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The Prevention of Schizophrenia

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A series of articles that speculate on the primary prevention of schizophrenia might seem overly optimistic, if not implausible. However, we do not share this degree of nihilism. Much has been learned about risk factors for schizophrenia over the last 3 decades. The incidence of schizophrenia varies between sites and over time.[1] Some ethnic groups are at increased risk of schizophrenia when they migrate to particular counties but not in their country of origin.[2,3] Almost certainly, these gradients are driven by environmentally mediated risk factors. It seems reasonable to expect that at least some of these exposures will be potentially modifiable. Epidemiologic research has revealed a range of candidate exposures related to infection and nutrition, which are reviewed in this volume (see Brown and Patterson,[4] McGrath et al,[5]), as well as a host of other putative risk factors such as psychosocial stress,[6,7] cannabis use,[8–10] and advanced paternal age,[11,12] and other exposures which, in our view, are worthy of careful scrutiny. The stage is now set for the "implausible"—the primary prevention of schizophrenia.

Schizophrenia—A Syndrome With Imprecise Boundaries

The readers of this journal will be familiar with the fact that schizophrenia has the nosological status of a clinical syndrome.[13] As such, the diagnosis of schizophrenia will encompass clinical outcomes that derive from many different etiological pathways. Heterogeneity is to be expected, and just as clinicians are comfortable with substantial variation in outcomes in individuals diagnosed with schizophrenia, researchers should expect that etiological processes will also be heterogeneous. Thus, it is implausible that any one intervention will be sufficient to "prevent" the full syndrome of schizophrenia.

On a related issue, many individuals in the community report isolated psychotic-like experiences,[14] and psychotic symptoms can also be associated with a range of other clinical disorders (eg, mood disorders).[15] Currently, there is debate about the utility of including an "At Risk" diagnostic category in *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*.[16] The boundaries of schizophrenia will need to be kept under continuous revision in response to advances in psychiatric research. With respect to the prevention of schizophrenia, it is feasible that future interventions designed to target the syndrome of schizophrenia may result in benefits in a wider range of adverse health outcomes. While lack of specificity between an exposure and an outcome can weaken the case that the variables of interest are causally related,[17] from a public health perspective, interventions that have nonspecific benefits are particularly attractive.[18]

The Science of Prevention

Primary prevention aims to reduce the incidence of a disease. The articles in this volume of *Schizophrenia Bulletin* will focus on primary prevention. Interventions related to primary prevention can be delivered to the general population or to different target populations.[19,20] A preventive intervention aimed at the general population regardless of risk status is termed "universal prevention." Rose[18] emphasized that such population-based interventions are best suited to risks that are distributed throughout the population, albeit not in equal measure. Those at high risk of disease, seemingly an obvious target for preventative action, may, in fact, be relatively rare. Those at medium risk may be more common and thus may account for a much higher proportion of those who eventually develop the disease. Rose[18] introduced the concept of the "prevention paradox"—a preventive measure may deliver benefits to the community at large but may offer little to the majority of that community who are, themselves, at low risk. Indeed, population-based (universal) intervention may mean that such low-risk individuals have to give up something (eg, wear a seat belt, eat fortified food, have vaccinations) in order to reduce the community burden—hence the paradox.

Selective preventive measures, which target particular subgroups of the population who may be more susceptible to a disorder, but who are still symptom free, offer a way of overcoming the prevention paradox.

However, selective intervention is not without its challenges because it relies on an efficient means of identifying those at increased risk (via single-stage or multistage screening). Apart from the increased risk of psychosis in those with a positive family history, our ability to identify these at-risk individuals prior to the onset of schizophrenia is currently poor and will therefore need to await future research efforts, discussed later in this article and in the other articles in the volume. The sensitivity and specificity of the screens must also be balanced with the safety and efficacy of any proposed intervention.

How Do We Measure The Potential Effectiveness of an Intervention?

When comparing the potential impact of different primary preventive approaches, the population attributable risk (PAR) serves as a useful index. The PAR is an estimate of how many cases of a disorder could be prevented if a particular risk factor were eliminated from a population, assuming that (1) the risk factor is causally related to the outcome and (2) all other contributing risk factors remained unaltered after the intervention.[21] Unlike better known measures in epidemiology, such as measures of effect size (eg, relative risk or odds ratio), the PAR is based on the fact that risk factors with small effect sizes, if prevalent in the community, may contribute to more cases than rarer risk factors associated with larger effect sizes. To illustrate this issue, consider the value of (1) using a cholesterol-lowering medication to treat hypercholesterolemia (high cholesterol is prevalent in the community but is associated with only a modest increased risk of cardiovascular disease) vs (2) protecting the population from asbestosis exposure (a rare exposure but associated with a very high risk of lung disease).

We wish to underline that the interpretation of PAR requires caution. Occasionally, researchers who find a PAR of a given percentage will claim that the risk factor(s) of interest "explain(s)" that percentage of liability to the illness. This statement is not accurate because the rationale for use of the PAR is based in part on the assumed interaction between different risk factors. Consequently, the removal of a given risk factor (that is necessary but not sufficient for development of a disease, or of a subset of diseases) will also prevent a portion of risk of that disease that is contributed to by other exposures or susceptibility genes (which interact with that risk factor). Hence, it is typical for the total PARs for various risk factors to surpass 100%. This clarification underscores the fact that one need not eliminate every risk factor or susceptibility gene to prevent the emergence of a disorder. Examples of the potential application of the PAR to specific exposures will be provided in articles in this volume.

While the PAR provides a percent of all cases that may be attributable to a particular exposure, it is also instructive from a public health perspective to estimate the number of individuals for whom a risk factor would need to be removed in order to prevent the onset of 1 new case. This metric is called the Number Needed to Prevent (NNP) and is comparable with the more familiar measures derived from intervention studies such as Number Needed to Treat or Number Needed to Harm. We exemplify this point using the evidence linking early cannabis use with an increased risk of psychosis outcomes in young adults.[22,23] A recent systematic review and meta-analysis of the association between cannabis use and psychotic outcomes reported a pooled odds ratio of 1.4.[22] While the effect size is modest, because the exposure (cannabis use) is prevalent, the PAR was estimated to be 14% (95% CI; 7–19). Based on data from observational epidemiologic studies of cannabis and psychosis, Hickman and colleagues calculated the NNP for heavy cannabis use and psychosis (ie, the number of heavy cannabis users who would need to stop using in order to prevent 1 case of schizophrenia). For men, the annual mean NNP ranged from 2800 in those aged 20–24 years to 4700 in those aged 35–39 years. For women, the NNPs for the 2 age groups were about twice as large. Considering the fact that interventions designed to stop people using cannabis are suboptimal (ie, such interventions are themselves associated with a high Number Needed to Treat), then the public health utility of reducing cannabis use as a primary prevention for schizophrenia seems a less attractive proposition.

A second method of evaluating the impact of a potential intervention is illustrated by the influential Global Burden of Disease project,[24,25] which used comparative risk assessments in order to rank order selected preventive interventions. The Global Burden of Disease project allows health planners to decide which disorders contribute most to death and disability and thus can help these agencies decide how best to allocate the limited health dollar. Governments have been urged to select preventive interventions that provide the best value in averting disability and death (ie, prioritize interventions with the cheapest dollar per Disability Adjusted Life Year value).[26] Safety is another criterion that has been used, though some interventions that seem safe may have unwanted effects. As examples, elaborated in detail in Brown and Patterson,[4] the long-term effects of vaccination during pregnancy on offspring outcomes has yet to be evaluated in epidemiologic and preclinical studies. Similarly, folic acid supplementation, which has been proven to reduce risk of neural tube defects, and possibly schizophrenia, may have a variety of potentially detrimental effects, including induction epigenetic modifications, which could be beneficial as well as possibly harmful (see McGrath et al[5]).

Does The Same Preventive Intervention Have The Same Impact in All Societies?

One limitation of most environmental epidemiologic and genetic studies is the lack of attention to the broader context in which they occur. The field of eco-epidemiology aims to address this shortcoming. Eco-epidemiology, first described by Susser and Susser,[27] is based on the concept that risk factors operate at multiple levels of causation, from molecular to individual to societal realms. In accord with an eco-epidemiologic framework, a risk factor that is related to a disorder in one population may have little or no effect on a disorder in a different population. This suggests that one must proceed with caution in recommending global preventive approaches based on the findings of studies from a limited number of populations. The implications of eco-epidemiology for preventive approaches in schizophrenia is discussed in detail by Kirkbride and Jones.[28]

Is It Too Early to Worry About the Primary Prevention of Schizophrenia?

Some might argue that it is premature to think about the primary prevention of schizophrenia. We have limited clues about the etiology and pathogenesis of this poorly understood group of brain diseases, and it could be argued that the best investment at this stage is in basic neuroscience. However, the history of medicine shows that there have been some spectacular applications of primary prevention based on incomplete knowledge. The miasma theory of ill health (that brackish, impure water and soil gave off noxious emanations) led to the call for improved sanitation long before microorganisms were suspected or discovered. The consumption of limes on long sea voyages was found to prevent scurvy without the benefit of an understanding of vitamin C. Conceivably, public health approaches that have already been implemented in the developed and increasingly in the developing world, including control of infectious diseases, improvements in obstetric and neonatal care, and nutritional supplementation, may already be reaping benefits with regard to the prevention of psychiatric disorders of neurodevelopmental origin, including schizophrenia.

Nonetheless, the implementation of approaches for the primary prevention of schizophrenia will require at a minimum that the putative risk factors derived from observational epidemiologic studies be substantiated, by methodologically rigorous replication efforts in independent populations. This is a challenging task, though there are at present a number of population-based cohorts throughout the world that should allow for this. The rationale for use of primary prevention strategies could be further bolstered by an experimental trial of a preventive approach for schizophrenia, in which subjects at high and low risk based on the presence/absence of exposure to environmental interventions are followed up for risk of schizophrenia.

The long latency between the primary insult and the onset of schizophrenia, however, creates a second, and no less daunting, challenge. One possible solution to this dilemma is the use of intermediate phenotypes during infancy or childhood, which can be ameliorated by the intervention and that are observed in schizophrenia. Ross et al[29] have recently proposed a translational primary prevention approach involving perinatal choline supplementation during pregnancy and use of the P50 auditory sensory gating intermediate phenotype to quantify psychophysiological deficits related to attentional impairment in schizophrenia. This proposition derives from a well-established literature on the alpha-7 nicotinic receptor's role in P50 gating deficits and attentional impairment, associations between schizophrenia and genetic variation in the *CHRNA7* gene (which encodes the alpha-7 receptor),[30] and evidence supporting the hypothesis that choline normalizes hippocampal development by stimulation of the alpha-7 nicotinic receptor.[31] Based on this evidence, a model whereby choline availability interacts with genetically mediated alpha-7 nicotinic receptor density to influence fetal brain development, thereby modifying P50 sensory gating and attention deficits in schizophrenia, suggests that perinatal choline supplementation may be 1 primary prevention strategy that could lessen these deficits, which may be assessed as early as infancy.

In the future, the positive predictive value (ie, the likelihood that prevention will be achieved by the intervention) may be further improved by combining data on known environmental risk factors with genetic variants and markers derived from longitudinal cohort studies (eg, cognitive, behavioral, and psychosocial antecedents of schizophrenia), other psychophysiological measures, and structural and/or functional neuroimaging.

With respect to other risk factors for schizophrenia, there is evidence linking advanced paternal age and risk of schizophrenia.[12] The PAR for paternal age of over 30 years was estimated to be approximately 10%. In theory, advice to couples about optimal age of parenthood could conceivably reduce these cases, but pragmatic cultural and societal factors may make this exposure unsuitable for primary prevention.

Secondary and Tertiary Prevention

Although the focus of this volume is on primary prevention, we would like to draw the readers' attention to the value of other forms of prevention. Secondary preventive measures aim to modify the course of an illness by early intervention. The importance of detecting and treating early psychosis is now well recognized and has been extensively covered in *Schizophrenia Bulletin*. The utility of a "risk syndrome for psychosis" is the focus of current debate.[16,32] Just as we will require different primary

preventive interventions to address different etiological pathways, we will need to tailor secondary prevention measures according to the various stages of pathogenesis.

Tertiary preventive measures aim to reduce the burden of established disorder by optimizing treatment and rehabilitation. With respect to schizophrenia, if secondary and tertiary prevention could increase remission rates, then the prevalence of the disorder would fall.[33] Furthermore, if interventions could (1) delay the onset of illness and/or (2) shift the profile of illness to "milder," less disabling forms of the disorder, then we could "compress" the burden of schizophrenia substantially. This type of research certainly warrants more attention and, in our opinion, should be included in any research programs related to the prevention of schizophrenia.

Conclusion

One of the greatest advances in 20th century medicine was the improvement of health outcomes through elimination of infectious diseases, nutritional interventions, and other public health measures. A growing body of evidence indicates that fetal and other early environmental determinants may increase the risk of schizophrenia. The fact that several of these exposures are relatively common in the population suggests that primary preventive strategies consisting of public health efforts aimed at ameliorating these putative risk factors could have a considerable impact on reducing the incidence of this disorder. Unlike many other approaches utilized in medicine, the majority of these interventions offer the advantage of being inexpensive, convenient, and potentially scalable for delivery to large populations. We therefore recommend increased investment in resources seeking to confirm these exposures as risk factors for schizophrenia, identification of new risk factors, implementation of primary preventive strategies, and monitoring of the biological effects of these measures. While we expect that the quest for the prevention of schizophrenia in the 21st century will be at least as formidable as those public health efforts that led to improvements in morbidity and mortality from illness in the 20th century, there is, in our view, considerable cause for optimism.

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