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New Targets for Prevention of Schizophrenia: Is It Time for Interventions in the Premorbid Phase?

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A number of influences have converged that make this Special Theme Issue timely: "A New Direction: Considering Developmentally Sensitive Targets for Very Early Intervention in Schizophrenia". These factors include: 1. the substantial knowledge about premorbid developmental vulnerabilities to psychosis, especially regarding schizophrenia; 2. the promising results emerging from interventions during the clinical high-risk (CHR) phase of psychosis and; 3. the recognition that the CHR period is a relatively late phase of developmental derailment. These factors have together led to a perspective that even earlier intervention is warranted. This paper briefly summarizes the articles comprising the Special Theme including new data on early neurocognitive development, proposed potential targets for psychosocial and psychopharmacological interventions during the premorbid period as early as pregnancy, and ethical challenges. These thought experiments must be empirically tested, and the ethical challenges overcome as posed by the various interventions, which range from relatively low risk, supportive, psychosocial to higher risk, experimental, pharmacological interventions. All of the interventions proposed require careful study of ethics, safety, potential stigma, feasibility, efficacy and tolerability, and the meaning to the people involved.

Key words: clinical high risk/family high risk/prodrome/premorbid/prenatal/perinatal/primary prevention/endophenotype/critical period/early intervention

The idea of early intervention and prevention for psychotic disorders, has taken hold in the past two decades.[1,2] This development likely reflects the current zeitgeist in which similar trends in early interventions for disorders like diabetes or cardiovascular disease,[3] dementia[4] and a focus on brain plasticity,[5] wellness and prolonging healthy aging are dominant. The idea that it might be possible to prevent disorders like schizophrenia has galvanized the field.[6] The characterization of a putative prodrome to psychosis, typically called the clinical (or "ultra") high risk (CHR) state, (or "At Risk Mental State") consisting primarily of attenuated positive symptoms, has provided a window for early, pre-emptive, interventions.[6–8] This syndrome, also named the Attenuated Psychosis Syndrome, is in section 3 of DSM-5, indicating that further study is required.[9] Paradoxically, this symptom picture, usually occurring in teenage years or young adulthood, has become recognized as a late stage in the development of psychotic disorders, with a number of earlier stages signaling that the full psychotic manifestations of the disorder could be predicted and perhaps prevented.[10,11] Other approaches point to earlier phases. The Basic Symptoms approach identifies internal mental experiences that are thought to characterize an earlier prodromal phase prior to the CHR period.[12] The staging perspective[10] provides a framework for research and conceptualization of earlier premorbid interventions, perhaps beginning with pregnancy (see figure 1).

In the last decade, five meta-analyses of individuals in the CHR phase have been published regarding interventions to prevent full-blown psychosis, delay its emergence or reduce the liabilities that are associated with its origin and evolution.[13–17] We briefly summarize the van der Gaag meta-analysis,[17] which is quite comparable in scope and results to the meta-analysis of Stafford et al,[16] which was published around the same time in 2013. Van der Gaag et al included five randomized control studies of cognitive behavior therapy (CBT),[18–22] two of "integrated

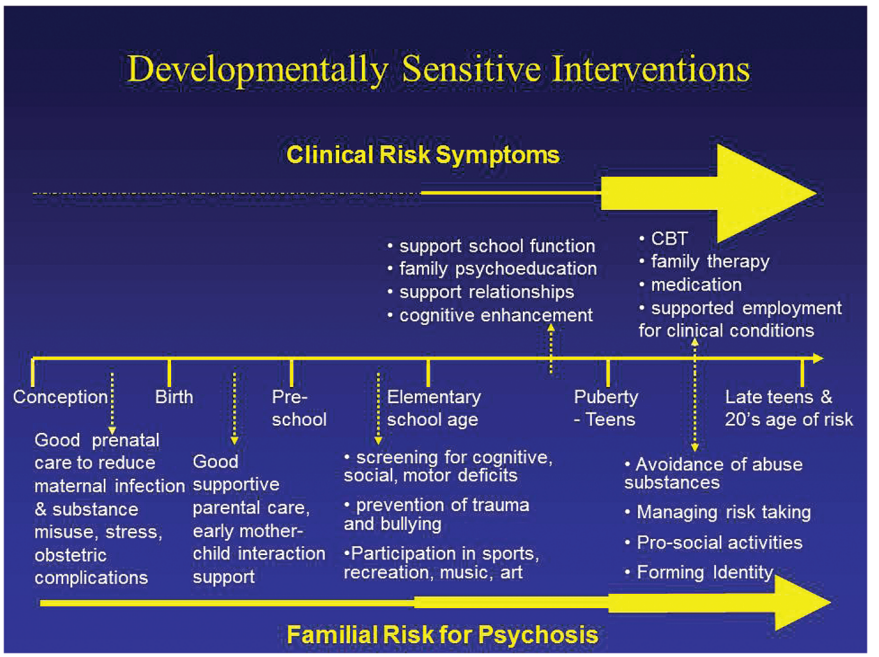

Fig. 1. Phase specific early intervention & prevention strategies for clinical and familial high risk. Clinical risk symptoms are contrasted with family risk for psychosis by depicting the greater likelihood of conversion to psychosis to occur in the clinical risk group by the larger yellow arrow. Interventions above the line for the clinical risk group begin around the end of elementary school reflecting the earliest period that prodromal symptoms are typically reported, whereas those below the line begin during pregnancy reflecting more of a primary prevention approach.

psychological therapies",[23,24] three of antipsychotic medication[25–29] and one of omega-3 fatty acids.[30] According to van der Gaag,[17] "overall the risk reduction at 12 months was 54% (RR = 0.463; 95% CI = 0.33–0.64)." After 24 to 48-month follow-up, risk reduction was 37% (RR = .635; 95% CI = 0.44–0.92). They concluded: "early detection and intervention in people at ultra-high risk of developing psychosis can be successful to prevent or delay a first psychosis." These results are comparable to those for prevention of depression.[31] These CHR results illustrate that early intervention can be successful in this late high-risk (HR) phase and set the stage for considering primary preventions.

These promising results give rise to the even more challenging notion, that earlier, pre-teenage interventions might be possible to alter the developmental pathway to schizophrenia. But if so, how would pre-prodromal youth be ethically identified for treatment when they are not seeking help? This is indeed complex. It is likely in the future that biomarkers (and "polygene scores") will be developed that may identify especially HR youth, that will also generate ethical issues. But for now, the primary viable strategy is to use the family high risk (FHR) approach, even though this approach will only yield roughly 10% of the individuals from these families who will develop psychosis if the sampling strategy is based on selecting offspring of individuals with schizophrenia. Liu et al[32] and Ross & Freedman,[33] in this issue, make the case, based on the extensive FHR literature that risk factors begin during pregnancy and that impairments which are present from the perinatal period onward can be treatment targets, and that interventions do not need to be limited to "preventing psychosis." A new generation of FHR studies (FORBOW,[34] The Danish High Risk and Resilience Study,[35] the Harvard Children's Development Study (Seidman LJ, Gabrieli J, Keshavan MS, unpublished data), and the Dutch Bipolar Offspring study[36]) all have early intervention with pre-teen children as a goal.

In essence, young offspring from a family in which schizophrenia is present in a parent (i.e., FHR) are a pre-disorder risk group rather than clinical cases as in CHR/Attenuated Psychosis Syndrome. This approach will only identify a modest number of future cases, because only about 10% of these FHR offspring go on to develop psychosis, and because individuals with schizophrenia with a positive history of schizophrenia in first-degree relatives are a modest minority of all cases of schizophrenia.[37] Despite this high false positive rate vis a vis future psychosis, Liu et al argue that there are a number of reasons why these children form a group deserving of low risk interventions: 1.They have a high rate of other behavioral, cognitive and neuromotor problems that could be treated, and 2. There are a variety of family-developmental problems associated with growing up with a parent suffering from schizophrenia.

Liu et al[32] propose that the treatment of the parents with illness is ethically appropriate and necessary (and

often overlooked), and that proper interventions with the parent provide a window into the treatment of the HR child. These FHR children are at risk not only for a psychotic disorder, but another 50%–60% of them for significant difficulties including socio-emotional, cognitive, neuromotor, and speech-language problems, and various forms of nonpsychotic psychopathology.[38–41] Thus, they recommend treating the family system as a unit by focusing on parents *and* children. While the FHR approach will only identify a modest subset of the HR population, the effects may be significant for that group. The interventions proposed are relevant to the top half of figure 2 and potentially could alter the trajectory to psychosis, CHR states, and other childhood, adolescent, and adult impairments.

Agnew-Blais et al[42] (this issue) illustrates the robustness of premorbid cognitive deficits in schizophrenia in their New England Family cohort studies paper on general intelligence in children who later develop schizophrenia spectrum disorders compared to those with affective psychoses; the latter are not significantly different than controls. The impairments are present at age 4 and 7, and had been found to occur in roughly 40%–45% in age 7 children who later developed schizophrenia spectrum disorder compared to about 7% who did not develop psychosis.[43] It's possible that such cognitive impairments are malleable, as they are milder than in later phases of the illness,[32] and that cognitive enhancing treatments designed for CHR adolescents,[44] adults with schizophrenia[45] or other disorders such as Attention-Deficit Hyperactivity Disorder[46] can be implemented with FHR children.

Liu et al[32] note that while there is an enormous literature on risk indicators for schizophrenia, beginning with the pioneering work of Barbara Fish in 1952[47], there is a paucity of research on remediation of these deficits. Liu et al[32] address potential psychosocial interventions from pregnancy through the elementary school years. They suggest that parents with psychoses may benefit from: "enhanced prenatal care, social support, parenting skills, reduction of symptoms, and family-centered care across development". For these children, they suggest a range of early socio-emotional interventions and cognitive remediation.[32] Many of these interventions are available in some places but not implemented, nor has their effectiveness been rigorously studied in the FHR population.

Ross and Freedman[33] suggest a novel approach toward identifying underlying mechanisms of risk for psychosis through the measurement of endophenotypes during the perinatal period.[48] This is innovative because schizophrenia is a neurodevelopmental disorder, whose onset is the end result of brain changes that begin prenatally, but most endophenotype studies have evaluated adolescents or adults who have entered or passed through the age of risk for the disorder. They suggest a treatment approach that targets a well-known schizophrenia endophenotype, P50 sensory gating.[49] They based a randomized control

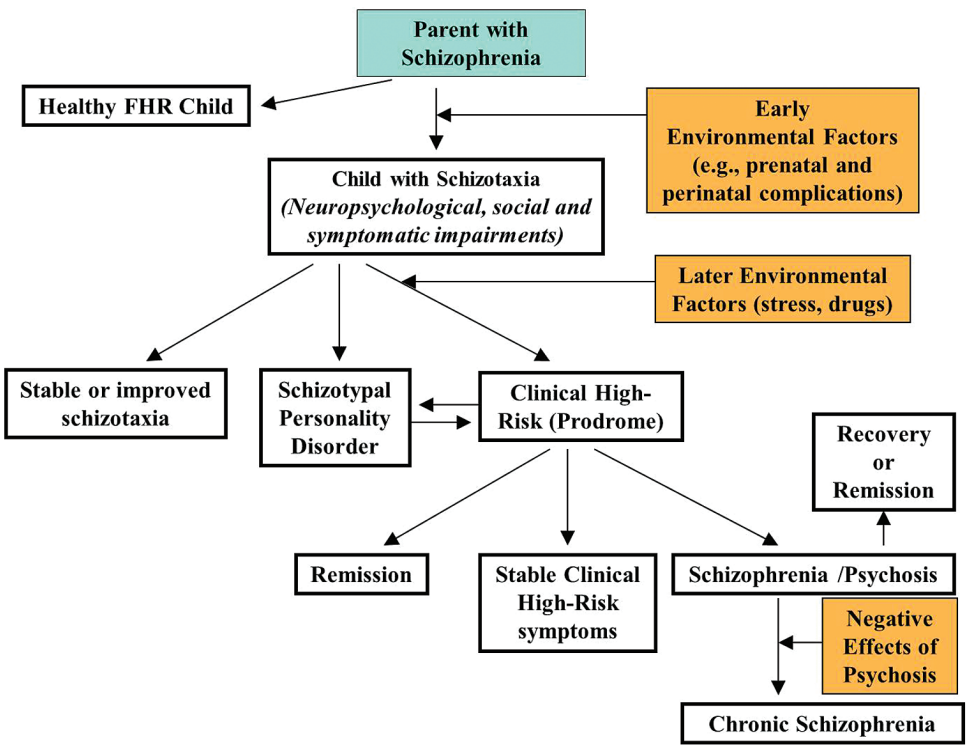

Fig. 2. Developmental pathway of familial high risk for schizophrenia (adapted from Thermenos et al.[59]). This picture depicts the potential development of children who have a parent with schizophrenia. Positive and negative outcomes are shown, as well as the possibility that negative outcomes such as "stable schizotaxia" or schizophrenia can be partially or significantly reversed.

trial in 76 healthy pregnant women on the hypothesis that perinatal choline supplementation would increase activation of alpha7 nicotinic receptors and normalize developmental defects associated with receptor deficiencies, including deficits in P50 sensory gating.[50,51] Infants whose mothers had received prenatal choline demonstrated improved infant P50 sensory gating, compared to those whose mothers received placebo.[51] There was an interaction between choline supplementation with infant genotype on CHRNA7 SNP re3087454 on P50 suppression ratio that increased plausibility. At 40 months follow-up, the children had significantly improved attention, which is often impaired in children who later develop schizophrenia. This preliminary work is promising, and if safe, could be considered for a neurobiologically informed primary prevention intervention for pregnant mothers with schizophrenia. Nevertheless, the idea that choline can prevent schizophrenia is quite speculative, and there are many steps needed to confirm this approach including whether improving P50 or accelerating the maturation of P50 can change the vulnerability to schizophrenia.

Do, Cuenod, and Hensch (this issue),[52] invoke developmental neurobiology to provide a framework for understanding the premorbid developmental evolution towards schizophrenia.[53] First the concept of "critical periods" (CP) is described as a window of time when a given behavior is especially susceptible to and requires specific environmental influences to develop normally.[54] A CP "opens" and should "close" based on environmental input. A potential mechanism for the risk of schizophrenia proposed is paravalbumin-positive interneuron maturation that is involved in contributing to the sequential timing of CP[55]. The authors propose two potential biomarkers that could be explored as targets for investigation of normalization of CPs: gamma oscillations (measured by event related potentials), and abnormalities of fiber tract connectivity, as measured by diffusion tensor imaging, both of which are associated with oxidative stress.[53] They suggest that drugs that target the "hub" of oxidative stress and related dysfunctions (neuroinflammation and NMDAR hypofunction) would be candidates for repairing these developmental anomalies, including Omega 3, sulforaphane and N-acetylcysteine (NAC). Not unlike Ross and Freedman's model, they consider experimental agents that are neurobiologically informed with respect to developmental risk for schizophrenia.

In the final section of this Special Theme Issue, Dr. Appelbaum evaluates the ethics of the various interventions, which range from low risk, supportive, psychosocial to higher risk, experimental, pharmacological interventions. All of the interventions proposed require careful study of ethics, safety, feasibility, efficacy, and tolerability, and the meaning to the people involved.[56,57] Nevertheless, while the idea of primary prevention of schizophrenia will require much study, we believe the time has come to consider this seriously.[58]

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