Ethical Challenges in the Primary Prevention of Schizophrenia

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Introduction

Primary prevention of schizophrenia is a concept with considerable appeal. When a debilitating and often progressive disorder frustrates efforts at effective treatment, prevention may offer the only realistic hope of avoiding its consequences. As illustrated by the papers in this Special Section and elsewhere, substantial efforts are being applied to develop creative models of risk and intervention prior to the onset of prodromal symptoms of the disorder, ranging from the prenatal period to early adolescence. However great the importance of exploring such possibilities, care will be required to minimize the chances of harming the very people we are seeking to help.

Given that efforts toward primary prevention of schizophrenia are still at the research stage, the field needs to consider carefully how studies aimed at moving the field forward can be constructed so as best to protect subjects. Key to this end, investigators will need to insure—in the words of the Common Rule that governs most federally funded health research in the United States—that “[r]isks to subjects are minimized...[and] are reasonable in relation to anticipated benefits.” With different target populations, interventions, and rationales across studies, this will require an individualized judgment about the relative balance of risks and benefits associated with each project. Here, without trying to be exhaustive, I suggest a set of questions that may assist investigators, funders, and IRBs to assess the ethical acceptability of such studies.

How Will the Target Population Under Study Be Selected?

The first generation of prevention studies focused on patients, usually adolescents, who were beginning to experience prodromal symptoms. As the field has evolved, however, the focus has shifted earlier in life, looking to intervene at prior stages in the progression of illness. How, in the absence of prodromal symptoms, will participants in prevention studies be identified? Most research to date has targeted children from families with histories of schizophrenia that put their offspring at increased risk. However, since children of a parent with schizophrenia account for only a small proportion of the affected population, broader strategies might use endophenotypes to identify at-risk participants from the general population. A major concern with early prevention is the impact of designating participants as “at-risk.” The effect of this designation is likely to be greater for groups that are not yet dealing with psychiatric symptoms (eg, children recruited from high-risk families and from the general population), who would not otherwise be suspected of being prone to schizophrenia, than for those already experiencing some degree of symptomatology that renders them candidates for treatment (ie, participants in clinical high risk or prodromal states). Stigma and discrimination on the basis of presumed risk status may be facilitated by inclusion of information about participation in electronic medical records, where it can easily be accessed by treaters, insurers, and others. Families of children in need of services often must authorize release of records to school districts, social service agencies, and legal counsel, compounding the risks that it will be used in ways adverse to the interest of the children.

What Is the Likely Conversion Rate?

Research with prodromal patients has identified groups with 30%–40% or greater likelihood of conversion to a psychotic disorder. In contrast, children of one parent with schizophrenia have roughly a 10% risk of developing the disorder. The risk associated with the more recently identified endophenotypes is unknown, but almost certainly less. As the proportion of a group that is likely to
develop schizophrenia decreases, the possible benefits for participants decrease as well, making the risks of participation, including the potential adverse effects of the interventions, more difficult to justify.

**Are Secondary Benefits Likely to Accrue?**

Since only a minority of the probable target populations in primary prevention studies will develop schizophrenia in the absence of intervention, the majority of participants are unlikely to experience benefit from even an effective preventive measure. However, interventions (especially psychosocial interventions) may target more proximate problems than the transition to psychosis per se, dysfunctions that may be worthy of treatment in their own right. Insofar as treatments have positive secondary consequences apart from reducing psychosis risk—such as improved social adjustment, better parent-child interactions, or enhanced cognitive function—it will be easier to justify their application to these groups.

**How Risky Is the Intervention?**

A good deal of the controversy stirred up by the early prodromal studies in Melbourne, New Haven, and elsewhere related to their use of antipsychotic medications, with all of the adverse effects those drugs can cause. Although the risk/benefit ratio of this class of medications may be acceptable when patients are already experiencing a psychotic disorder, it is more difficult to justify administration to a group of adolescents, the majority of whom will not progress to schizophrenia. In contrast, primary prevention in younger populations is more likely to employ non-pharmacologic interventions, such as cognitive-behavior therapy or nutritional supplements, with much lower intrinsic risks. The less prominent the risk profile of an intervention, the more acceptable its use will be in populations that are not yet experiencing symptoms.

**What Will Participants Be Told?**

Informed consent to studies involving the validation of endophenotypes or the efficacy of prophylactic interventions will require revealing to participants why they are being asked to participate in the study. In many cases, that will be because they are suspected to be at increased risk for schizophrenia. Whereas prodromal populations may know or suspect that something of consequence is wrong, that will not necessarily be true for other participant groups. Even families with one affected member may be unaware of other family members’ elevated risk for the disorder. Identification of members of the general population on the basis of endophenotypes as belonging to an at-risk group—if that becomes possible—will come as an even greater shock. It seems probable that some, perhaps many, participants and their families will react with anxiety and distress, a response that may be greater in groups that have less reason to suspect vulnerability to schizophrenia. This is one more reason for caution in recruiting from such groups.

**Will Steps Be Taken to Reduce Negative Impact of the “At-risk” Designation?**

One way to reduce the potential negative consequences of disclosing subjects’ at-risk status is to help participants and their families put the information into perspective. There may be a tendency for persons giving consent (usually parents for minor participants) to assume that “at risk” implies “certain to develop the disorder,” when only a minority even of the highest risk groups will do so. Offspring of parents with schizophrenia may be particularly prone to overestimate their own risk. Investigators owe it to their subjects to provide carefully framed information regarding the risks they face. For example, use of relative risks (eg, “a ten-fold increase in the risk of schizophrenia”) can lead ordinary people and clinicians alike to overestimate the likelihood that a person will be affected; in contrast, absolute risks (eg, “a 10% risk of developing schizophrenia”) may be less likely to mislead, especially if expressed as frequencies (eg, “one out of ten”) rather than in percentage terms. In addition, framing disclosures positively to emphasize the probability that illness will not develop (eg, 10% risk means that 90% of participants will not develop the disorder) may be reassuring.

**Will On-going Treatment/Support Be Provided?**

Some interventions may turn out to be successful in modifying endophenotypes associated with schizophrenia, thus presumably reducing the risk of the illness. As ideal as it would be if brief, targeted interventions had a permanent effect on disease risk—perhaps because they were sustained until the close of a critical window in development—that will be difficult to determine in the absence of extended follow up. Can researchers, having demonstrated a positive effect on a likely risk factor, simply walk away from participants, leaving them to their own devices to sustain the intervention or face a return to their baseline levels of schizophrenia risk? Medical researchers in general are recognizing that engaging people as research participants often implies an ongoing obligation to maintain an effective intervention, especially when participants may otherwise be at increased risk of serious illness. Studies that acknowledge this ongoing relationship will raise fewer concerns about exploitation of participants than those that do not. However, discharging such obligations is complicated by the reality in many studies that the efficacy of the intervention may not be determined until months or years after a given person’s participation ends.
Conclusion: This enumeration of issues evoked by research on the primary prevention of schizophrenia should not be taken to indicate that the enterprise is ethically unacceptable—only that it is ethically complex. Investigators should be encouraged to grapple with these questions and develop innovative approaches. Data on the frequency of anticipated adverse effects (e.g., distress at learning that a child is at increased risk) will be essential to help gauge the likelihood of their occurrence. The prospect of effective prevention is so appealing an outcome that every effort should be made to encourage it, without sacrificing the interests of the people without whose participation it cannot be achieved.

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