Scandinavia, and New Zealand reveal a decrease in the incidence of schizophrenia of the order of 40 to 60 percent over 10- to 15-year periods from the late 1960s to the late 1980s. All these studies rely on service-contact data, increasing the likelihood that the observed changes are artifacts resulting from changes in
diagnostic and treatment patterns, a discussion of which follows.

Parker et al. (1985), for example, found that the decrease in the treated incidence of schizophrenia in New South Wales, Australia, was accompanied by an increase in the diagnosis of affective psychosis after the introduction of lithium carbonate. Other studies (Dickson and Kendell 1986; Eagles et al. 1988) show a similar increase in the prevalence of affective psychoses, although others do not. Kendell et al. (1993), in a study of first admissions to psychiatric facilities around Edinburgh, Scotland, showed that the proportion of those diagnosed with schizophrenia by hospital psychiatrists decreased by more than one-fifth between 1971 and 1989, but when diagnoses were made by computer algorithm, there was no such decline. A comparison of diagnostic practices and longitudinal trends in the incidence of schizophrenia in France and Britain between 1973 and 1982 suggests that diagnostic drift occurred in opposite directions in the two countries, producing a diverging incidence of the disease (van Os et al. 1993).

Problems surround the definition of "first admission" used in many of these studies because the diagnosis at the time of first contact or admission may change subsequently. However, de Alarcon et al. (1990) found that a decrease in the incidence of schizophrenia could be shown to have occurred in Oxford, England, at the time of both first contact and first diagnosis of schizophrenia. Other researchers (Munk-Jorgensen 1986; Munk-Jorgensen and Jorgensen 1986), similarly, determined that a decline in first admission rates had occurred even when this factor was taken into account.

A shift away from hospital treatment and toward community care has occurred in all developed countries since 1960; this may have resulted in an increase in the number of cases missed by treatment-based statistics (Crow 1990; Munk-Jorgensen and Mortensen 1992). Some estimates of first contact with any type of psychiatric facility (as opposed to first hospital admission) show a significant decrease in the incidence of schizophrenia (Eagles et al. 1988; de Alarcon et al. 1990), whereas other first-contact-based statistics do not (Hafner and an der Heiden, 1986; Bamrah et al. 1991; Castle et al. 1991; Harrison and Mason 1993).

It is likely that the increased use of antipsychotic drug treatment has led to a greater number of psychotic patients being treated successfully by general practitioners and, consequently, never being referred to any type of psychiatric treatment agency or included in service-based incidence statistics (de Alarcon et al. 1990; Graham 1990). The size of the population that remains undetected and the extent to which it may have increased in postwar years is not known but could be considerable.

Several reviewers conclude that the case for the declining incidence of schizophrenia is so far unproven but merits further investigation (Jablensky et al. 1992; Castle 1993; Harrison and Mason 1993; Warner and de Girolamo 1995). If there is, in fact, a true decrease in the incidence of schizophrenia, the finding could be of considerable etiologic significance. Possible explanations for the phenomenon include a decrease in the fertility of people with schizophrenia, a reduction in social or economic stress, a change in the herd immunity to a causative infectious agent, or a decrease in neurodevelopmental risk factors resulting from improvements in obstetric care.

Looking more closely at the last of these potential explanations, the apparent decline in the occurrence of schizophrenia in England and Wales parallels a decrease in the infant mortality rate with a 20-year delay—as would be expected for an illness that often begins around age 20 (Gupta and Murray 1991). If obstetric care and complications were important in bringing about changes in the incidence of schizophrenia, these factors would help explain why the decrease was greatest in the most prosperous regions of Britain (Gupta and Murray 1991) and why the districts showing no decrease were those with high rates of poverty and large immigrant populations (Eagles 1991). Bad obstetric outcomes are more common among the poor and immigrants; children born to Afro-Caribbean immigrants to Britain, for example, are more likely to be of low birth weight than those in the general population (Terry et al. 1987; Griffiths et al. 1989).

An educational program on the risks of obstetric complications in schizophrenia. It is possible that minimizing obstetric complications will lead to reductions in the occurrence of schizophrenia, particularly if we target those who are at greatest risk for bearing children who will develop the illness.

Ironically, obstetric complications are particularly common among infants who already have a high risk for developing schizophrenia—the children of people who themselves suffer from the illness. For people with schizophrenia, the risk that any one of their children will develop schizophrenia approaches 10 percent, and, where both parents suffer from the illness, the risk for each child is close to 50 percent (Gottesman 1991). But this hazard is compounded by the fact that women with schizophrenia are more likely than other women to experience complications of pregnancy. For women with schizophrenia in the United States, the risk of premature delivery and of bearing low birth weight children is increased by as much as 50 percent (Sacker et al. 1996; Bennedsen et al. 1999). This is to a great extent a result of the fact that women with schizophrenia (and other psychiatric illnesses) receive less adequate prenatal care than do others in the general population (Kelly et al. 1999). In Oregon, for
example, the rate of inadequate prenatal care is five times greater for women with mental illness than for women in the general population (Miller et al. 1992).

The increased risk of complications for pregnant women with schizophrenia could also be due to their higher rates of smoking, to their use of alcohol and other substances, or to poverty. It might, theoretically, also be caused by a gene that increases the risk of both schizophrenia and obstetric complications, but this does not appear to be the case. One group of researchers points out that the increased risk of obstetric complications occurs when the mother, but not the father, suffers from schizophrenia; a genetically determined risk of obstetric complications and schizophrenia would not be confined to the mother (Sacker et al. 1996). Another group points out that a genetic link between obstetric complications and schizophrenia is unlikely because there is no increase in risk of obstetric complications in those who have a family history of schizophrenia (and, therefore, a greater likelihood of carrying a gene for the illness) (Marcelis et al. 1998).

Since the advent of deinstitutionalization in the 1950s, fertility rates for people with schizophrenia have increased (Burr et al. 1979). In Britain in the 1960s, although men with schizophrenia had half the number of children, on average, as males suffering from neurosis, women with schizophrenia bore almost as many children as women with neurosis (Gottesman 1991). In the United States in the 1970s, the fertility of women with schizophrenia was similar to the general population’s (Burr et al. 1979). The main factor reducing fertility in schizophrenia is the low marriage rate of males with schizophrenia. When married, males and females with schizophrenia have as many children as others in the general population (Burr et al. 1979; Gottesman 1991).

Based on this information, it would be feasible to attempt to decrease the incidence of schizophrenia by educating people with schizophrenia, their blood relatives (particularly those in or approaching childbearing years), and their treatment providers about the added risk of schizophrenia from complications of pregnancy and delivery that contribute to perinatal brain injury. High-risk prospective mothers would be cautioned that smoking in pregnancy or maternal illnesses such as diabetes and heart disease may contribute to chronic fetal hypoxia and increase the risk of schizophrenia in the offspring. Where one or both parents has a family history of schizophrenia, obstetricians should be aware that fetal oxygen deprivation, prolonged labor, placental complications, and conditions of pregnancy leading to early delivery and low birth weight may present an added risk of schizophrenia to the newborn later in life. In such cases it would be appropriate to establish a low risk threshold for the use of Caesarean section and to take aggressive precautions to prevent early delivery and low birth weight.

One of the most effective interventions would be to ensure that all women with schizophrenia get adequate prenatal care (Kelly et al. 1999). Several studies have shown that the provision of adequate prenatal care leads to better obstetric outcomes and fewer low birth weight babies. The babies of cocaine-using women in New York who attended four or more prenatal appointments, for example, were half a pound (0.25 kg) heavier, on average, than those whose mothers attended three appointments or fewer (Racine et al. 1993). Similarly, the birth weight of babies of cocaine users who were enrolled in a comprehensive program of prenatal care in Chicago was more than 1.5 lb (0.75 kg) greater than for women who had made two or fewer prenatal visits (MacGregor et al. 1989). Some studies show that the same benefits of prenatal care accrue to the infants of mothers who are not cocaine users (Zuckerman et al. 1989), but the results in this field are inconsistent. Many researchers feel, nevertheless, that the provision of good prenatal care to women with schizophrenia, or more broadly in the population, regardless of the effect on birth weight, is a clinically and ethically important element of health service provision.

To provide the necessary education, one could (1) establish a panel of psychiatric and neonatal epidemiologists and obstetricians to review the data on obstetric complications and the risk of schizophrenia and make recommendations for obstetric counseling and practice; (2) publish the panel report in obstetric and psychiatric journals; (3) distribute brochures summarizing the recommendations to waiting rooms of mental health agencies; (4) emphasize the provision of prenatal care among case management services for women with schizophrenia; and (5) train residents in primary care, psychiatry, and obstetrics to provide genetic and obstetric counseling to people with schizophrenia and their families. Such an educational program could be conducted by an international or national professional group or foundation.

Costs and Benefits. The impact of such a program at a population level is not likely to be great, however. The population attributable risk of obstetric complications as a cause of schizophrenia is less than 20 percent (Geddes and Lawrie 1995; Geddes et al. 1999), and no more than one-third of people with schizophrenia have a family history of the disorder (Gottesman 1991). Preventing the excess risk of obstetric complications in all relatives of people with schizophrenia would reduce the incidence of the illness by less than 20 percent of one-third, or less than 7 percent. This fraction would be substantially reduced, perhaps to less than 1 percent, by various other imponderable factors.
• What proportion of the target population would the education reach?
• What impact would the educational intervention have on obstetric care?
• What effects do improvements in prenatal and perinatal care have on obstetric outcomes?

On the other hand, the total direct and indirect costs for a person with schizophrenia (in California) are $35,000 a year (Hu et al. 1996), which over a 30-year period amounts to $1 million. At this rate, a 5-year educational program on schizophrenia and obstetric complications costing, say, $2.5 million could pay for itself if it prevented just three cases of schizophrenia. The intervention, moreover, might have a greater effect on incidence in the developing world, where obstetric complications are more common and the potential for their reduction is proportionately greater.

The potential for causing harm by educating people about obstetric complications and increasing access to prenatal care appears very limited. Maternal and infant health and survival should only be improved, regardless of whether the infant was at increased for schizophrenia. To avoid creating undue personal concern or stigma, educational efforts should make it clear that there is a relatively low risk that a person who is a first degree relative of someone with schizophrenia will bear a child who will develop the illness. The risk is increased from the general population rate of 1 percent to around 4 or 5 percent (Gottesman 1991).

Secondary Prevention

Intervention With At-Risk Individuals. There is current interest in the possibility of reducing the incidence of schizophrenia by treating people who exhibit some premorbid features of the illness and who have other risk indicators before developing the full syndrome. The excitement has been generated, in large part, by the work of McGorry and colleagues at the Early Psychosis Prevention and Intervention Center (EPPIC) in Melbourne, Australia, and by a project pursuing the same line of research launched by McGlashan in the United States. Articles in the New York Times (Goode 1999) and research newsletters (Lieberman 1999) have publicized the approach, and health regions in Italy and Canada have listed it as a public health priority. Is such enthusiasm supported by the research and epidemiological data? To answer this question we should examine (1) the screening tests being used and (2) the effectiveness of the treatment interventions (U.S. Department of Health and Human Services 1996).

Accuracy of the Screening Test. McGorry and colleagues examined the possibility of using, as an instrument for screening adolescents in the general population, DSM-III-R prodromal symptoms of schizophrenia—namely, social isolation or withdrawal, impairment in role functioning, peculiar behavior, impairment in personal hygiene, blunted or inappropriate affect, digestive speech or poverty of ideas, odd beliefs or magical thinking, unusual perceptual experiences, and lack of initiative, interests, or energy (Yung and Jackson 1999). This measure, it appeared, was too inclusive, because 10 to 50 percent of Australian 16-year-olds (depending on the length of the time period in question) reported experiencing at least two of the symptoms (McGorry et al. 1995).

To refine the screening instrument, McGorry’s team (Yung and Jackson 1999) added other at-risk indicators to the presence of prodromal symptoms: attentional or cognitive symptoms, neurological soft signs, structural brain abnormalities, transient psychotic symptoms, and family history of psychosis. The accuracy of the instrument with clinical samples is reported to be 20 to 40 percent in predicting those who will develop a psychotic illness (Yung and McGorry 1997). The positive predictive value of the instrument with a clinic population, therefore, is modest.

If applied to a broad community population, the measure would present another problem: it would fail to detect a large proportion of those who develop the illness—that is, it would have a high false negative rate. Although about three-quarters of people with schizophrenia exhibit prodromal symptoms (Hafner et al. 1998), only a third have a family history of schizophrenia (Gottesman 1991) and only a quarter show signs of cerebral atrophy in brain imaging (Weinberger and Kleinman 1986). Thus, it seems that the measure used by the McGorry team will detect, at most, a quarter of those who will eventually develop schizophrenia, or, if the variables in the screening instrument are independent of one another, as little as 3/4 x 1/3 x 1/4 or 6 percent. The sensitivity of the instrument, therefore, could not exceed the range of 0.06 to 0.25.

Recent research from a German group suggests a substantially greater predictive capacity for the 66-item Bonn Scale for the Assessment of Basic Symptoms (BSABS), which measures prodromal symptoms of disturbance in thought, language, perception, bodily sensations, stress tolerance, affect, energy, concentration, memory, emotional reactivity, social contacts, and nonverbal expression. After an average followup of nearly 10 years, 49 percent of a group of outpatients who did not have schizophrenia subsequently developed the illness. Of those who gave evidence of at least one prodromal symptom during the initial evaluation with the BSABS, 70 percent subsequently developed the illness (Klosterkötter et
Bayes's probability theorem is widely used in public health to estimate the predictive capacity of screening measures (Everitt 1999). The theorem makes it possible to write the conditional probability of event A (e.g., a person has schizophrenia) given that event B has occurred (e.g., the screening test is positive), in terms of the conditional probability of event B given that A has occurred and the unconditional probabilities of events A and B, using the following formula:

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Pr(A/B) = \frac{Pr(B/A) \times Pr(A)}{Pr(B)}
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In determining the likelihood that a person with a positive screening test will, in fact, develop the illness—Pr(A/B)—Bayes's theorem requires that we take into account three factors: (1) the likelihood of obtaining a positive result when the illness is present (sensitivity)—Pr(B/A)—in the case of the BSABS, 0.98; (2) the likelihood of obtaining a negative result when the illness is absent (specificity), in this case, 0.59; and (3) the base rate of the illness—Pr(A)—in the case of schizophrenia, around 1 percent. Applying Bayes's theorem, we find that the likelihood that a person will develop schizophrenia if he or she has a positive BSABS result becomes a mere 2 percent. Thus, the most promising measure yet reported would be very limited in value as a community screening instrument. As a screening measure with clinical populations, BSABS would be more useful.

Many early intervention researchers shy away from the suggestion that any of the current screening measures are suitable for general population screening and insist that their intent is to screen only clinic populations. This reasonable caution, however, does not significantly change the public health value of the approach as an illness prevention measure. Screening only at-risk individuals attending psychiatric clinics will considerably decrease the number of people wrongly labeled as being at risk for schizophrenia, but it will leave undetected a large number of those in the community who will eventually develop the illness.

Effectiveness of Interventions. McGorry et al. (1999) speculate that a variety of measures may be effective in preventing the onset of schizophrenia in high-risk cases. The suggested approaches include the use of low-dose antipsychotic medication; stress reduction measures such as social skills training, instruction in problem-solving techniques, and family education, support, and therapy; "lifestyle restructuring"; and training to enhance coping skills. All these approaches, however, were developed to help people with symptoms of schizophrenia and their family members cope better with the illness and to reduce relapse rates. Their effectiveness in symptom-free individuals is unknown and, on the face of it, not particularly likely to be effective. How does one assess the benefit of antipsychotic medication, for example, before psychotic symptoms are apparent? How does one teach social skills before they have declined? What support and therapy is to be given to the family before significant problems have emerged?

The potential for harm with these interventions is significant, given the number of false positives that are expected. Is it appropriate to prescribe antipsychotic medications for someone with no positive symptoms of the illness and, if so, for how long? How much harm will be done to people who never develop the illness but who were told they are at risk for schizophrenia, need treatment, and must adjust their future expectations? Critics are concerned that the "lifestyle restructuring" proposed by McGorry may lead people who are labeled "preschizophrenic" to believe that they should downgrade their life expectations, avoid marriage, and not attend college (Goode 1999).

One published report of a preventive intervention with presymptomatic individuals reports on a program established in a semirural catchment area of 35,000 in Buckinghamshire, England (Falloon 1992). Falloon's team worked with primary health practitioners to screen the population for the DSM-III prodromal symptoms of schizophrenia. The mental health team evaluated possible cases. People suspected of being in the prodrome of schizophrenia were provided individual and family education about schizophrenia, a stress management program, and, in some cases, low doses of antipsychotic medication. These measures were continued until several months after all of the presenting features had resolved. During the 4 years the program was in place, only one catchment area resident progressed to display the full features of schizophrenia. Falloon suggests that the observed incidence of...
schizophrenia during the program was ten times less than in the same area a decade before. It is difficult to conclude, however, that the program reduced the incidence of schizophrenia because it is possible that a number of young people vulnerable to schizophrenia migrated out of the area to seek training and education in urban areas. Given the small size of the catchment area, a handful of cases lost to migration would produce an apparently large decrease in incidence.

The cost of such preventive interventions as these is likely to be similar to that of high-quality treatment for established cases of schizophrenia. Given that this expense is likely to draw treatment away from people with the illness and that the effectiveness of preventive intervention has yet to be proven, many mental health systems will be unwilling to invest in such preventive approaches until their cost-effectiveness has been more definitively demonstrated.

To summarize, the positive aspect of preventive intervention with those people considered to be at risk for schizophrenia is limited to the hope of preventing a disabling and costly illness. The negative aspects are substantial and include a significant false positive rate and considerable risk of iatrogenic damage to those wrongly labeled, a substantial false negative rate, the likelihood that the accurate detection rate will be extremely low when targeted at the general population, a paucity of interventions of proven effectiveness in nonsymptomatic individuals, and the diversion of funds from established cases, where the interventions are known to be effective.

**Tertiary Prevention**

**Early Detection and Treatment.** Finally, we may consider the concept of early treatment for those who demonstrate the full syndrome of schizophrenia—a form of tertiary prevention, in Caplan's terminology.

Crow et al. (1986) found that first admission patients with schizophrenia whose onset of psychotic symptoms preceded the start of antipsychotic medication by more than a year were more likely to relapse at followup than those whose symptoms went untreated for less than a year; these workers suggested that failure to initiate early treatment may heighten the risk of relapse. Further theoretical support for early intervention rests in the data which indicate that the duration of untreated psychosis is associated with psychosocial decline (Jones et al. 1993), prolonged morbidity (Wyatt et al. 1997), increased treatment costs (Moscarelli et al. 1991), worse course and outcome (Helgason 1990; Haas et al. 1998), and increased duration of the acute episode (Loebel et al. 1992; McGorry et al. 1996).

Early intervention advocates suggest that this association is a direct effect of prolonged psychosis; some have even suggested that untreated psychosis itself may be toxic to brain function (Wyatt et al. 1997). This possibility is rendered less likely by recent studies that have demonstrated a lack of association between duration of untreated psychosis and loss of cortical mass, ventricular enlargement, or decrements in cognitive functioning (Fannon et al. 2000; Hoff et al. 2000).

The association between prolonged psychosis and poor outcome may not be causative at all. We know that first episodes of schizotypalike conditions progress to remission of psychotic symptoms in about 50 percent of cases in the developed world (World Health Organization 1979; Ciompi 1980; Shepherd et al. 1989; Warner 1994). Samples of patients with a long illness will exclude such good-prognosis cases, but patients who progress rapidly to remission will be included in samples with a short duration of psychosis. Early detection samples, therefore, are biased to include more good-prognosis cases. Craig et al. (2000), whose epidemiologically based study of first admission patients found no association between duration of psychosis and clinical course and outcome in any diagnostic group of psychotic disorders, confirm this conclusion. These researchers argue that the inclusion of a 6-month duration of illness (DSM-IV) criterion for the diagnosis of schizophrenia, which excludes acute-onset, good-prognosis cases, eliminates the predictive effect of duration of psychosis on outcome from schizophrenia. Similarly, a study of people with DSM-IV schizophrenia (Ho et al. 2000) found that the duration of untreated psychosis did not predict a better quality of life or symptom remission in first episode schizophrenia. These researchers point out that McGorry's sample, which appeared to show a correlation between short duration of psychosis and good outcome, included a large number of patients with schizophreniform and affective disorder in which the psychosis would be brief in duration.

**Historical antecedents of early intervention.** Claims for the benefits of early intervention go back more than 200 years to the leaflets and advertisements of the proprietors of the earliest private madhouses (Parry-Jones 1972). Scull (1979) writes:

> Throughout the nineteenth century, it was an article of faith among those who dealt with lunatics that the deranged were more easily restored in the early stages of the disorder, so that delay in seeking help could be disastrous. Whatever its scientific merits, as ideology such a belief was of great assistance to the asylum doctors. (p. 111)

Scull argues that belief in the effectiveness of early treatment helped asylum administrators explain the low proportion of recoveries and to blame their failure on the public's delay in bringing patients for treatment. The belief also provided private madhouse operators with an
attrative motive for potential customers to bring in for expert assistance disturbed family members who might otherwise have been managed at home.

In 1844, the British Metropolitan Commissioners of Lunacy reported that in various private and public asylums:

- tables are published, exhibiting the large proportion of cures effected in cases where patients are admitted within three months of their attacks, the less proportion when admitted after three months, and the almost complete hopelessness of cure when persons are not sent into proper asylums until after a lapse of a year from the period when they have been first subject to insanity. (Scull 1979, pp. 111–112)

So attractive was the "very great probability of cure in the early stages of insanity" (Westminster Review, 1845, cited in Scull 1979, p. 112) that the Commission's report became the instrument for the passage of legislation, in 1845, that required every British county and borough to erect a lunatic asylum. The end result of the 1845 Asylum Act was the eventual construction of a network of massive institutions for the insane, some housing more than 2,000 inmates.

It is easy for us now to perceive the self-promotion of the early asylum proprietors in citing these recovery figures and the lack of scientific rigor of the psychiatric reformers and politicians of the time in accepting them. It is less obvious, because of current enthusiasm, that the data now being offered to support early intervention suffers from many of the same weaknesses as the early asylum tables.

**Effectiveness of Treatment.** The treatment proposed for early intervention in schizophrenia is optimal modern treatment, including, in the EPPIC in Melbourne, short-term inpatient care, low-dose antipsychotic medication, outpatient case management, day care, vocational rehabilitation, family support and education, and cognitive therapy (McGorry et al. 1996).

McGorry et al. (1996) have reported a comparison of their EPPIC-treated patients with a similar sample drawn before they instituted their early detection and treatment procedures. As expected, early detection resulted in the EPPIC sample having a shorter duration of untreated psychosis than the pre-EPPIC cases. Results after 1 year of treatment favored the EPPIC cases; patients spent less time in the hospital, took lower doses of antipsychotic medication, and demonstrated better functioning, but there was no significant difference in symptomatology at the 1-year followup. The possible reasons for the better outcome in the EPPIC group are (1) early detection leads to the inclusion of more good-prognosis cases, (2) early detection enhances the effectiveness of treatment, or (3) the treatment provided to the latter group is superior (and unrelated to early detection).

Because the treatment provided was fairly standard care for patients who would certainly have required treatment, the cost implications are not great.

Although there is no clear evidence that early intervention in schizophrenia carries substantial benefits, the prevention of psychosocial decline secondary to prolonged illness is an attractive concept. The provision of optimal, well-coordinated treatment as early as possible in the disorder could reduce relapse and maximize benefits for the patient and his or her family. The EPPIC approach of targeting early treatment failure by using clozapine sooner in the course of the illness (Kulkarni and Power 1999) is one that will require further evaluation, given that the drug has serious side effects. We should be alert to the possibility that the naturally benign course of some brief psychotic episodes may go unrecognized and some people who would have had a good outcome regardless of treatment may receive more treatment than they need.

**Summary**

The field of prevention in schizophrenia is in an early stage of development. Two interventions, one primary and one tertiary, appear safe, but their effectiveness is in question. Educating providers and consumers of psychiatric and obstetric services about the risk of obstetric complications in increasing the risk of schizophrenia could bring about a small decrease in the incidence of the illness, safely and at low cost. Early intervention with people who have developed the full schizophrenia syndrome may yield benefits and is likely to have few negative effects, except, perhaps, for the overtreatment of good-prognosis cases.

On the other hand, attempts to treat people who manifest high-risk indicators of schizophrenia before developing the illness have a low probability of reducing the incidence of the illness and a high probability of unintended negative consequences.

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**The Author**

Richard Warner, M.B., D.P.M., is Medical Director, Mental Health Center of Boulder County, and Clinical Professor of Psychiatry and Adjunct Professor of Anthropology, University of Colorado, Boulder, CO.