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Is Prevention a Realistic Goal for Schizophrenia?

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Abstract Over the past 2 decades, increased efforts have focused on identifying those at genetic or clinical risk for psychosis and promoting interventions that may alter the onset or trajectory of schizophrenia. We review studies published between 2010–2013 that: (1) investigate at-risk states for psychosis in larger epidemiological studies; (2) identify causes of certain clinical presentations of the schizophrenia phenotype and (3) investigate focused and multidisciplinary approaches to treat early clinical symptoms. The article places these recent studies within the context of prior research and the concept of potential measures to prevent or ameliorate the onset of psychosis.

Keywords Schizophrenia · clinical risk · genetic risk · psychosis · prodrome · early intervention · treatment · prevention

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Introduction

Schizophrenia is a severe mental illness that places a large burden on individuals, families and society at large, affecting about 1 % of the population in the United States [1]. The US annual economic burden of schizophrenia in 2002 was estimated to be $62.7 billion, including direct health care cost, direct non-health care cost and productivity loss [2]. Because schizophrenia is associated with significant disability and impaired functioning, interventions early in the development of psychosis in theory could have an enormous impact on public health expenditure.

Schizophrenia evolves from abnormal development of cortical networks, which produce pre-illness manifestations in pre-frontally mediated cognitive behaviors and symptoms, within weeks to years before individuals present for treatment. A major obstacle to studying and understanding these early processes is the difficulty inherent to identifying at-risk individuals early enough in the evolution of psychosis. Although the first clinical signs of psychosis are often evident in childhood or early adolescence, there is a high degree of non-specificity in symptom presentation in the early course [3]; thus, the symptoms are not uniquely predictive of eventual psychosis.

The past 20 years have seen increased efforts in identifying those at genetic or clinical risk for psychosis and promoting interventions that range from nonspecific behavioral supports to more specific and focused cognitive interventions, medications and comprehensive therapeutic models. Early identification and treatment of psychosis carries the potential to prevent or delay the onset of illness and, therefore, ameliorate the trajectory and functional impairment associated with chronic schizophrenia. Based on the current state of knowledge regarding clinical progression and spotential interventions, the field supports a stepped-care approach regarding the location and types of behavioral and medication interventions.

This review summarizes the rapidly growing area of research focusing on identification and intervention of young persons who appear to be at risk for psychosis and, in line with the mission of this publication, places particular emphasis on studies published since 2010. In particular, these publications: (1) expand the investigations of at-risk states for psychosis to larger epidemiological studies; (2) elucidate novel findings regarding causes of certain clinical presentations, given the multifactorial origin of the schizophrenia phenotype; (3) investigate focused and multidisciplinary approaches to treat clinical symptoms such as pre-psychotic symptoms, social withdrawal and cognitive dysfunction in order to prevent clinical progression.

Definitions of At-Risk States

Historically, there have been two primary symptom-based approaches to identify young people at risk for psychosis, each with its strengths and limitations. The classical, or genetic, high-risk (HR) strategy involves early identification and prospective investigation of children who have a biological relative, usually a parent, with clinical symptoms of schizophrenia. This strategy yields transition rates to psychosis that are higher than the general population, but the transition rate is relatively low and late in coming, i.e., approximately 6-15 % transition to psychosis over 25–30 years [4]. Moreover, because the strategy can only be applied to a small subset of individuals who later develop psychosis (those with a family history of schizophrenia), results with genetic high-risk individuals may not generalize to the larger group of "sporadic" cases (those without a family history of schizophrenia).

The second approach involves identifying at-risk young people based on reported clinical signs and symptoms. There are three primary variants of this clinical high-risk strategy. The early psychometric or psychosis proneness strategy implemented surveys of young adults, usually college students, using standardized, usually self-report, measures ([e.g., 5–7]). This approach promised greater generalizability than genetic high-risk paradigms, but long follow-up periods are required, and transition rates are relatively low at 1-2 %, making it necessary to screen large numbers of individuals to identify those at greatest risk. In the more recently developed "prodromal" or "ultra-high" risk (UHR) strategy [e.g., 8, 9], researchers aim to identify individuals, typically help-seeking young people in the age range of 14–29, who appear to be on the brink of developing a psychotic disorder based on instruments like the Structured Interview for Prodromal Syndromes (SIPS) [10]. This strategy yields the highest transition rate: recent meta-analytic results found the risk of developing a psychotic episode in SIPS identified individuals across studies to be 18 % at 6-month follow-up, 22 % at 1 year, 29 % at 2 years and 36 % after 3 years [11••]. However, this approach captures individuals relatively late in the development of psychosis during which associated functional impairment and/or distress has led to help-seeking. Despite the higher transition rate, the majority of UHR individuals still do not transition to psychosis within current follow-up periods [3]. This limitation represented a core controversy surrounding the proposed inclusion of *Attenuated Psychosis Syndrome* in DSM5 and contributed to the decision to instead include it as a condition for further study in the DSM5 appendix [12].

The third variant of the clinical high-risk strategy involves epidemiological surveys of sub-psychotic or "psychotic-like experiences" in the general population. Meta-analytic results of this growing literature suggest that approximately 5-8 % of the population experience sub-clinical psychotic symptoms, of which 20 % develop psychotic-like experiences and ≤10 % develop a psychotic disorder [13••]. Transition to psychosis in those groups appears to be moderated by several features, including the severity and persistence of initial symptoms [14], substance use and comorbid psychopathology [15]. Much of this research has been conducted in adults and older adolescents despite evidence that the initial prodromal period often begins in early adolescence or younger [16]. Consequently, much less is known about the clinical relevance, stability and predictive accuracy of symptoms in younger children and adolescents [17]. In a large, systematic study to evaluate psychosis spectrum symptoms in US youth (age 11–21; n=7,054), our research team found that among medically healthy youths, 20 % reported significant psychosis spectrum symptoms [18•]. Despite the functional significance of negative symptoms in schizophrenia, the developmental trajectory of early negative symptoms has received limited research attention [19]. In our cohort, a not insubstantial number of youths with spectrum features (12.7 %) reported experiencing only negative/disorganized symptoms without positive symptoms. Altogether, it appears that the very young onset age of both positive and negative subthreshold symptoms in the general population, as well as their as yet unknown developmental trajectory, raise unique challenges for identification and intervention [17] in the critical window preceding untreated psychosis.

Across symptom-based risk strategies, a major focus of study has been the longitudinal outcome, usually the rate of conversion to psychosis. Yet, recent increasing attention on "non-converters" has suggested that some clinical risk individuals continue to show attenuated symptoms and poor social and role functioning as long as 2 years following initial presentation, despite having not converted to psychosis [20]. Similarly, community and population studies have shown that early sub-clinical psychotic symptoms are associated with comorbid psychopathology including depression [18•, 21–24], anxiety [18•, 21] and substance use [15, 18•, 21, 25]; impaired global functioning [18•, 26] and increased suicidality [18•, 26]. Together, these investigations indicate

that regardless of eventual psychosis, the psychosis risk state is not benign and can itself require clinical attention and intervention.

Potential Causative Factors

The categories of potential differential diagnoses to be considered in the presence of subsyndromal symptoms of psychosis and early psychosis are broad, ranging from medical illnesses, genetic/congenital conditions and substance use to the spectrum of psychiatric diagnoses such as mood disorders, anxiety disorders and primary psychotic disorders.

Medical/Congenital Medical conditions that may manifest with psychosis spectrum symptoms include autoimmune diseases, endocrinopathies, CNS infections, metabolic diseases, neurologic disorders, and nutritional deficiencies and congenital conditions [27]. Of these, NMDA receptor encephalitis has received attention as a newly identified disease with anti-NMDA receptor antibodies that manifests with psychotic symptoms within a constellation of neurologic and physiologic symptoms [28–31]. A large retrospective study [28] reported that despite the high prevalence of psychiatric symptoms, in particular psychosis, as early manifestations of NMDA encephalitis, only 21 persons out of almost 1,500 patients diagnosed with schizophrenia and related psychosis tested positive for the IgG subclass of the anti-NMDA receptor antibody. Ninety-four tested positive for IgA and/or IgM, but negative for IgG, but the relevance of this finding for the possible presence of encephalitis remains unclear. Virtually all the studies have been published since 2011, and, as the knowledge about his syndrome expands, further findings may elucidate the potential presence of anti-NMDA encephalitis, particularly at the onset of psychosis.

Genetic/congenital syndromes that may first present with psychotic symptoms include acute intermittent porphyria, Gilbert syndrome, glucose-6-phosphate dehyrogenase deficiency, Huntington's disease, neurofibromatosis type 1, fragile X-syndrome and XXX karyotype [32]. The genetic syndrome that has been most extensively examined for its risk for psychotic symptoms and schizophrenia is the 22q 11.2 deletion syndrome [33]. In a recent study on 112 persons between ages 8–45 years, carefully assessed with psychiatric interviews for affective disorders and psychosis, the diagnoses of psychosis were made in 11 % and attenuated psychosis syndrome in 21 %. Peak occurrence of psychosis risk was during adolescence (62 % of those aged 12–17 years) [34].

Substance use either acutely or chronically, particularly PCP, ketamine and cannabis, has been associated with the emergence of psychotic symptoms of various durations. More recently, psychotic symptoms associated with withdrawal after chronic gamma-hydroxybutyric acid (GHB) use have been reported [35, 36].

Psychiatric Disorders and Psychotic Symptoms Studies of help-seeking individuals with psychotic symptoms who do not meet full threshold diagnostic criteria for a DSM-IV (or −5) psychotic disorder have identified mood disorders and anxiety disorders as the most common Axis I disorders in this population. Substance use disorders and common disorders of childhood including ADHD, other externalizing disorders, developmental disorders and learning disorders have also been reported among prodromal and clinical risk populations [27].

A prospective study replicated these diagnostic comorbidities among clinical high-risk patients [37•]. Of these, 34 % had diagnoses of depressive disorders, 39 % of anxiety disorder, 4 % of bipolar disorder and 6.5 % of somatoform disorder. Bipolar disorder, unipolar depressive disorder and somatoform disorders were positively correlated with later transition to psychosis, whereas anxiety disorders were negatively correlated with later transition to psychosis [37•]. Accumulating studies suggest that early identification and treatment of trauma may have a protective role for premorbid functioning and severity of symptoms [38••]. While there are few reports of prospective assessment of PTSD as an Axis I diagnosis in this population, bidirectional links between childhood trauma such as bullying and physical assault have been reported as increasing the risk for psychotic symptoms [39, 40].

Association with Drugs Links between substance use and psychosis have long been reported, but the role of substance use as a causal factor in the emergence of psychotic symptoms and transition to primary psychotic disorders remains an area of active investigation. In a recent thorough review of the literature on substance use in the clinical risk population, Addington et al. [41] reported on a total of ten studies examining the role of substance use, including cannabis, alcohol, tobacco and other substances. The reported studies document rates of substances as follows: cannabis from 33 % to 54 %, alcohol 17 %-44 %, tobacco 16 %-34 %, hallucinogens 7 %-19 % with remaining substances such as opioids, sedatives and stimulants with rates from 0-9 %. Prospective risk for conversion with substance use was positive in two of the ten studies [25, 42]. Numerous methodological issues were identified in these studies, thus leaving the question of the role of substance use in the risk for transition to full threshold psychotic illness unanswered. At the same time, two studies found that younger age at onset of cannabis use was correlated with younger age at onset of psychotic symptoms [43•, 44], and one study reported that recent increased rate of cannabis and tobacco use correlated with onset of psychotic symptoms

[45]. Such reports highlight the need for additional study of this potentially modifiable risk factor.

Interventions and Potential Prevention Methods

Prevention methods can be categorized in a three-tiered model that includes *universal* measures for the general population, more *selective measures* for those who meet criteria for increased risk (e.g., genetic and family history) and *indicated* measures for those with specific clinical risk (i.e., prodromal manifestations of psychosis). While schizophrenia has been associated with general factors affecting pregnancy and childhood development, which would fall under universal or selective prevention measures, almost all recent studies have focused on indicated measures in the UHR period as the most proximal to emergence of psychosis and the highest potential for interventions. The fact that the majority of persons with UHR symptoms do not progress to psychosis within a few years [see 11] highlights the importance of providing interventions that are both focused on symptom stabilization or improvement with few side effects and offer the potential of retaining young persons in follow-up to decrease the duration of untreated psychosis should illness emerge.

Psychotherapy Psychotherapeutic interventions offer the potential benefits of symptom amelioration, increased ability to cope with emerging clinical symptoms and retention in treatment with few, if any, relevant risks. Several psychotherapeutic treatments have been systematically studied in the high-risk period. Five randomized controlled trials have evaluated the effect of cognitive behavioral therapy on rates of transition and symptom reduction [46–51]. Overall, CBT reduced conversion rates and positive symptoms, but this effect was similar to supportive therapy and not necessarily specific to CBT [46]. There were inconsistent data on the maintenance of such gains in the follow-up period [46, 50, 51], though a recent meta-analysis concluded that there was evidence of continued protection against conversion at 18 months [52].

Cognitive Remediation Recently, cognitive remediation therapy (CRT) has been investigated as a behavioral intervention to treat cognitive deficits and improve functional outcomes in high-risk patients [review: 53]. CRT promotes lasting cognitive benefits and social and occupational functioning in schizophrenia patients, with greatest effects seen when CRT is paired with psychosocial training [meta-analysis: 54]. In a pilot study, Rauchensteiner et al. [55] found that HR patients showed greater improvement than schizophrenia patients in several cognitive domains, including long-term memory functions and attention, after ten computerized CRT sessions using CogPack [56], suggesting that HR patients are more amenable to cognitive intervention. Despite the promising results of this pilot study, it has several limitations. Although all recruited participants completed the study, the statistical power was limited because of the small sample size. The average age of the HR group, at 27.20 years, is perhaps higher than anticipated given that peak age of incidence for schizophrenia is between 10–25 years [57]. Lastly, higher rates of antipsychotic medication in the schizophrenia patient group than in the HR group could potentially confound the findings of the study. Another study found that cognitive remediation as part of a comprehensive intervention program reduced the rate of psychosis conversion of UHR individuals compared to those undergoing enriched supportive therapy over a 24-month period [58]. Urben and colleagues [59] reported that computerized CRT promotes enhanced reasoning and inhibition abilities in adolescents with psychosis or in the HR state as compared to a control treatment (computer games) in a 6-month follow-up. However, cognitive gains were not associated with changes in symptom severity, and in one of these studies [58], the specific preventative effect of CRT was not assessed in a multimodal treatment approach including several therapeutic strategies. Taken together, these studies suggest that CRT may be an effective treatment for cognitive deficits associated with the UHR state. Future studies should incorporate longitudinal design, increased sample sizes and well-defined functional outcome measures to assess the differential success of particular CRT methods to promote lasting benefits and prevent psychosis conversion.

Medications There have been four randomized controlled trials and a handful of trials with more naturalistic designs examining the effect of antipsychotic treatment in the UHR period [60–66]. Overall, results have supported clinically significant differences between experimental and placebo arms for symptom reduction and psychosis conversion rates. However, such improvements were not universally maintained during a medication-free post-treatment interval. Furthermore, significant side effects were associated with antipsychotic treatment, including weight gain [61, 63], movement side effects [65, 66] and higher dropout rates [65, 66]. A recent study on 115 UHR patients who were randomized to a double-blind, placebo-controlled 12-month trial of low-dose risperidone, cognitive therapy or supportive therapy found neither treatment to be superior in preventing psychosis, while all forms of treatment improved psychiatric symptoms, psychosocial functioning and quality of life [67]. Antidepressant treatment has not been systematically studied, yet several naturalistic studies found that antidepressants were associated with lower conversion rates and reduced positive symptoms [68, 69] (though one study failed to show symptomatic improvement [62]). In these prior studies, medication choice was likely impacted by the presenting symptoms of participants. Overall, antidepressants were significantly better tolerated by participants than were antipsychotics, and in one study

Table 1 Findings from selected recent empirical investigations

	Topic	Cohort	Description	Results	Limitations
Definitions of at-risk states					
Calkins et al. [18•]	Psychosis spectrum features in young community members	7,054 children age 11–21 and their caregivers from the Philadelphia Neurodevelopmental Cohort	Young people from the community were screened for major domains of psychopathology and psychosis spectrum symptoms	20.0 % of medically healthy youths reported significant psychosis spectrum symptoms; male sex, younger age and non-European-American race were significant predictors of spectrum status; youths with spectrum symptoms had reduced neurocognitive and global functioning, and increased odds of depression, anxiety, behavioral disorders, substance use and suicidal ideation	Predictive validity of screening criteria not yet established; screen for negative and disorganized symptom domain may have reduced sensitivity compared to clinician-administered assessments
Fusar-Poli et al., 2012 [11••]	Transition outcomes in clinical high risk groups	2502 clinical high-risk patients from 27 studies published through January 2011	Conducted meta-analysis of studies examining risk to psychosis transition in clinical high risk	The risk of developing psychosis in ultra-high risk individuals was 18 % at 6-month follow-up, 22 % at 1 year, 29 % at 2 years, and 36 % after 3 years. Risk was moderated by age of participants, treatments, diagnostic criteria and publication year	Necessarily limited to primarily help-seeking populations; transition rates may differ in other groups
Linscott et al. 2013 [13••]	Epidemiology of psychotic experiences in children and adults	411 prevalence rates of psychotic experiences and 35 incidence rates from 61 cohorts	Conducted meta-analysis of incidence and prevalence of psychotic experiences	The median annual incidence of psychotic experiences was 2.5 %, and the prevalence was 7.2 %. Approximately 20 % of those reporting psychotic experiences developed persistent symptoms, with approximately 7.4 % developing a psychotic disorder. Multiple demographic factors were predictors of psychotic experiences	Incidence, prevalence and persistence estimates are necessarily limited by varying research methods and follow-up intervals across primary studies
Wigman et al. 2011 [15]	Predictors and persistence of mild positive psychotic symptoms in youths from the general population	2,230 children from the Tracking Individual Lives Survey (TRAILS); age 10–11 at baseline	Examined longitudinal trajectories of self-reported positive psychotic experiences assessed three times over a 6-year period	Growth mixture modeling suggested four different trajectories of psychotic experiences: low, decreasing, increasing and persistent. Persistence was associated with several demographics	The age range of the participants (age 10–16) does not fully cover the onset window of psychotic disorders. Self-report measures rather than clinical interviews were used, which limits interpretations

Table 1 (continued)

	Topic	Cohort	Description	Results	Limitations
				characteristics, other psychopathology, cannabis use and particular environmental risk factors	related to symptom severity and context, and ability to delineate transition to psychotic disorder
Potential causative factors					
Arseneault et al. 2011 [40]	Childhood bullying associated with psychotic symptoms at age 12	2,232 twin children	At age 12, assessment of past bullying and present psychotic symptoms	Relative risk of psychotic symptoms increased 2–3 times in those who endorsed trauma	Nonclinical sample, but large cohort
Salokangas et al. 2012 [37•]	Diagnoses associated with later risk of psychosis	245 young patients with clinical HR	SCID diagnosis based on interview During 18-month follow-up, 37 developed psychosis	Diagnoses of bipolar disorder, unipolar depressive disorder and somatoform disorders were positively correlated with transition to psychosis. Anxiety disorders were negatively correlated	
Dragt et al. (2012) [43•]	Relationship between substance use and onset of psychosis	245 help-seeking UHR individuals ages 16–35 in the European risk for psychosis study	Cannabis consumption at onset of study Followed for a mean duration of 465 days Assessed onset of HR symptoms	Age at onset of cannabis use was correlated with earlier age of onset of HR symptoms. Onset of cannabis use preceded symptoms in most participants. No association between cannabis use and conversion from HR symptoms to psychosis	Cannabis use was assessed by participant report only. The timing of onset of HR symptoms was retrospective by participant report. The number of HR participants who reported both cannabis use and symptoms was small; thus, sample size was limited for the assessment of conversion to psychosis
Kelleher et al. (2013) [38••]	Relationship between childhood trauma and psychosis	1,113 school-based adolescents ages 13–16 years	Children were assessed for trauma and psychotic symptoms at baseline, 3 months and 12 months	Trauma found to be highly predictive of psychotic symptoms. Relationships between trauma and psychotic symptoms were also bidirectional. Cessation of trauma was correlated with decreased subseqent psychotic symptoms	Psychosis assessment was limited to experience of hallucinations. Trauma experiences were by self-report, and the degree of subjective sense of trauma was not assessed
Pollak et al. 2013 [28]	Prevalence of NMDA receptor autoantibodies in schizophrenia	1,441 patients from 7 studies with schizophrenia and related psychosis	Review of published descriptions	115 patients tested positive for any Ig antibody type to NMDA NR1 21 patients (1.4 %) were positive for IgG antibodies to NMDA NR1	Specific investigations of new onset psychosis patients and testing of different receptor subunits may further clarify this potential association
Tang et al. 2013 [34]	Association between 22q DS and psychiatric disorders	112 persons ages 8–45 with 22q11 DS	Structured psychiatric interviews of probands and caretakers	79 % met criteria for psychiatric disorder	

Table 1 (continued)

	Topic	Cohort	Description	Results	Limitations
				11 % experienced psychosis and 21 attenuated psychosis symptoms	Uncertain influence of cognitive limitations on presence of symptoms
Tikka et al. 2013 [39]	Childhood trauma, premorbid adjustment and psychosis	20 clinical HR and 30 controls ages 14–35 years	Self report of premorbid adjustment and childhood trauma	HR group had poorer premorbid adhjustment and higher trauma scores with negative correlation	Small sample size and self-assessment that is not confirmed
Addington et al. 2013 [41]	Relationship between substance use and onset of psychosis	Total of ~800 patients	Review of 10 studies	Limited evidence to suggest an association between increased substance use and transition to psychosis	
Psychotherapy					
Addington et al. 2011 [46]	CBT for HR individuals	51 clinical HR individuals ages 14-30	Single-blind RCT of CBT vs. ST for 6 months with 12-month follow-up Stratified by gender and severity of psychotic symptoms	Three subjects converted to psychosis, all in ST group, all before 16 weeks of treatment.Both groups showed improvements in positive symptoms. There was no significant difference between CBT and ST groups in positive, negative, affective or anxiety symptoms, or in social functioning	After attrition, sample sizes were small (CBT n=15, ST n=13) at 12-month follow-up. Conversion rates were lower than predicted, and the study was underpowered to detect differences. Number of sessions was low
Morrison et al. 2012 [47]	CT for HR individuals	288 help-seeking individuals between ages 14-35	Multi-site single blind RCT, 6 months of CT vs. mental state monitoring, follow-up at 12 months, 24 months for a subset	Only 8 % of participants converted to psychosis (n=23). There was no difference between groups on conversion rates or distress CT group had larger improvements in psychosis No differences between groups on depression, social anxiety, quality of life	In both groups subjects also received "treatment as usual" from local providers. Such care varied by site and provider. The mean number of therapy sessions was 9.1, which may have been too low to confer further benefit
van der Gaag et al. 2012 [50]	CBT for HR individuals	201 help-seeking individuals ages 14-35	Multi-site single-blind RCT of CBT vs. TAU × 6 months. Follow-up was 18 months	10 subjects in the CBT group and 22 subjects in the TAU group converted to psychosis. NNT= 9. CBT group also showed higher remission rates of sub-psychotic symptoms	Five subjects violated exclusion criteria and were removed early from the study. If they are included in intent-to-treat analysis, the significance of the results is converted to a trend
Cognitive remediation					
Rauchensteiner et al. (2011) [55]	Cognitive remediation	HR patients and patients with schizophrenia	Cognitive effects of cognitive training on HR patients and patients with schizophrenia	After 10-week training session, HR patients demonstrated greater improvement in long-	Small sample size, high age of HR sample

Table 1 (continued)

	Topic	Cohort	Description	Results	Limitations
				term memory functions and attention as compared to patients with schizophrenia	Study did not control for medication effects
Urben et al. (2012) [59]	Cognitive remediation	HR patients and patients with schizophrenia	Cognitive effects of 8-week CRT vs. control (computer games) in adolescents with schizophrenia and at high risk	CRT training improved inhibition and reasoning abilities as compared to control at 6-month follow-up. Benefits of CRT were not simply related to symptom amelioration	Study could not determine differential effects for adolescents with schizophrenia as compared to adolescents in HR state
Medications					
Liu et al. 2013 [60]	Aripiprazole in HRP and FEP	20 FEP and 11 HR individuals (11 FEP and 7 HRP who were medication-naïve)	Open-label, 4-week study	Improvement in positive but not negative symptoms, high rate of aripiprazole-related side effects	Very small HRP sample size, open label design, short duration
McGorry et al. 2013 [67]	Risperidone and CBT in HR individuals	115 HRP individuals	Double-blind RCT comparing treatment with CT + risperidone, CT + placebo, ST + placebo	Transition rates to psychosis over 12 months: CBT + risperidone = 11 %, CT + placebo = 10 %, ST + placebo = 22 %. Differences did not reach statistical significance	Sample sizes were small, study was likely underpowered to detect a significant difference
Nutritional Supplements					
Amminger et al. (2010) [76]	ω-3 fatty acid	81 UHR (41 treatment, 40 placebo)	RCT (12-week treatment and 40-week follow-up)	4.9 % vs. 27.5 % (rates of conversion to psychosis in ω-3 fatty acid vs. placebo)	Relatively short follow-up period Allowed concomitant antidepressant and benzodiazepine use. Small sample size
Woods et al. 2013 [78]	Glycine in HR individuals	2 studies, total of 18 patients	10 persons on 8-week open label, 8 persons on glycine versus placebo followed by open label for 24 weeks total	Large effect sizes for drop in total prodromal score: Study 1: ES −1.39 Study 2: ES −1.15	Small sample sizes Open label design
Multimodal interventions					
Bechdolf et al. (2012) [58]	Integrated Psychosocial Intervention (IPI) in HR subjects	128 high-risk patients	To investigate the preventative effects of IPI (including CBT, group-skills training, cognitive remediation, psychoeducation) vs. supportive counseling on preventing psychosis conversion in HR patients	IPI was associated with reduced conversion to psychosis compared to ST at both 12 (3 % vs. 16 %) and 24 months (6 % vs. 20 %)	Specific preventative effects of individual IPI components could not be assessed. Subjects in the ST group received fewer sessions than those in the IPI group

participants showed cognitive improvements after 6 months of antidepressant treatment, whereas no cognitive changes were observed in participants who received antipsychotics or who no medications [70]. Again, presenting symptoms likely impacted treatment choice. Given the risks associated with antipsychotics and the low conversion rates of risk groups, expert consensus suggests using a stepped-care approach to medications in the high-risk period, with antipsychotic medications reserved for those with worsening positive symptoms.

Nutritional Supplements Lack of adequate nutrients during critical developmental periods is associated with increased risk of neurodevelopmental disorders including schizophrenia. Notably, the Dutch and Chinese famine studies have demonstrated increased risk of schizophrenia in birth cohorts exposed to early prenatal nutritional deficiency [71, 72]. Furthermore, both animal and epidemiological studies have underscored the importance of micronutrients such as vitamin D, vitamin B12, folic acid and iron in neurodevelopment [73]. While their role in neurodevelopment is clear, there is still a paucity of evidence for their role in prevention of schizophrenia *per se*. Nutritional supplements such as amino acids and polyunsaturated fatty acids (PUFAs) are attractive alternatives to pharmacological interventions given their favorable side effect profile. Among supplements, PUFAs have received significant attention because of their role in brain development and antioxidant defense [74], and studies have demonstrated positive effects in different psychiatric conditions including depression, borderline personality, antisocial behaviors, ADHD, bipolar disorder and schizophrenia [75]. To date, only one randomized controlled trial of PUFA in the UHR population has been conducted. Amminger and colleagues [76] administered approximately 1.2 g/day of omega-3 PUFAs to 41 UHR individuals for 12 weeks and monitored for rate of transition to psychotic disorders. At the end of the 40-week follow-up period, 4.9 % of the omega-3 PUFA group had converted to psychotic disorders compared to 27.5 % of the placebo group (P=0.007). Additionally, the omega-3 PUFA group showed improvements in their subthreshold psychotic symptoms. While the results are promising, the study was underpowered to detect the effects of other concomitant medications (antidepressants and benzodiazepines) used by some participants, and it has yet to be replicated.

Glycine has been shown to be efficacious as an adjunctive treatment for schizophrenia through actions on NMDA receptor [77]. Woods et al. [78] conducted two pilot studies in small patient groups. In the first study, ten UHR individuals received open-label glycine at doses titrated to 0.8 g/kg/day for 8 weeks, and in the second study, eight UHR individuals were randomized to double-blind glycine vs. placebo for 12 weeks, followed by another 12 weeks of open-label glycine. In both studies, participants were evaluated with the Scale of Prodromal Symptoms every 1–2 weeks, before and after treatment. They observed large effect size changes (−1.39 for open label study and −1.15 for double-blind glycine vs. placebo) in total prodromal symptom scores. Similar to previous investigations, the small sample, even for a pilot study, was the major limitation of these studies, and the results should be interpreted with caution.

Multimodal Two studies have compared different versions of multisystemic, integrated treatment paradigms to either standard care or supportive counseling [58, 79]. The components of the multisystemic treatments include CBT, group skills training, cognitive remediation and multifamily group psycho-education in the one study [58] and an assertive community treatment (ACT) model of care, social skills training and multifamily group psycho-education in the other [79]. Both studies demonstrated significant reductions in transition rates and symptom levels in the integrated treatment models. Transition rates continued to be lower at the 1-year follow-up period and were maintained at the 2-year follow-up in one of the studies [58]. While treatment with medications in the high-risk period appears fraught with inconsistent benefits, side effects, and poor compliance, psychosocial treatments appear to confer significant and lasting benefits.

The study by Bechdolf et al. (2012) found that Integrated Psychological Intervention (IPI), which included cognitive therapy and cognitive remediation, social skills training and family interventions, reduces the rate of psychosis conversion of UHR individuals compared to treatment with supportive therapy over a 24-month period [58]. Compared to previous risk intervention studies, this study included larger samples sizes, and medication effects were better controlled. The study also had several limitations, while rates of attrition were comparable to previous studies; over 30 % of participants received <50 % of the intervention across treatment conditions. Over 25 % of participants across groups were also lost to follow-up at the end of the study. Lastly, as mentioned previously, because the IPI included several therapeutic strategies, the specific preventative effect of CRT was not assessed.

Interventions for possible substance use disorders deserve specific attention, as almost 50 % of persons at risk of psychosis have comorbid substance use. In addition, substance consumption may confer increased sensitivity regarding adverse behavioral effects [80] and prescribed treatment adherence. Furthermore, substance abuse interferes with education, social and emotional development, and brain maturation [81]. Given the prevailing rationale to limit and intervene in substance use in the general population, there have been no randomized interventions that would demonstrate the specific effects of such treatment.

Conclusion

Schizophrenia represents a severe mental illness affecting approximately 1 % of the population in the US and

worldwide. While the outcome of acute schizophrenia may range from full recovery to treatment resistance, in general, the illness of schizophrenia is associated with a staggering amount of personal loss and societal burden. Potentially modifiable mediators of clinical outcome at illness onset include, among others, shortened duration of untreated illness, treatment adherence and abstaining from recreational drug use. Over the past 15 years, the field of early psychosis intervention, similar to other psychiatric and medical disorders, has extended from early treatment of first-episode psychosis to at-risk states of psychosis, and mostly UHR individuals.

This article outlines the growing efforts over the past 2 decades regarding prevention of psychosis with closer emphasis on studies published since 2010. Selected representative studies in this area are presented in Table 1. At the present time, the answer to the question of whether schizophrenia can be prevented is theoretical, given a number of factors including our inability to predict with sufficient specificity illness onset in those with at-risk symptoms. Nevertheless, the recent publications offer several considerations for the clinician confronted with the patient who has emerging psychotic symptoms. The utility of prevention methods should not be limited to calculation of rates of conversion to psychosis, but also to whether treatment provided improves symptoms and functioning. Of young persons who fulfill attenuated psychosis symptoms at-risk criteria, only a small minority will progress to acute psychosis. Because those who do not progress still experience lower level of functioning despite remission of at-risk symptoms, the potential beneficial effect of intervention is not limited to those who would otherwise develop psychosis. In addition, when considering that the onset of psychosis tends to occur during the critical period of personal individuation and academic development in adolescence and young adulthood, postponement of psychosis for even several months to years may permit attainment of higher functioning and resilience to endure clinical symptoms.

Currently available pathophysiology data support a similar phenotype associated with heterogeneous causation and interactions between environmental and genetic factors. The publications on NMDA autoantibody encephalitis or 22q11 DS and psychosis indicate that while psychosis may be common in these conditions, the phenotype differs according to the underlying cause. Exposures to psychological and physical trauma are other potential factors that could contribute to the emergence of illness, even years later. This warrants attention in respect to both risk assessment and prevention. The issue of drugs remains vexing, and the magnitude of the contribution of common recreational drugs, such as cannabis, in the emergence of psychosis requires further study.

The present state of knowledge regarding the progression of at-risk symptoms and potential interventions supports a stepped-care approach, starting in community-placed settings such as juvenile outreach programs and clubhouses to decrease the potential stigma associated with interventions in tertiary care settings and progressing to psychiatric facilities in those with established illness. Potential *universal measures* for preventing psychosis include general health measures to prevent malnutrition, exposure to infections and toxins, insufficient medical care and exposure to different types of abuse, and lack of rearing in the period spanning pregnancy to childhood. *Selective measures* for prevention of psychosis include increased accessibility to psychological and scholastic support and an emphasis on drug abstinence, in particular during the formative years. *Indicated* measures, as most proximal to potential onset of illness, represent the most rapidly growing area, as clinical symptoms represent targets for interventions and outcomes over a few years can be more readily measured. A specific algorithm to stage psychosis was developed by the Early Psychosis Prevention and Intervention Centre group [82]. The staging includes individuals with increased risk (e.g., first-degree teenage relatives) without symptoms (stage 0), and progresses through the prodrome (stage 1a , with nonspecific symptoms, and stage 1b, subthreshold psychosis) to acute (stages 2–3) and chronic stages of psychosis (stage 4). Within this concept, universal and indicated measures are most applicable for persons at stage 0, adding selective measures for stages 1a and 1b. Interventions that map onto this construct include improved coping skills and behavioral and cognitive resilience, such as cognitive behavioral therapy and cognitive remediation, as potential measures during stages 0 and 1a. Family education and treatment, nutritional supplements and antidepressants could be added for stages 1a with antipsychotics, and multimodal treatment programs reserved for stage 1b and higher.

When we consider current at-risk research and treatment, we should hope that the field may develop more quickly over the next decade, based on the recent emphasis to investigate domains of brain functions associated with specific neural substrates and behavior, rather than with diagnostic categories. This would permit the study of individual phenotypic measures and their relationship to a person's clinical condition and its progression.

Compliance with Ethics Guidelines

Conflict of Interest James Yi declares that he has no conflict of interest.

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- • Of importance
- •• Of major importance

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