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Research in People with the Psychosis Risk Syndrome: A Review of the Current Evidence and Future Directions

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Abstract

After decades of research, schizophrenia and related psychotic disorders are still among the most debilitating disorders in medicine. The chronic illness course in most individuals, greater treatment responsiveness during the first episode, progressive grey matter decline during early disease stages, and retrospective accounts of “prodromal” or early illness signs and symptoms formed the basis for research on the psychosis risk syndrome,, known variably as “clinical high risk”(CHR), or “ultra-high risk“ (UHR), or “prodromal”. The pioneering era of research on the psychosis risk syndrome focused on the development and validation of specific assessment tools and the delineation of high risk criteria. This was followed by the examination of conversion rates in psychosis risk cohorts followed naturalistically, identification of predictors of conversion to psychosis, and investigation of interventions able to abort or delay the development of full psychosis. Despite initially encouraging results concerning the predictive validity of the psychosis risk syndrome criteria, recent findings of declining conversion rates demonstrate the need for further investigations. Results from intervention studies, mostly involving second-generation antipsychotics and cognitive behavioral therapy, are encouraging, but are currently still insufficient to make treatment recommendations for this early, relatively non-specific illness phase. The next phase of research on the psychosis risk syndrome just now beginning, has moved to larger, “multi-site” projects to increase generalizability and to ensure that sufficiently large samples at true risk for psychosis are included. Emphasis in these emerging studies is on: 1) identification of biomarkers for conversion to psychosis; 2) examination of non-antipsychotic, neuroprotective and low-risk pharmacologic and non-pharmacologic interventions; 3) testing of potentially phase-specific interventions; 4) examination of the relationship between treatment response during yhre of psychosis risk syundrome and prognosis for the course of illness; 5) follow-up of patients who developed schizophrenia despite early interventions and comparison of illness trajectories with patients who did not receive early interventions; 6) characterization of individuals with outcomes other than schizophrenia spectrum disorders, including bipolar disorder and remission from the psychosis risk syndrome, including false positive cases; 7) assessment of

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meaningful social and role functioning outcomes. While the research conducted to date has already yielded crucial information, the translation of the concept of a clinically identifiable psychosis risk syndrome into clinical practice does not seem justified at this point.

Keywords

Schizophrenia; Psychosis; Risk Syndrome; Prodrome; Early Recognition; Early Intervention; Biomarker; DSM-V

Despite advances in pharmacological and psychotherapeutic interventions and decades of research, schizophrenia continues to be one of the most severe and debilitating disorders in all of medicine (Hegarty et al. 1994). The chronic and relapsing illness course in most individuals with schizophrenia, greater treatment responsiveness during the first episode of psychosis, documented progressive grey matter decline during the early illness phases and retrospective accounts of “prodromal”, early illness signs and symptoms has led to the development of early recognition programs around the world (Olsen and Rosenbaum 2006; Cannon et al. 2007; Cornblatt et al., 2003; de Koning et al. 2009). The field of research on the psychosis risk syndrome focuses on the identification and treatment of individuals at a clinical phase when first symptoms and/or impairments emerge. These might present as “attenuated” psychotic symptoms that are present below the threshold of full psychosis, brief and self-limiting psychotic symptoms, or a significant decrease in functioning in the context of a genetic risk for schizophrenia (Yung and McGorry 1996) as well as early subjective disturbances of cognitive processes and the perception of the self and the world (Klosterkoetter et al. 2001, Schultze-Lutter et al. 2008).

This article will examine the data generated by the field of research on the psychosis risk syndrome to date, evaluate the relevance of the currently available findings for clinical practice, and identify areas where additional research is needed. Specifically, we will:

- review the theoretical and practical rationale for early identification and interventions during the pre-psychotic illness phase
- provide an overview of assessment methods and challenges
- review naturalistic studies of individuals with the psychosis risk sundrome
- discuss risk factors and putative biomarkers for conversion to psychosis
- summarize completed and ongoing intervention studies for people with the psychosis risk syndrome and
- identify areas that the field needs to address before research findings can be implemented in general clinical practice.

The Psychosis Risk Syndrome

Although prodromal symptoms of psychosis have long been recognized (Meares, 1959), the focus of attention has been most often on the florid symptoms of psychosis. Retrospective studies from the 1980's redirected attention to the fact that patients with schizophrenia often showed early, less severe manifestations of the illness for days up to years (on average for five years) prior to onset of full psychosis (Hafner et al 1999, Hafner et al. 1995). These data and the development of reliable measurement tools to identify persons at risk for developing psychosis led to increased enthusiasm for the potential of prevention of schizophrenia around 15 years ago. Since that time, early intervention programs have been initiated worldwide beginning with McGorry, Yung and colleagues in Australia in 1994 and then moving to the United States and Europe shortly thereafter. The Australian group defined the

"ultra-high" risk state for psychosis as the period between the first noticeable changes in behavior to the appearance of overt psychotic symptoms (Yung et al., 1996). This high risk syndrome for schizophrenia is variably known as "clinical high risk" (CHR) "ultra-high risk" (UHR) or "(putatively) prodromal". While all three of the risk syndrome labels are used interchangeably, CHR is most typically used in North America, UHR in Europe and Australia. The term "prodrome" is the most popularized, but least accurate of the terms, since, adapted from medical terminology, it tends to imply an inevitability of illness rather than a possible risk, as conveyed by the UHR and CHR labels. As UHR and CHR labels refer to similar but not identical, yet very specific sets of risk criteria that do not include a further set of "basic symptom" criteria defined by a German approach to early recognition, in this paper, we will use the general term "psychosis risk syndrome" most often, with the understanding that this indicates a possible risk of as yet undetermined magnitude based on the presence of equally sensitive signs and symptoms known retrospectively to characterize affected patients in the early stages of their psychotic illness. We decided to use the term "psychosis risk syndrome" (PRS), as it indicates a potential risk for psychosis based on a sundromal level, i.e., based on a constellation of symptoms and signs, differentiating it from the genetic or familial high risk research. Moreover, this terminology has also been used in the DSM-V discussions about the potential inclusion of a dimensional risk syndrome for psychosis and schizophrenia (http://www.psych.org/MainMenu/Research/DSMIV/DSMV/DSMRevisionActivities/DSM-V-Work-Group-Reports/Psychotic-Disorders-Work-Group-Report.aspx).

However, although the psychosis risk syndrome indicates only a probability of disease progression, the serious impact that schizophrenia-spectrum disorders have on a person's psychosocial, educational and vocational functioning makes prevention an urgent goal. Moreover, the symptoms and signs summarized in table 1, which may suggest the presence of a prepsychotic or subthreshold psychotic phase, in and of themselves, can impair patients' functioning and quality of life (Bechdolf et al. 2005;Ruhrmann et al. 2008).

Patients may evolve through several phases of the psychosis risk syndrome (Ruhrmann et al. 2003, Cornblatt et al. 2003). Accordingly, the putatively prodromal symptoms and signs can be divided into those thought to be more distal to the onset of psychosis and those more proximal to the onset of psychosis. The early psychosis risk syndrome (also known as early initial prodromal state, EIPS) is characterized primarily by subtle, self-experienced deficits also termed "basic symptoms". These include disturbances of self-perception, stress tolerance, thought organization, and social and nonverbal interactions that are generally not observed by others (Schultze-Lutter 2009). In addition, attenuated negative symptoms of schizophrenia are often present, including social isolation, decreased expression of emotion, rigid or simplistic thinking, odd behavior or appearance, and impairments of personal hygiene (also known as the clinical high risk negative (CHR−) state) (Lencz et al. 2004). These mostly non-specific symptoms are thought to be the earliest expression of disrupted neural circuits that can precede and herald further development of psychosis (Cornblatt et al. 2003). The later psychosis risk syndrome is characterized to a greater extent by attenuated positive symptoms of psychosis, which tend to be more specific for psychotic disorders. These include subpsychotic levels of unusual thought content, suspiciousness, grandiosity, perceptual abnormalities, and cognitive disorganization (Yung and McGorry 1996). Although (attenuated) negative symptoms are not among the internationally applied sets of risk criteria defining a psychosis risk syndrome, there is some suggestion that (attenuated) negative symptoms are present to an equal degree in individuals with the early psychosis risk syndrome compared to those with a later psychosis risk syndrome that includes attenuated positive symptoms (Cornblatt et al. 2003; Lencz et al. 2004). Moreover, there is also the suggestion that the presence of significant (attenuated) negative symptoms is associated with higher conversion rates (Schultze-Lutter et al. 2007).

Rationale for Early Recognition and Intervention in Psychosis

The rationale for early identification and intervention in schizophrenia and related psychotic disorders initially was based mostly on theoretical considerations and indirect evidence. Subsequent research findings from the last 15 years have provided direct evidence for the value of early recognition efforts. One chief argument for early intervention in schizophrenia includes the severity, chronicity, and functional impact of the full-blown disorder, despite treatment advances (Robinson et al. 2004; Lieberman et al. 2005; Lewis et al. 2006; Tandon et al 2009). Although course and severity vary, the illness is generally characterized by recurrent episodes, residual negative symptoms, and enduring cognitive impairment (Tandon et al, 2009). In addition, prognosis is worse in early onset cases (Luoma et al, 2008). However, there has been a debate whether earlier illness onset is a poor prognostic factor in and of itself or whether it is related to a prolonged duration of untreated psychosis (DUP). At least in one recent data set, the effect of earlier illness onset disappeared when controlling for DUP (Schimmelmann et al. 2008). Research has shown that the most pronounced functional decline occurs within the first years after illness onset with stabilization thereafter (for reviews see McGlashan & Johannessen 1996, Tandon et al. 2009). However, because in retrospective studies, patients dated the onset of their functional decline back to the prodromal, pre-psychotic phase (Hafner et al 1995), early interventions were hoped to avert or, at least, minimize or delay the onset and further development of biological and psychosocial damage (McGlashan and Johannessen 1996; Yung and McGorry 1996).

Since then, evidence for early deterioration has become available from cross-sectional comparison studies and prospective investigations (Niendam et al 2009; Yung et al. 2004; Fusar-Poli et al 2009; Shim et al 2008; Cornblatt et al 2007 (for details see Risk Factors and Putative Biomarkers and Table 3 below)). The early beginning of functional decline is of particular importance for the overall severity and impact of the illness due to the young age at which it can occur. Especially, adolescents have not established their social, educational and occupational foundations yet. Thus, early recognition and intervention are hoped to, at least, help improve the course of illness and reduce its long-term impact.

Further support for the importance of early recognition and intervention strategies is provided by investigations concerning the duration of untreated psychosis (DUP). A great body of evidence confirms an association between longer DUP and worse psychopathology and functional outcomes (Norman & Malla 2001; Perkins et al 2005; Marshall et al 2005). Based on these findings, it has been theorized that in addition to non-specific factors and mediators of outcome associated with a longer DUP, psychosis itself may be noxious and treatment response may be diminished over time (Wyatt1991; Wyatt & Hunter 2001).

While this hypothesis has not been proven to date (McGlashan et al 2006; Haroun et al 2006), preliminary support for this idea has been mounting from a number of cross-sectional as well as longitudinal imaging studies in PRS individuals (for details see Risk Factors and Putative Biomarkers and Table 4 below). These studies have shown that brain changes are already present in individuals compared to healthy controls (e.g., Pantelis et al. 2003; Borwardt et al. 2007; Phillips et al 2003; Takahashi et al. 2009; Walterfang et al. 2008; Wittaus et al. 2008; Ziermans et al. 2009). More importantly, additional progressive brain changes have been documented in PRS individuals who convert to psychosis compared to those who did not convert to psychosis (Pantelis et al. 2003; Takahashi et al. 2009; Walterfang et al. 2008). Further, in one study, a longer duration of the prodrome was associated with greater volumetric abnormalities in first-episode patients (Lappin et al. 2007). This suggests that the progressive volumetric brain changes documented during early psychosis (Whitford et al 2006, Ziparro et al 2008) might already begin in the prodromal illness phase.

The presence of more or less severe behavioral and cognitive abnormalities in children who later develop psychosis point to the influence of early neurodevelopmental disturbances, even if they are not themselves causative of the illness (for a review see Walker et al 1994, Walker et al 1999, Marenco & Weinberger, 2000). In a comprehensive review of structural imaging data, Pantelis and colleagues (2005) concluded that brain changes found in individuals with the psychosis risk syndrome and with schizophrenia seem to occur as a result of a cascade of early and late neurodevelopmental disturbances, as well as of other factors associated with the actual onset of psychosis. According to this theory, pre- and perinatal disturbances would lay the ground for an underlying brain vulnerability for later neurodevelopmental processes that occur during adolescence, leading to abnormal brain changes in that phase. As a consequence, this could then lead to increased grey matter loss and anomalous connectivity, particularly in prefrontal regions (Pantelis et al 2005). However, it is still unclear which endogenous and exogenous factors trigger the biological processes that lead from the vulnerability stage to the evolution of suprathreshold pathology. In addition, it is important for early intervention approaches to consider the differences between genetically mediated brain abnormalities that occur also in unaffected relatives and those brain changes that are specific to individuals who develop psychosis (for a review see Cannon et al 2003). Identification of these additional brain regions can potentially aide the identification of mechanisms involved in the progression to psychosis that might lead to the development of etiologically targeted, secondary preventive treatments.

Finally, the last generation of prospective clinical studies provided additional support for the utility of early identification and intervention programs. Naturalistic studies have shown that the DUP can be reduced through early identification efforts (for review see Yung et al 2007) and that samples of individuals with the psychosis risk syndrome can be identified who progress to full psychosis at levels that are much higher than chance, with clinically meaningful conversion rates of between 10% and 40% over 1-2 years (Olsen and Rosenbaum 2006) (see Naturalistic Studies in Individuals with the Psychosis Risk Syndrome section below). These findings were complemented by a recent generation of controlled intervention studies documenting that putatively prodromal psychophathology and functional impairment can be reduced and that the onset of psychosis can be delayed or prevented (McGorry et al 2009, de Koning et al. 2009; Ruhrmann et al. 2009) (see Controlled Intervention Studies below).

Early Identification Methods

The primary goals of early intervention programs are to identify those persons at greatest risk for the development of psychosis, to treat the presenting symptoms, to help the person return to his/her previous level or maintain his/her current level of functioning, and ultimately to delay or prevent the onset of psychosis. Thus, the reliable identification of a person with the psychosis risk syndrome is the first step toward prevention. The important step of conducting prospective, naturalistic and controlled studies in individuals with the psychosis risk syndrome was made possible only through the development of standardized, valid and generally accepted assessment tools and psychosis risk syndrome criteria that have since been used around the world (Olsen and Rosenberg 2006). This approach succeeded by following the ‘close-in’ strategy suggested by Bell (1992). In comparison to earlier genetic high risk studies, this strategy lead to a higher rate of transition to psychosis, lower false positive rates and a shorter follow-up period than necessary when following offspring with a family history of schizophrenia. The important turn was concentrating on individuals who met several risk associated factors at once (e.g. clinical features, behavioral problems, help-seeking individuals, adolescent age of individuals) (McGorry et al. 2003).

Symptoms and Signs of the Psychosis Risk Syndrome

The pioneering work conducted by McGorry, Yung and colleagues in Australia in the mid 1990's began to delineate putative prodromal symptoms through the use of standard rating scales designed for patients with full psychosis or schizophrenia (Yung et al. 1996; Yung et al. 2005). Ratings on specific positive symptoms from the Brief Psychiatric Rating Scale (e.g., unusual thought content, suspiciousness, hallucinations, conceptual disorganization; Overall & Gorham, 1962) and the Comprehensive Assessment of Symptoms and History (i.e., delusions; Andreasen et al., 1992) formed the basis for the first set of criteria to define a putative prodromal state or "at risk mental state" (ARMS). This psychosis risk syndrome constellation has been expanded by various research groups to include negative symptoms, disorganized symptoms, non-specific symptoms. However, a different approach to early recognition was taken by German research groups, resulting in a set of criteria that are known as self perceived cognitive and perceptual deficits, or "basic symptoms" (Table 1). The roots of these criteria go back to the work of Huber, Gross and co-workers in the 1960s who first described the presence of basic symptoms during the clinical course of schizophrenia, culminating in the development of the BSABS (Bonn Scale for Assessment of Basic Symptoms) (Gross et al., 1987). Subsequent prospective investigation of these symptoms (Klosterkoetter et al. 2001) enabled the definition of subsets of basic symptoms (cognitive-perceptive basic symptoms [COPER] and cognitive disturbances [COGDIS]) (Schultze-Lutter et al. 2006) as psychosis risk syndrome criteria. Individuals who are known/suspected to exhibit substance abuse/dependence or a physical illness that might account for the symptoms are excluded from studies of individuals with the psychosis risk syndrome by most groups, as they are believed to be in a conceptually and etiologically different putatively pre-psychotic state (i.e. the psychosis risk syndrome due substance abuse/dependence or due to a medical condition). Nevertheless, particularly the association between the psychosis risk syndrome and substance (ab)use is just beginning to be investigated (see table 3, clinical risk factors).

Two interview measures have been developed to operationalize the ARMS criteria first outlined by McGorry and Yung. Yung et al. created the Comprehensive Assessment of At-Risk Mental States (CAARMS; Yung et al., 2005). McGlashan and colleagues developed the Structured Interview for Prodromal Syndromes (SIPS) and the companion Scale of Prodromal Symptoms (SOPS; McGlashan et al., 2001; Miller et al., 1999), which has become the prevailing prodromal instrument in North American studies. Both the SIPS/SOPS and the CAARMS are semistructured interviews that assess for positive, negative, disorganized and general symptoms. The CAARMS also includes more prominently cognitive symptoms and has a predominating influence in Australia and many studies in Europe. The German concept of basic symptoms has been operationalized by the Schizophrenia Proneness Instrument Adult Version (SPI-A), which allows for a frequency-based severity rating of basic symptoms (Schultze-Lutter et al., 2007). This inventory focuses on the self perceived experiences of cognitive and perceptual changes thought to represent the early phases of the pre-psychotic period. The SPI-A is widely used in Europe and usually applied together with the SIPS/SOPS and to a lesser degree with the CAARMS in order to allow for the assessment of the the psychosis risk syndrome according to both approaches. In addition, the SPI-A has also recently been incorporated into studies in North America and Australia, which may increase the accuracy of risk prediction (Simon et al. 2006). All interviews require training generally of masters or doctorate level clinicians, although good to excellent interrater reliability has not been difficult to achieve (Yung et al., 2005; Miller et al. 2003, Schultze-Lutter et al. 2007).

Putative Psychosis Risk Syndromes for Psychosis and for Schizophrenia

Although there are regional differences in the psychosis risk syndrome interview selection, most programs have adopted (or adapted) the "ultra-high risk" syndrome criteria first introduced by Yung and McGorry (1996) and later operationalized by Miller, McGlashan and colleagues (2002) (Table 2). These criteria include individuals who are deemed at high risk of developing psychosis based upon the presence of: 1) brief, limited psychotic level symptoms that spontaneously remit– the Brief (Limited) Intermittent Psychotic Symptom (BIPS or BLIPS) Syndrome; 2) attenuated positive symptoms in the prodromal severity range occurring in the past year – the Attenuated Positive Symptom (APS) Syndrome; or 3) presence of either schizotypal personality disorder or a first degree relative with a psychotic disorder in combination with a ≥30% decline in functioning based upon Global Assessment of Functioning (GAF; DSM IV) score – the Genetic Risk and Deterioration (GRD) Syndrome. The onset, frequency, and duration required to meet the criteria depend on the whether the SIPS or the CAARMS instrument is used. A further syndrome particularly applied in Europe and increasingly recognized internationally is defined by 4) the presence of basic symptoms according to COPER or COGDIS criteria (Schultze-Lutter et al. 2006). The German Research Network on Schizophrenia has delineated an Early Initial Prodromal State (EIPS) and a Late Initial Prodromal State (LIPS). EIPS is characterized by the presence of at least one cognitive-perceptive basic symptom (COPER criteria) or two cognitive disturbances (COGDIS criteria) in the past 3 months and/or meeting the GRD. By contrast, the Late Initial Prodromal State (LIPS) corresponds closely to the APS and BIPS groups outlined above (Bechdolf et al 2005; Ruhrman et al 2007). Other research groups have adapted the criteria and/or measurement instruments. For example, the Recognition and Prevention (RAP) Program, which uses the SIPS, has developed criteria to classify participants as Clinical High Risk (CHR) based upon the presence of positive and negative symptoms with one category, CHR Positive (CHR+), closely approximating APS criteria (Cornblatt et al. 2003). In addition, the RAP program includes as the most distal putatively prodromal phase 5) an attenuated negative symptom only (CHR Negative, CHR−) group (Lencz et al. 2004), as well as 6) a Schizophrenia-like Psychosis (SLP) group that is similar to the DSM-IV diagnosis of Psychotic Disorder, Not Otherwise Specified (NOS) as the most proximal putative prodrome, yet not to psychosis, but rather to schizophrenia (Correll et al. 2005; Correll et al. 2008). All of these classifications follow the idea of a staging model that has been used widely in medicine but that was only recently comprehensively adapted to the psychosis risk syndrome (McGorry et al 2006). The theoretical framework of "staging" is very useful for the conceptualization of etiopathological processes, and for individualized and targeted identification and intervention strategies. Participants can simultaneously be classified in more than one risk group (Cannon et al. 2008). Looking only at the APS, BIPS/BLIPS and GRD syndromes, most participants who are included in psychosis risk syndrome programs meet APS criteria (Cannon et al. 2008). However, when including the COPER/COGDIS syndrome, most participants are shown to meet these criteria, followed by APS criteria (Schultze-Lutter et al. 2009). Nevertheless, the maximum duration of the psychosis risk syndrome symptoms prior to enrollment into research studies is arbitrary, and might actually relate to different outcome groups. Vice versa, with regard to basic symptoms, it has been argued that different basic symptoms, related to the different duration of the putative prodrome and different underlying deficits may lead to the same outcome, i.e. schizophrenia (Schultze-Lutter et al. 2007).

Conversion

Although the impetus for research on the psychosis risk syndrome has been the prevention of schizophrenia, the outcome used in most studies is defined as having psychotic level intensity on at least one positive symptom item occurring at a certain frequency (e.g., at least 1 hour per day) for a specified period of time (e.g., >1 week), as this level and duration is

thought to require clinical interventions (McGorry et al. 2002). However the exact frequency and duration is somewhat arbitrary and varies with instrument. For example, patients fulfilling criteria for Brief Psychotic Disorder or Psychotic Disorder, NOS are used as a psychosis risk syndrome group when psychotic symptoms either do not meet a) duration criteria for psychosis (i.e., less than 7 days in the Australian criteria [Yung et al., 1998; McGorry et al. 2003], or less than 4 days in the American criteria [McGlashan et al. 2003; Woods et al. 2003]) and that remit without intervention, or b) if they do not meet frequency criteria (frequency score of at least 3 on the on specific CAARMS subscales [Yung et al. 2005]). Conversely, when symptoms are present with a higher frequency or for one day longer, then these patients are used as a psychosis “outcome” group. Thus, using these criteria, patients with limited psychotic symptoms are combined with patients fulfilling criteria for schizophrenia or schizoaffective disorder as a group that converted to “psychosis”. However, this is problematic for research of clinical predictors and biomarkers, as studies have shown that Brief Psychotic Disorder or Psychotic Disorder, NOS have a heterogeneous outcome when followed as a distal schizophrenia (not psychosis) risk syndrome group in its own right (Correll et al. 2005; Correll et al. 2008).

Outcome of Naturalistic Follow-Up Studies

The value of the psychosis risk syndrome criteria is in their ability to identify individuals who have a high likelihood of converting to psychosis over a relatively short period of time. This predictive validity has been examined in a number of studies in which PRS samples were identified and followed prospectively measuring naturalistic conversion rates. The problem with such studies is the uncontrolled treatment that patients might receive that can affect the observed base rates of conversion. The design and outcomes of such naturalistic studies has been reviewed by several groups (DeKoning et al. 2009; Haroun et al. 2006; Olson and Rosenbaum 2006).

In the reviewed studies with somewhat varying inclusion criteria and outcome definitions, the proportions of patients belonging to individual psychosis risk syndrome groups subgroups varied substantially, i.e., BLIPS: 0% to 36.7%, APS: 48.3% to 95%, and GRD: 0% to 37.5%. Mean follow-up periods ranged from 6 months to 9.6 years, with most studies having a mean duration of follow up of 6 or 12 months. Except for the study with the 9.6 year follow-up where a 70% conversion rate was reported in patients identified by basic symptoms (Klosterkotter et al. 2001), transition rates to psychosis ranged from 6.6% (Skeate et al. 2004) to 54% (Miller et al. 2002). Of note, the highest likelihood of conversion was found to occur within the first year after recognition of the psychosis risk syndrome with no or significantly smaller further conversion rates thereafter. This suggests that, at least, in samples ascertained based on current psychosis risk syndrome criteria that impose a maximum duration of newly emergent or worsened attenuated positive symptoms, the majority of conversions occur within the first 6-12 months (Yung et al. 2008; Cannon et al. 2008). It is unclear whether this is due to a selection bias of excluding patients with a slow and incipient psychosis risk syndrome, or a function of censoring of patients who dropped out over time and who might be at highest risk for later conversion. Moreover, it is possible that longer follow-up durations are needed for further conversions to occur, in that there could be a bimodal distribution of early and late conversions to psychosis, in contrast to a more continuous, linear risk progression model. In this context, it will be relevant to characterize in long-term studies the subgroup of patients who do not convert and remain impaired and/or continue to fulfill criteria for the psychosis risk syndrome and those who fully recover over time, even in the absence of ongoing treatment.

Recently, the field has been facing reduced transition rates from initially over 40% within 6 months (Yung et al 1998, Miller et al 2002) or 12 months (Phillips et al 2000, Miller et al

2002) to only 7% within 6 months (Skeate et al 2004), 12% within 12 months (Haroun et al 2006) and 16% within 2 years (Yung et al. 2008). Similarly, the two largest multicenter studies to date, conducted in Europe (EPOS, Ruhrmann et al. in press) and in North America (NAPLS, Cannon et al. 2008) and including 245 and 291 psychosis risk syndrome patients, respectively, reported transitions rates of 19% and 26.8% at 18 months follow up. While still substantial, clinically relevant and validating selection criteria for the psychosis risk syndrome, these 18-month rates are substantially lower than the rates that had been reported in initial studies. Several potential reasons have been put forth for this trend (Yung et al 2007). These include a “lead-in” effect, in that patients tend to be identified earlier as psychosis high risk clinics and referral sources mature. A related factor could be that during this process, specialized high risk centers for individuals with the psychosis risk syndrome separate more from first episode schizophrenia clinics where patients in the most proximal prodromal stages might be seen more frequently. The resultant, earlier recognition could either lead to possibly enhanced prevention due to intervening after a shorter duration of an untreated psychosis risk syndrome, or to a longer lag time to conversion. Alternatively, the referral sources could become overinclusive and refer more false positive cases, thereby diluting the sample. It is also possible that appropriate early intervention efforts in a region have begun to deplete true at risk individuals, as the annual incidence rate for psychosis is very small. It is unclear to what degree the decreasing transition rates with increasing early recognition efforts apply to research settings alone, or whether this is a general phenomenon that could also be observed in clinical settings over time. Nevertheless, whatever the reasons for the observed decline in conversion rates are, these trends further highlight the need for additional research regarding the identification of clinical and biological risk factors for conversion, as well as for phase-specific, and/or benign intervention strategies.

Furthermore, the particular diagnostic outcome of those who convert to psychosis and of those who do not convert to psychosis needs to be determined. This will also help to differentiate patients whose outcome will include affective psychotic or non-psychotic disorders from those who develop schizophrenia-spectrum disorders. In this context, the delineation of a bipolar disorder risk syndrome has become an increasing focus of attention (Bauer et al. 2008; Conus et al., in press; Conus et al. 2008; Correll et al. 2007a, Hauser et al. 2007; Ozgürdal et al 2009b). Ideally, this area of research should not be pursued in isolation of the established research of the psychosis risk syndrome. A linking of these two research areas will help to delineate the putative prodrome to schizophrenia from prodromal presentations preceding bipolar disorder (Correll et al. 2007b). This differentiation, which includes questions about the specificity of symptoms and predictors and about the potential presence of respective hallmark symptoms, is of increasing relevance, as treatments for each of these risk syndromes may need to differ substantially (Cornblatt et al. 2007).

Outcome Predictors and Biomarkers

Although, as discussed above, earlier psychosis risk syndrome studies showed conversion rates to psychosis of up to 40% (Yung et al 1998, Phillips et al 2000, Miller et al 2002,), still a high number of patients of 60% or more did not convert to psychosis during the observation period. Thus, adding specific predictors and biomarkers to the clinical psychosis risk syndrome approach that could increase the predictive power of current PRS criteria and enhance the ability to predict outcomes is a crucial step for early recognition and intervention efforts (Keshavan et al. 2005). While endophenotypes, illness and risk factors that are more closely related to the underlying biology of a disease have been investigated in schizophrenia (see Allen et al 2009), this field of study is more recent in the area of psychosis risk syndrome research.

Table 3 summarizes clinical risk factors for transition to psychosis, and Table 4 provides an overview of potential biological risk factors and biomarkers assessed in individuals with the psychosis risk syndrome. An increasing body of literature is accumulating in this area, with most of the studies dating back to the last 6 years. While younger age (particularly before age 18) of psychiatric symptom onset was strongly associated with conversion to psychosis (Amminger et al. 2006), presence of obstetric abnormalities has yielded mixed results (Yun et al. 2005,Cannon et al. 2002). In preliminary work, IgG antibody levels to toxoplasma gondii, but not to Herpes simplex virus were associated with greater attenuated positive symptom severity in individuals with the psychosis risk syndrome (Amminger et al. 2007). Reduced functioning is a core feature of the psychosis risk syndrome and, as such, is included in the GRD syndrome. Several recent studies characterizing the psychosis risk syndrome reported that functional decline begins prior to onset of acute illness and predicts conversion to psychosis (Yung et al. 2004;Yung et al. 2006;Cornblatt et al. 2007;Cannon et al. 2008;Velthorst et al. 2009). Specifically, the North American Prodrome Longitudinal Study (NAPLS) found in 291 patients from 8 diverse sites that five baseline features predicted psychosis independently: genetic risk for schizophrenia with recent deterioration in functioning, higher levels of unusual thought content, suspicion/paranoia, greater social impairment, and a history of substance abuse (Cannon et al. 2008). In an earlier study, development of psychosis was predicted by poor and recent onset of significantly decreased functioning, long symptom duration, high levels of depression and reduced attention, recent experience of subthreshold psychotic symptoms combined with a family history of psychosis (Yung et al. 2006). In addition, a study by Fusar-Poli and colleagues (2009) also suggested that longer duration of the psychosis risk syndrome (defined by COPER criteria) was associated with less improvement in functioning. Thus, impaired functioning seems to be both an at-risk state and an outcome factor. However, more detailed research is needed to assess the relevance of different dimensions of functioning. This is suggested by a recent study in PRS individuals finding that role functioning declined over the year prior to ascertainment and improved over 12-month follow-up, whereas social impairment remained constant across time and predicted later psychosis (Cornblatt et al 2007). In addition, symptoms of depression have also been reported to constitute very early symptoms of the emerging illness (Yung et al 1996,Hafner et al, 1998). Exploratory models suggest that depressive symptoms may worsen (attenuated) psychotic symptoms by more negative evaluations and related higher distress of the experiences due to depression, thereby enhancing risk of transition to psychosis (Yung et al. 2007). Although substance use in general was one of five independent risk factors for conversion to psychosis in the longitudinal NAPLS study, data on cannabis use as a risk factor in PRS subjects have remained inconsistent (Table 3).

However, although the above mentioned clinical markers are of interest and important, functional capacity and severity of putatively prodromal psychopathology may be impaired due to environmental factors and comorbid conditions that may not trigger or be part of psychosis. Thus, clinical predictor models are relatively non-specific if used in isolation and if compared to other clinical samples.

The most extensively studied biological factors are in the area of neuroimaging and cognition (Table 4) An increasing number of studies have recently begun to focus on neuroimaging as a way to identify early predictors of later illness. However, the field is just beginning, there are many technological details to work out, and the methodology is often variable from study to study, as are the areas of the brain selected for particular interest. As a result, the findings reported in imaging results, in general, are quite diverse and inconsistent. It is assumed that some neuroanatomical abnormalities present before transition may reflect an underlying vulnerability for psychosis, whereas others may be associated with progression due to acute illness (Pantelis et al 2003). Therefore, longitudinal studies are of

great importance. However, the majority of studies report on cross-sectional comparisons between PRS individuals and first-episode patients or healthy controls, as well as on cross-sectional baseline comparisons between PRS individuals who later went on to develop psychosis and those who did not convert. The number of studies is growing, but the regions investigated are very diverse across studies, so far, making it difficult to draw conclusions. Categorizing the findings based on anatomical and functional brain location (Table 4), generally three or fewer studies have yielded results for each individual region. As an exception, the temporal lobe is the most comprehensively studied region with the most consistent results, showing predominantly grey matter volume reductions in PRS individuals compared to healthy controls, and in PRS individuals who subsequently converted to psychosis compared to those who remained psychosis free. A similar picture is seen in the cingulate cortex. Reviewing the imaging results in the psychosis risk syndrome field, Pantelis and colleagues (2007) concluded that most changes associated with transition to psychosis were found in grey matter of the medial temporal and prefrontal lobe. Despite this promising progress, much more research is needed to be able to apply neuroanatomical abnormalities to current or future illness severy and expression, functional impact, and possibly, treatment response.

Neurocognition has also been investigated relative extensively in PRS individuals as potential risk and vulnerability factors. Reviewing data on cognitive deficits in PRS samples, Brewer and colleagues (2006) concluded that some cognitive deficits were present prior to psychosis, that general cognitive ability seemed intact, but also that cognition was likely a poor predictor for the emerging onset of psychosis. However, the authors pointed out that deficits in spatial working memory were a relatively potent feature. Over the past years, additional and more specific studies emerged, suggesting a different picture concerning cognitive deficits in PRS individuals. As can be seen in Table 4, PRS individuals show deficits in cognitive performance over a broad range of domains, a feature that is accentuated in those who subsequently convert to psychosis. The most conclusive results are found in the domains of processing speed, working memory and verbal memory. Nevertheless, results need to be interpreted with caution due to the implementation of diverse assessment tools across studies. To advance the filed, the standardization of methods is crucial (Brewer et al 2006). Like for imaging, the results concerning cognition are inconsistent and not specific enough to include specific cognitive abnormalities as additional risk factors to the symptom approach at this point.

Relatively few studies have been conducted that investigated neurophysiological predictors PRS samples, finding disruptions in P300 amplitude and latency, P50 and N100 suppression and mismatch negativity (Frommann et al. 2008; Cadenhead et al. 2005; Brockhaus-Dumke et al. 2005; Brockhaus-Dumke et al. 2008; Shin et al. 2009). Only one study (Gschwandter et al. 2009) evaluated EEG patterns in a PRS sample, finding some abnormalities. Additional areas of study in PRS individuals have included disturbances in olfaction (Brewer et al. 2003), eye tracking (Nieman et al. 2007) and cortisol levels (Thompson et al. 2007). Of endophenotypes, risk factors and biological predictors that have been investigated in schizophrenia, data in PRS samples are currently lacking for genetics, neurological soft signs, and minor physical anomalies.

In summary, despite an increasing number of individual studies, information about specific factors influencing outcome in individuals at true risk for psychosis is still quite limited and often based on small, heterogeneous samples (Yung et al 2004). To date, the most areas include functional and cognitive deficits as well as neuroanatomical abnormalities. However, the current absence of valid indicators of true risk for psychosis and outcome predictors severely hampers decisions about the timing and type of interventions for help seeking PRS individuals, as well as about the advisability to stop interventions that might or

might not have been instrumental in reducing psychosis risk syndrome psyhopathology or in preventing progression to psychosis. Since psychosis can be present in a heterogeneous group of disorders, future studies should be large and long enough to follow sufficiently large numbers of patients who can be characterized into subgroups of psychotic disorders and outcome trajectories. It is likely that the reduction in the heterogeneity of the prediction endpoint will yield a greater possibility to identify specific predictors with clinically sufficient predictive power. In this regard, the recent development toward large, multisite studies is clearly beneficial.

Interventions

Early reports on the high predictive power of PRS criteria encouraged research on interventions in individuals with the psychosis risk syndrome prior to the onset of frank psychosis. Early interventions aim to reduce symptoms as well as possibly delay or, even, fully prevent the onset of psychosis. Interventions during the psychosis risk syndrome are a type of secondary or “indicated” prevention (Mrazek & Haggerty, 1994), as they target subjects with minimally detectable symptoms below the threshold of a psychotic disorder diagnosis. Although primary prevention, aiming to reduce the incidence of psychosis in the absence of emerging signs of the illness, would be preferable, neither universal nor selective prevention strategies are available to date due to the absence of information on the specific etiological risk factor constellations (de Koning et al 2009).

The beginning of indicated, early intervention in the pre-psychotic state was accompanied by ample ethical discussions concerning the potential benefits and risks (McGorry 1998, Schaffner et al. 2001, Cornblatt et al. 2001, McGorry et al., 2001, DeGrazia, 2001, McGlashan, 2001). Generally, the prevention or delay of psychosis as well as the improvement of course and outcome of the disorder are considered potential benefits. These possible gains have to be weighed against potential risks of stigmatization and provocation of anxiety by confronting individuals with the threat of a psychotic disorder and of possible short- and long-term side-effects of the interventions. Previously, these concerns had been mitigated by the fact that patients were not enrolled simply by meeting symptomatic threshold criteria, but PRS individuals were also help seeking and/or markedly impaired so that friends, families and others identified the patients as being in need of help. However, the potential risk-benefit ratio of early interventions changes depending on the chance of treating individuals who are false positives. This is becoming important, as several research groups across the world have observed decreasing transition rates, at least over the short and medium term. This has raised concerns about a growing proportion of false positive individuals who are referred for treatment. These considerations have led to increased attention devoted to phase-specific and more benign treatment options than low-dose antipsychotic treatment, which were the focus of the first generation of pharmacologic intervention studies for the psychosis risk syndrome (Haroun et al 2006, Yung et al 2008, McGorry et al 2009; Ruhrmann et al. 2009). Thus, utilizing a clinical staging model in the treatment of PRS individuals that reserves higher risk interventions for the later, more symptomatic disease stages is a logical approach (McGorry et al 2006). Following this general idea, Haroun and colleagues (2006) proposed the following four treatment stages tailored to match the symptom presentation of the psychosis risk syndrome: 1) diagnostic assessment and differential diagnosis; 2) psychoeducation regarding symptoms and risk of psychosis; 3) psychosocial treatment crisis intervention, stress reduction, ongoing support, and cognitive-behavioral therapy; and 4) pharmacologic interventions. Concerning antipsychotic medications, the authors suggest brief trials targeting the worsening of subsyndromal psychotic symptoms stating that the long-term use of these medications should be taken into account only in cases of actual DSM-IV psychotic disorders. However, although there is a modest amount of randomized clinical trials (RCTs) investigating non-

paharmacologic and pharmacologic interventions in PRS individuals (see below), the comparative effectiveness of staged, sequential or combined approaches, either short-term or longer-term, has not been determined.

Psychosocial Interventions

Psychosocial treatments include a broad range of interventions of different intensity and focus that are often combined and applied based on the individual's need. Supportive counseling and needs-based interventions are consistently used in PRS programs and consist of assessment, educational features and empathic, but unstructured support. The focus of this approach is on providing ongoing support, reducing stress and enhancing coping skills. These basic strategies are either provided alone or combined with other, more specific psychosocial treatments or with pharmacologic interventions. Supportive counseling and needs-based intervention have only been evaluated against more elaborated interventions as a control condition in RCTs of PRS individuals. In such trials, these relatively non-specific treatments were generally less effective than the active treatments, consisting either of an intensified psychosocial treatment (e.g., CBT), a pharmacologic intervention, or a combination of the two (see Table 6). Despite this inferiority in clinical trials, these non-specific treatments are still considered important for the overall management of these patients. Although authors have speculated that providing ongoing support to PRS individuals might be related to the reduced transition rates observed in their CARE program (Haroun et al. 2006), the effects of psychoeducation itself has barely been investigated in PRS individuals against a no treatment or wait list control condition. In a preliminary report on a sample of 16 PRS individuals, psychoeducation about psychotic disorders and the potential risk factors for psychosis alone had very good acceptability and was perceived as reassuring (Hauser et al. 2009). This reassurance was related to the fact that most PRS individuals had relatively high levels of anxiety, thinking that they already had a psychotic disorder based on the information they had gathered themselves before presenting at the program. Therefore, crisis intervention, psychoeducation, support for the patient and their family, and assistance with social and role functioning are considered basic, required interventions in the PRS state.

Cognitive-behavioral therapy (CBT) as a more elaborate psychosocial intervention has been evaluated in two randomized-controlled trials to date, showing advantages of CBT in comparison to monitoring as well as compared to supportive counseling alone (Morrison et al. 2004; Morrison et al. 2007; Bechdolf et al. 2008). The CBT interventions utilized written manuals and were based on general principles of cognitive-behavioral therapy, applying modifications necessary to meet the specific needs of PRS individuals . Central features throughout the therapeutic process included decatastrophizing symptoms and fear of exacerbation, normalization of experiences, generation and evaluation of alternative, more reality based interpretations, as well as testing them in behavioral experiments (Morrison et al 2004, Bechdolf et al 2005; Bechdolf et al. 2006). In addition, CBT interventions include stress management, problem solving, coping, and psychoeducational features. In comparison to antipsychotic medication, CBT offers the advantages of being more acceptable and less stigmatizing, not exposing potentially false-positive PRS individuals to side-effects, as well as providing effective treatment even to false-positives (McGorry et al 2009). In adidition to CBT based programs, other psychosocial interventions are also being investigated for efficacy in PRS patients. In an ongoing study in Maine, McFarlane and colleagues are comparing a treatment package of multifamily psychoeducational groups (McFarlane et al. 2003), family-aided assertive community treatment, supported education and employment services, and antipsychotic medication with medication alone (McFarlane, personal communication). Treatment is provided by a multidisciplinary team, and the main psychosocial intervention, multifamily group, has a structured problem solving focus. In a

related, 5-site study, funded by the Robert Wood Johnson Foundation, this integrated family-based psychosocial treatment package is being given in addition to antipsychotic medication based on putatively prodromal symptom severity and will be compared to a demographically matched control group at each site (McFarlane, personal communication). Thus, within the framework of a clinical staging model, CBT (and potentially other psychosocial interventions) has been proposed as a preferable and efficacious treatment strategy (McGorry et al 2009). However, more research is needed to investigate the optimal timing and efficacy of psychosocial interventions in PRS individuals. Moreover, it is unclear if CBT approaches are equally effective for patients with more severe psychosis risk syndrome psychopathology and for patients who lack insight and who would thus refuse participation in a more involved psychosocial or cognitive behavioral treatment program.

Psychopharmacologic Interventions

Based on the fact that antipsychotic agents are helpful in the treatment and relapse prevention for psychosis and schizophrenia, these agents have been tried in the first generation of PRS trials (McGorry et al. 2002; Woods et al. 2004; McGlashan et al. 2006; Ruhrmann et al. 2008; Woods et al. 2008). However, more recently, the field has broadened the pharmacologic intervention focus to non-antipsychotic medications. This is relevant in the context of the reported decrease in transition rates and the increased interest in using the lowest risk interventions possible. Table 5 summarizes agents with preclinical or clinical evidence that they might have neuroprotective properties, making them potential candidates forPRS intervention studies (Krebs et al. 2006; Berger et al. 2007).

The general idea of neuroprotection in PRS individuals lies in the inhibition of apoptopic processes during the critical period of brain vulnerability in adolescence and early adulthood, that is, in the critical phase of greatest risk of developing a psychotic disorder (Berger et al 2007). While cell death generally is a normal biological process, it may occasionally become uncontrolled and pathological. Thus, applying neuroprotective agents may help control cell death. Since the specific mechanisms underlying cell death and protection are complex and only partially understood, a number of potentially neuroprotective agents with varying mechanisms hold promise and should be investigated further. Limited data on the effects of possibly neuroprotective agents, namely antidepressants (Cornblatt et al 2007; Fusar-Poli et al. 2007) and omega-3-fatty acids (ethyl EPA) (Amminger et al. 2008) are already available in PRS individuals, and several (i.e., D-serine, sacrosine and omega 3 fatty acids) are currently being investigated in randomized controlled trials of PRS individuals (see below).

Published and Presented, Randomized Controlled Trials

To date, seven randomized controlled trials regarding interventions in the PRS state have been conducted (Table 6). Four studies were double blind, two were single blind and one used masked assessors. Five studies were single site trials, and two had 4 sites, each. Altogether, 603 PRS individuals were included in these trials. The mean age was 19 years (range: 12-45 years), 69.2% were male. The RCTS had an active treatment phase that lasted either 3 months (N=1), 6 months (N=2) or 12 months (N=4). Active treatments included low-dose antipsychotic medication: risperidone+CBT (N=1), olanzapine (N=1), amisulpride (N=1), CBT (N=2), or ethyl EPA (N=1), as well as risperidone plus cognitive therapy or CBT in one three-arm study. Three studies were placebo-controlled. After the conclusion of the active treatment phase, the treatment was withdrawn and completers were followed off treatment to assess the maintenance effect. Additional follow up durations after the active treatment phase had been stopped lasted 6 months (N=2), 9 months (N=1) and 12 months (N=4), with 3 studies having an additional follow up 2-3.5 years after the active treatment

phase had ended (two studies lasting originally 6 months and one lasting originally 12 months).

Of these seven trials, five showed significantly lower transition rates for CBT (Morrison et al 2004; Bechdolf et al. 2008), amisulpride (Ruhrmann et al. 2008), ethyl EPA (Amminger et al. 2008) and risperidone plus CBT (McGorry et al. 2002). In one of the two negative studies with very high dropout rates and subsequently reduced power, a trend toward significance was found in favor of olanzapine compared to placebo (p=0.08) (McGlashan et al. 2006). In the second negative trial, conversion rates in the treatment and in the control condition were exceedingly low, calling into question whether sufficient numbers of patients with imminent risk for conversion to psychosis were enrolled (Yung et al. 2008). In addition to favorable outcomes regarding reducing transition rates to psychosis, most of the studies with available data show a reduction in psychopathology and improvement of functioning by the end of the active treatment phase. Nevertheless, only two studies report the effect on psychopathology to be significantly superior compared to the control condition, and one study found nonsignificant change in psychopathology or functioning.

Despite the encouraging results on active treatment, the lower risk for transition to psychosis compared to the control condition was not maintained in three of the four studies with available longer-term data (Philips et al. 2007; McGlashan et al. 2006; Morrison et al. 2007). Rather, patients who had been on treatment tended to catch up with the control condition, whereas transition rates in patients who originally had been randomized to the control condition did not increase to a relevant degree over time. The only study where a maintenance effect has been described is the 3-month, acute trial with ethyl EPA (Amminger et al. 2008). In this study, the transition rates of 2.6% vs. 21.1% ($p<.05$) after the acute 2.5-3.5 months treatment with ethyl EPA vs. placebo remained remarkably stable (4.6% vs. 27.5%, $p<.05$) over the next 9 months post treatment in both groups, a finding that is difficult to understand.

Overall, it appears that across studies with different samples and methodology, active treatment with CBT, low dose antipsychotic or combined low-dose antipsychotic plus CBT effectively reduces psychopathology and transition rates to psychosis, but this effect only last as long as patients receive the active treatment. One single study suggests that ethyl EPA may be an exception.

Ongoing Randomized Controlled Trials

To our knowledge, seven ongoing, randomized controlled studies are currently registered on the webpage for clinical trials (www.clinicaltrials.gov) (Table 7). Most of these studies are double blind, placebo controlled trials. Five of the seven studies test psychopharmacological treatment options, with three of these focusing on non-antipsychotic agents, such as ethyl EPA, D-serine and sarcosine. Only one of the trials applies a psychosocial treatment strategy alone (i.e., neuroadaptive cognitive training), while another has a CBT arm as a comparator to aripiprazole. Compared to the completed studies, the active treatment duration tends to be shorter, lasting 3, 4 and 6 months, except for one 12 month trial. Similarly, the duration of follow-up is also shorter, lasting 2, 3, 4 and 6 months, respectively. It will be interesting to evaluate the results from these studies and to see how they will inform clinical management recommendations and further research directions.

Challenges and Open Questions

Like any area of research, PRS studies have to deal with a whole host of methodological considerations (Kane et al. 2003). Relevant design decisions in this area have to focus on the following points:

1. Selection, generalizability and risk enrichment of the patient population;
2. Selection and definition of proximal and distal, clinical and biological target symptoms and outcomes;
3. Definition and assessment of clinical and biological moderator and mediator variables;
4. Selection of meaningful assessment instruments and outcome tools;
5. Selection, staging/threshold and duration of intervention(s);
6. Selection, staging/threshold and duration of comparators, control conditions or comparison groups;
7. Exit strategies;
8. Duration and nature of follow up after intervention study completion;
9. Statistical considerations (power, clinically meaningful effect size, sample size, number of sites);
10. Ethical considerations.

Table 8 summarizes relevant questions for the area of the risk syndrome for schizophrenia and psychosis. Questions that require further attention include: 1) how to ascertain and retain PRS patients who are enriched for true psychosis risk; 2) how to increase the sensitivity, specificity and predictive power of true prodromal symptoms and syndromes; 3) which intervention(s) have an acute and/or lasting effect, at which psychosis risk syndrome phase and for which symptoms or outcomes; 4) what are the predictors and mechanisms of true prodromal symptom emergence, progression and remission; and 5) if and when can the research diagnosis and assessment of the psychosis risk syndrome be introduced into clinical diagnostic criteria and care.

The latter question of transferability to clinical care is of relevance, as the number of false positives identified by current PRS criteria can prompt potentially inappropriate diagnostic assignments and interventions in clinical practice where the expertise and time are lacking to conduct comprehensive assessments. On the other hand, research has shown that patients with the psychosis risk syndrome and first episode psychosis symptoms are not adequately identified by primary care physicians (Platz et al. 2006; Simon et al. 2005), clearly calling for more educational programs and outreach (Simon et al. 2009).

In the work toward a new classification as part of DSM-V, dimensional and longitudinal aspects of psychiatric disorders are to be given more importance in the definition and characterization of psychiatric disorders. Since research on the psychosis risk syndrome has at its core the dimensional measurement of psychopathology and the prospective evaluation of outcomes, it is one of the “disease” areas that is being considered for inclusion in DSM-IV as part of the newly introduced risk syndromes section, which will also include mild cognitive impairment as a risk for Dementia. While this change, in keeping with the movement toward a more dimensional view of psychiatric illness, in general, has been viewed as a positive new development, there is nevertheless considerable controversy specifically about the inclusion of the psychosis risk syndrome A number of logistic difficulties have been pointed out, such as the amount of training required to accurately recognize very subtle and precisely defined symptoms and signs of the psychosis risk syndrome. Perhaps the strongest opposition, however, is in response to the academic findings discussed above that the number of true positive has been on the decrease in many major studies, and, as a result, the false positive rate has been growing and is now very substantial (well above 50% in nearly all recent studies). Given the lack of training and

increasing difficulty in detecting “true positives” even in an academic setting, it is possible that in the community, early intervention programs may ascertain individuals with a false positive rate as high as in the mid-90%. The possibility of such a prohibitively high rate suggests that it might well be premature to conduct early intervention studies outside of highly controlled and rigorous academic programs and that it is premature to include this risk category in DMS-V for broad clinical use, without prior support by results of substantial field trials. Although inclusion of the psychosis risk syndrome in DSM-V might well lead to furher field trials, which would be a welcome effect, the fear is that the inclusion in DSM-V would medicalize phenomena that are not necessary predictive of future psychosis and that this would legitimize treatment with interventions that are not necessarily benign. Such a critical position toward the inclusion of a clinical risk syndrome for schizophrenia into DSM-V will be tempered as the specific types of intervention become less invasive and more applicable to a broader population with prodromal-type symptoms, both positive and negative, using treatment strategies, such as psychosocial therapies, or relatively benign medications, such as omega-3 fatty acids.

Summary and Conclusions

The first fifteen years of psychosis risk syndrome research have focused on the development and validation of specific assessment tools, definition of high risk criteria and outcomes, and on the application of these methods to naturalistically followed PSR cohorts. Further, during this first phase, ascertainment and assessment methods have proven sufficiently valid, initial clinical risk markers and predictors of conversion to psychosis have been identified, and interventions that can abort or delay the development of full psychosis have been examined. In the next phase that has already begun, the field of psychosis risk syndrome research needs to expand the focus to enrichment strategies to ensure that a sufficiently large part of the samples are at true risk for psychosis. Moreover, putative biomarkers and intermediary phenotypes that are predictive of conversion and readily measurable during the psychosis risk syndrome need to be developed and tested. In addition, non-antipsychotic, neuroprotective and low-risk pharmacologic and non-pharmacologic interventions (alone and in combination), including their potential phase-specificity, need to be assessed. Patients who develop psychosis or schizophrenia despite early interventions need to be followed beyond the point of conversion and the illness trajectory be compared with patients who received treatments only after the onset of psychosis. Finally, the relationship between early psychosis risk syndrome and functional symptom response and later outcomes needs to be assessed, and meaningful social and functional outcomes should be studied as intermediary and ultimate endpoints. It is hoped that the results from ongoing and future studies will contribute substantially to the refinement of highly sensitive and specific identification methods that can ultimately be generalized to broad clinical settings. It is further hoped that phase- and disease subgroup-specific interventions can be discovered that will substantially improve the outcomes of people with the psychosis risk syndrome and those that ultimately develop a psychotic illness.

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Table 1

Symptoms and Signs Commonly Present During the Psychosis Risk Syndrome

Basic (self-experienced) symptoms		(Attenuated) Negative Symptoms/Signs	Attenuated Positive Symptoms/Signs	Brief Self-Limited Psychotic Symptoms
Cognitive-Perceptive (COPER)	**Cognitive Disturbances (COGDIS)**			
Thought interference	**Thought interference**	**Social isolation or withdrawal**	**Unusual thought content**	**Delusions**
Subjective experience of unrelated and emotionally neutral thoughts cutting into the stream of thoughts	Subjective experience of unrelated and emotionally neutral thoughts cutting into the stream of thoughts	Awkward or anxious, socially disinterested or reluctant, few friends outside of family, loner	Mind tricks, unanticipated beliefs, “magical” thinking, overvalued ideas	Fixed belief that can not be reasoned about and that is not shared by a subcultural group
Thought blockages	**Thought blockages**	**Avolition**	**Suspiciousness**	**Paranoid delusion**
Subjective experience of thoughts fading out or being abruptly cut off	Subjective experience of thoughts fading out or being abruptly cut off	Less/waning interest in pleasurable activities, diminished productivity, avoidance or abandonment of goal-directed activities	Wariness, hypervigilance, distrust, overvalued ideas of danger	Specific delusion
Thought pressure	**Thought pressure**	**Decreased expression of emotion**	**Grandiosity**	**Grandiose delusion**
Subjective experience of a large amount of thoughts being present at the same time	Subjective experience of a large amount of thoughts being present at the same time	Blunted affect, speech lacking in character, unengaging, aspontaneous, constricted or flat affect	Private thoughts of superiority, preoccupation with overvalued ideas	Specific delusion
Thought perseveration	**Inability to divide attention**	**Decreased ideational richness**	**Perceptual abnormalities**	**Hallucinations**
Subjective experience of thoughts perseverating	Inability to pay attention to two separate actions that used to be doable simultaneously	Rigidity, simplicity or concrete thinking, repetitiveness, restriction to yes/no answers	Change in perceptual sensitivity, distortions, illusions, brief/vague hallucinations	Perception in the absence of a stimulusd
Disturbance of receptive speech	**Disturbance of receptive speech**	**Deterioration in role functioning**	**Conceptual disorganization**	**Conceptual disorganization**
Subjective experience of trouble understanding common words or content of speech	Subjective experience of trouble understanding common words or content of speech	More effort needed to maintain achievement, difficulties, drop in performance, failing requirements	Vague, confused, inconsistent thoughts, circumstantial, paralogical thoughts, tangentiality	Disorganized speech and/or behavior
Decreased ability to discriminate between ideas/perception, fantasy/true memories	**Disturbance of expressive speech**	**Odd behavior or appearance**		
Uncertainty if something is real and experienced or a product of imagination	Difficulty with word retrieval and use of correct grammar, more perceived effort to translate thoughts into language	Eccentric, odd, awkward, unconventional, strange or bizarre hobbies, appearance, or behavior		
Unstable ideas of reference	**Unstable ideas of reference**	**Impairment in personal hygiene and social attentiveness**		
Notion that independent	Notion that independent	Less attentive or indifferent to,		

Basic (self-experienced) symptoms		(Attenuated) Negative Symptoms/Signs	Attenuated Positive Symptoms/Signs	Brief Self-Limited Psychotic Symptoms
Cognitive-Perceptive (COPER)	**Cognitive Disturbances (COGDIS)**			
external events are related to the self	external events are related to the self	or neglectful of, social norms or hygiene		
Derealisation	**Disturbances of abstract thinking**			
Subjective experience of the common environment as strange and unfamiliar	Subjective experience of troubles understanding the abstract meaning of speech			
Visual perception disturbances (excl. hypersensitivity to light or blurred vision)	**Captivation of attention by details of the visual field**			
objects appear smaller/bigger, closer/ further away, color or size appear distorted	Inability to draw attention away from the visual detail			
Acoustic perception disturbances (excl. hypersensitivity to sounds)				
sounds appear to be louder/less loud or distorted				
(Non-specific) mood disturbances, anxiety, sleep problems, etc.				
Decreased role and social functioning				

Adapted from: Correll CU & Kane JM (2004), Adv Schizophr Clin Psychiatry; Schultze-Lutter F, Klosterkotter J, Picker H, Steinmeyer E-M & Ruhrmann S (2007). *Clin Neuropsychiatry.*

Table 2

Most Commonly Used Criteria for the Psychosis Risk Syndrome

	Early Initial Prodromal State (EIPS)		Late Initial Prodromal State (LIPS)	
	Basic Symptoms (COPER, COGDIS)	**Genetic Risk Deterioration Syndrome (GRD)**	**Brief (Limited) Intermittent Psychotic Symptom Syndrome (BLIPS, BIPS)**	**Attenuated Psychotic Symptom (Symptoms) Syndrome (APS, APSS)**
CAARMS	-	Genetic risk: first-degree relative with a psychotic disorder or schizotypal personality disorder, OR an individual with schizotypal personality disorder AND significant decrease in mental state or functioning (≥ 30% drop in Global Assessment of Functioning Scale score from premorbid baseline); decrease in mental state or functioning; maintained for at least 1 month and for ≤ 5 years	Transient psychotic symptoms: symptoms in the realm of delusions hallucinations,disorganization; duration of the episode < 1 week; frequency score of 4-6 on the CAARMS; spontaneous remission; symptoms occurred within 1 year but for not longer than 5 years	Subthreshold attenuated positive symptoms: e.g. ideas of reference, “magical” thinking, perceptual disturbance, paranoid ideation, odd thinking and speech); held with either subthreshold frequency or subthreshold intensity;;; present for ≥ 1 week within the past year and for ≤ 5 years
SIPS	-	First-degree relative with a psychotic disorder OR an individual has schizotypal personality disorder AND ≥ 30% drop in Global Assessment of Functioning (GAF) Scale score in past month compared to one year ago	Transient psychotic symptoms: symptoms in the realm of delusionals, hallucinations, disorganization; onset in past 3 months; frequency: at least 1 hour/day at min. average frequency of 4day/week over a one month period or symptoms are seriously disorganizing/dangerous	Subthreshold attenuated positive symptoms: e.g. unusual ideas, paranoia/suspiciousness, grandiosity, perceptual disturbance, conceptual disorganization; without psychotic level conviction; onset or worsening in the past year; frequency: at least once per week in the past month
SPI-A	Subtle subjective disturbances of cognition and perception (COPER): at least 1 of 10 Basic symptoms with a score of ≥ 3 within last 3 months and first occurance ≥1 yr or cognitive disturbances (COGDIS): at least 2 of 9 basic symptoms with a score ≥ 3 within last 3 months	GAF score drop >30% for >1 month AND 1st degree family member with schizophrenia or ante/prenatal complications	-	-

SPI-A: Schizophrenia Proneness Instrument - Adult Version

CAARMS: Comprehensive Assessment of At-Risk Mental States

SIPS/SOPS: Structured Interview for Prodromal Syndromes/Scale of Prodromal Symptoms

Table 3

Clinical Risk Factors for Psychosis Described in Individuals with the Psychosis Risk Syndrome (PRS)

Domains	Findings in Patients with the Psychosis Risk Syndrome (PRS)
Obstetric Complications	Mixed results regarding association with the later development of psychosis PRS(Yun et al 2005; Cannon et al. 2002)
Microbial Infections	Amminger et al 2007: -↑ levels of serum Toxoplasma gondii IgG antibodies significantly associated w/ more severe attenuated positive symptoms -No significant association between human herpes viruses antibody levels and psychiatric sx measures
Age of sx onset	- Age of any psychiatric sx onset (particularly < 18 y) significantly predicted conversion to non-affective psychosis (Amminger et al 2006)
Premorbid adjustment/ Functional Decline	-↓ in social relationships, work/school functioning + daily living skills in PRS patients (Niendam et al 2009) -global assessment of functioning at intake: PRS-P < PRS-NP (Yung et al. 2004) -↓ improvement in global assessment of functioning at 12 mo f/u correlated to longer duration of PRS sxs (Fusar-Poli et al 2009) -↓ social functioning in PRS > GHR > HC (Shim et al 2008) -↓ 'interpersonal behavior' associated w/ longer duration of sxs, ↓ independence-competence' associated w/ disorganized + general sxs (Shim et al 2008) -↑ conflictual communications correlated to ↑ positive sxs at 6 mo f/u (controlled for sxs severity at baseline) (O'Brien et al 2009) -decline in role functioning over yr prior to assessment but ↑ at 12 mo f/u (w/ rx) while social functioning stayed stable (Cornblatt et al 2007) Psychosis predicted by: -↑ levels of social impairment and recent deterioration in functioning (Cannon et al. 2008) -↑ social anhedonia (Yung et al. 2006) -↑ social anhedonia and withdrawal, and a ↓ GAF score at baseline (Velthurst et al. 2009)
Severity of PRS Sxs	-psychosis predicted by higher levels of unusual thought content, suspicion/paranoia (Cannon et al. 2008) -psychosis predicted by by recent experience of subthreshold psychotic symptoms (Yung et al. 2006) -psychosis predicted by more bizarre thinking (Velthurst et al. 2009) -psychosis predicted by negative symptoms (Schultze-Lutter et al. 2007)
Depression	-depression levels (HRSD) at baseline PRS-P > PRS-NP (Yung et al 2004) -depression levels at baseline associated with ↑ symptom load (Schultze-Lutter et al. 2007) -PLEs (psychotic-like experiences) reduced in conjunction w/ improvement in depression level + remission of mood d/o dx (Yung et al 2007) -psychosis predicted by higher levels of depression (Cannon et al. 2008)
Cannabis Use	-more cannabis use comorbidity in PRSPRS than control subjects (Rosen et al 2006) Cannabis use/dependence in the year prior to recruitment not associated with ↑ risk of developing psychosis over the 12-month (Phillips et al 2002) -PRS patients with lifetime cannabis abuse/dependence (not at study entry) showed sign. > conversion at 1 yr f/u point than PRS patients without lifetime cannabis abuse/dependence (Kristensen & Cadenhead, 2007) -Substance abuse in general (not specifically cannabis abuse) was one of five significant clinical factors predicting psychosis (Cannon et al 2008) -neither cannabis use nor abuse predicted conversion to psychosis at mean f/u of 3 yrs + cannabis use not associated w/ ↑ attenuated positive symptoms at baseline (Auther et al. presented at 63rd Annual Meeting of the Society of Biological Psychiatry, 2008) -↑ age of PRS individuals w/ history of cannabis use at baseline but same clinical picture (Corcoran et al 2008) -↑ perceptual disturbances + ↓ functioning in PRS w/ cannabis history at baseline during epochs of ↑ use (not w/ other drugs or meds) (Corcoran et al 2009)

FEP= First-Episode Psychosis, PRS= Ultra-high risk, PRS-P= Ultra-high risk patients converted to Psychosis, PRS-NP= Ultra-high risk patients not converted to Psychosis, GHR= Genetic High Risk, HC= Healthy Controls; PRS= Psychosis Risk Syndrome

Table 4

Biological Risk Factors for Psychosis Described in Individuals With the Psychosis Risk Syndrome (PRS)

Domains	Findings in Prodromal Patients		
Brain Imaging (structural / functional)	Brain Region- Method	Cross-sectional	Longitudinal
	Temporal Lobe - MRI	- white matter volume in right superior temporal lobe PRS < HC (Witthaus et al 2008) - left medial temporal volume PRS < HC (Borgwardt et al 2007) - plaum temporale male PRS-P < HC (Takahashi t al 2009) - temporal lobe volume, grey and white matter PRS=HC (Ziermans et al 2009) - lateral and medial temporal volume PRS < HC (Meisenzahl et al 2008) - grey matter in right medial, lateral PRS-P < PRS-NP (Pantelis et al 2003) - superior temporal gyrus PRS-P < PRS-NP (Borgwardt et al 2007) - white matter volume bilaterally FEP < PRS (Witthaus et al 2008) - grey matter volume in posterior temporal region PRS-P > FEP (Borgwardt et al 2007) - grey matter in temporal gyrus bilaterally PRS-P < FEP (Borgwardt et al 2007) - superior temporal gyrus PRS < HC but = FEP (Borgwardt et al 2007) - planum temporale + cuadal temporal gyrus FEP < PRS=HC (Takahashi et al 2009) - ↑ variability of cortical thickness asymmetry in lateral and medial occipito-temporal gyrus FEP > PRS and HC (sign), PRS > HC (trend) (Haller et al 2009)	MRI - ↓ (~ 2-6%/yr) in grey matter in planum polare, planum temporale + caudal region in PRS+FEP compared to HC and PRS-NP (Takahashi et al 2009)
	Proton MRS	- medial temporal region metabolic ratio PRS=HC (Wood et al 2003)	
	Frontal Lobe - MRI	- grey matter in inferior fontal cortex PRS-P < PRS-NP (Pantelis et al 2003, Borgwardt et al 2007) - white matter (particularly left) PRS-P > PRS-NP (Walterfang et al 2008) - frontal lobe volume, grey and white matter PRS=HC (Ziermans et al 2009) - grey matter volume PRS < HC (Meisenzahl et al 2008)	MRI - grey matter in orbitofrontal PRS-P < PRS-NP (Pantelis et al 2003) -↓ right prefrontal volume PRSP > PRS-NP (Sun et al 2009)
	- Proton MRS	- NAA/Creatin + Choline/Creatine ratios dorsolateral prefrontal rgion PRS > HC, PRS-P=PRS-NP (Wood et al 2003)	- ↓white matter volume left fronto-occipital fasciculus PRSP in longitudinal comparison (Walterfang et al 2008)
	- fMRI	- ↓ differential activation between task-relevant and task-irrelevant stimuli in the medial and inferior frontal gyrus PRS < HC and trend towards early SCZ group (Morey et al 2005)	
	Occipital Lobe - MRI	- occipital lobe volume, grey and white matter PRS=HC (Ziermans et al 2009)	-
	Central Cortex - MRI	- grey matter volume paracentral lobe bilaterally PRS-P < HC (Borgwardt et al 2007)	-

Domains	Findings in Prodromal Patients		
Brain Imaging (structural / functional)	Parietal Cortex - MRI	- left superior parietal lobe PRS-P < HC (Borgwardt et al 2007) - left parietal grey matter volume PRS-P > FEP (Borgwardt et al 2007) - parietal lobe volume, grey and white matter PRS=HC (Ziermans et al 2009) - ↑ variability of cortical thickness asymmetry in superior parietal lobe FEP > PRS and HC (sign), PRS > HC (trend) (Haller et al 2009)	MRI - ↑ in white matter in region subjacent to the right inferior parietal lobule in PRS-NP in longitudinal comparison (Walterfang et al 2008)
	Cingulate Cortex- MRI	- grey matter volume in posterior cingulate gyrus PRS-P < HC (Borgwardt et al 2007) - rostral paralimbic ACC region bilaterally PRS-P < HC, negatively correlated w/ negative sxs, differences between PRSP and PRS-NP predicted time to psychosis onset independent of sxs (Fornito et al 2008) - cingulate cortex bilaterally PRS-P < PRS-NP (Pantelis et al 2003) - left anterior cingulate region (paracingulate folding + cingulate sulcus interruptions) PRS without fx of SCZ < PRS w/ fx of SCZ (ns) (Wood et al 2005) - cingulate gyrus PRS < HC but=FEP (Borgwardt et al 2007)	MRI - cingulate gyri PRS-P < PRS-NP (Pantelis et al 2003)
	- fMRI	- ↓ differential activation between task-relevant and task-irrelevant stimuli in the anterior cingulate gyrus PRS < HC and trend towards early SCZ group (Morey et al 2005)	
	- Proton MRS	- glutamine in anterior cingulus in PRS > HC (Stone et al 2009)	
	Hippocampus - MRI	- volumes of PRS-P=PRS-NP=HC Velakoulis et al 2006) - left hippocampal volumes PRS without FHx of SCZ < PRS w/ fx of SCZ (Wood et al 2005) - left and right hippocampal volumes FEP+PRS < HC (Phillips et al 2002) - left hippocampal volume PRS-P > PRS-NP+FEP but =HC (Phillips et al 2003) - right hippocampus PRS-NP < HC but=FEP (Phillips et al 2002) - subsequent development of FEP associated w/ larger (or non-reduced) left hippocampal volume rather than smaller volumes at intake (Philips et al 2002)	MRI - grey matter left parahippocampal PRS-P < PRS-NP (Pantelis et al 2003)
	Fusiform Gyrus	-	MRI : - grey matter PRS-P < PRS-NP (Pantelis et al 2003)
	Cerebellum - MRI	- cerebellum PRS=HC (Ziermans et al 2009)	MRI : - grey matter cerebellar cortices PRS-P < PRS-NP (Pantelis et al 2003) -↓ cerebellar grey matter in PRS-NP (Pantelis et al 2003)
	Caudate - PET:	- ↓5-HT(2A)R binding potential consistent w/ ↑ levels of risk - ↓ binding potential in PRS-P > PRS-NP - not confounded by differential distribution of single nucleotide polymorphisms (SNPs) genotype (Hurlemann et al 2008)	-

Domains	Findings in Prodromal Patients		
Brain Imaging (structural / functional)	Cavum Septum Pellucidum - MRI	- large cavum septum pellucidum (> 5.6 mm) chronic SCZ=FEP=PRS=HC (Takahashi et al 2008)	-
	Adheasio inter-thalamica (AI) - MRI	- length of AI in chronic SCZ, FEP, PRS < HC and PRS-NP=PRS-P (Takahashi et al 2008) - negative correlation between AI length and lateral ventricular volume (SCZ, FEP, PRS) (Takahashi et al 2008) - Absence of AI chronic SCZ > FEP, PRS, HC (Takahashi et al 2008)	-
	Amygdala - MRI	- volumes of PRS-P=PRS-NP=HC (Velakoulis et al 2006) - grey matter volume PRS-P < HC (Borgwardt et al 2007) - volume PRS < HC but =FEP (Borgwardt et al 2007)	-
	Thalamus - Proton MRS/MRI	- glutamate in left thalamus PRS < HC (Stone et al 2009) and - glutamate in thalamus directly correlated with grey matter volume in the medial temporal cortex and insula (Stone et al 2009)	-
	Insula - MRI	- left insula PRS < HC but =FEP (Borgwardt et al 2007) - grey matter in right insula PRS-P < PRS-NP (Borgwardt et al 2007) - bilaterally PRS-P < PRS-NP, PRSP < HC (esp. short insula region) (Takahashi et al 2009) - more severe negative sxs in PRSP at baseline associated w/ ↓ volumes of right long insular cortex (Takahashi et al 2009) - ↑ variability of cortical thickness asymmetry FEP > PRS and HC (sign), PRS > HC (trend) (Haller et al 2009)	MRI - grey matter bilaterally PRS-P > PRS-NP and PRS-P > HC (Takahashi et al 2009)
	Limbic System - MRI	- dorsal + rostral limbic areas PRS-NP > HC, positively correlated w/ anxiety ratings (Fornito et al 2009)	-
	Associative Striatum -PET	Howes et al 2009 -↑ striatal ^{18}F-dopa uptake in PRS > SCZ (effect size 1.25) - correlated w/ total CAARMS score + neuropsychological impairments but not anxiety/depression	-
	Pituitary - MRI	Garner et al 2005 : - volume in PRS-P > PRS-NP, risk of psychosis ↑ 20% for every 10% ↑ in baseline volume (cox regression survival analysis) - volume in PRS-NP < HC	-
	Precuneus - MRI	- ↑ variability of cortical thickness asymmetry in the precuneus FEP > PRS and HC (sign), PRS > HC (trend) (Haller et al 2009)	-
	Intracranium - MRI	- PRS=HC (Ziermans et al 2009)	-
	Sulci - MRI	- ↑ variability of cortical thickness asymmetry in collateral and intraparietal sulcus FEP > PRS and HC (sign), PRS > HC (trend) (Haller et al 2009)	-

Domains	Findings in Prodromal Patients		
	Ventricles - MRI	- lateral ventricles and third ventricle PRS=HC (Ziermans et al 2009)	-
	Total Brain - MRI	- PRS=HC (Ziermans et al 2009) - cerebral grey and white matter PRS=HC (Ziermans et al 2009) - direct cortical thickness analysis PRS=FEP=HC (Haller et al 2009) - ↑ variability in cortical thickness asymmetry in 7 regions in FEP > PRS > HC (Haller et al 2009)	-
Brain Imaging (structural / functional)	Neuroanatomical Pattern Classification - MRI	Koutsouleris et al 2009: - cross-validated classification accuracies (baseline): 86% (HCs vs PRS-Early+PRS-Late), 91% (PRS-Early vs HC+PRS-Late), and 86% (PRS-Late vs PRS-Early+HC) - 96% (baseline) classified correctly in independent HCs	Koutsouleris et al 2009: -cross-validated classification accuracies (baseline according to transition): 90% (HCs vs PRS-P+PRS-NP), 88% (PRS-P vs HC+PRS-NP), and 86% (PRS-NP vs PRS-P+HC) -93% (baseline according to transition) classified correctly in independent HCs
EEG	(temporal lobe) - pathological EEG (more frequently in temporal or fronto-temporal regions) FEP+PRS > HC, PRS > FEP (twice as much) (Gschwandter et al 2009) - specificity of prediction of psychosis ↑ from 59% to 73% by considering EEG+psychopathology, sensitivity unchanged (Gschwandter et al 2009)		
Event-related Potentials (ERP)	P300	- P300 amplitude at Pz: (non-medicated) PRS, FEP, chronic SCZ < HC (Ozgürdal et al 2008) - P300 amplitude: PRS < HC - P300 latency + N100: PRS = HC (Bramon et al 2008) - P300 amplitude at midline + left hemispheric electrodes: LIPS < HC - P300 amplitude at left temporo-parietal site (TP7): ↓ in EIPS - ↓ posterior P300 amplitudes associated w/ fx of SCZ in PRS - P300 amplitudes (midline): < in LIPS w/ BLIPS (Frommann et al 2008)	
	P50	- P50 suppression: PRS < HC - P50 suppression: PRS w/ FHx < all other PRS groups (Cadenhead et al 2005) - P50 suppression: PRS-P, PRS-NP, FEP (P50 amplitude ratio) and SCZ (difference + ratio) < HC (Brockhaus-Dumke et al. 2008)	
	Loudness Dependence of the Auditory Evoked Potential (LDAEP)	- LDAEP (N1/P2 component): PRS, FEP, chronic SCZ < HC - age, gender, medication, age of onset, psychopathology had no influence (cross-sectional) - LDAEP same after 10 mo f/u (Gudlowski et al 2009)	
	N100	- N100 suppression: PRS-P, FEP (N100 difference) and SCZ (N100 difference + ratio) < HC - N100 suppression: PRS-NP = HC (Brockhaus-Dumke et al. 2008)	
	Mismatch Negativity (MMN)	- MMNm dipole latency: PRS < HC - left MMNm dipole moment negatively correlated with CAARMS psychopathology (Shin et al 2009)	

Domains	Findings in Prodromal Patients	
		- MMN amplitude: SCZ < HC, PRS < HC (not sig) (Brockhaus-Dumke et al. 2005)
		- MMN FEP=PRS < HC (not sig), PRS-P < PRS-NP (Schall et al. 2008)
Sensorimotor gating		- prepulse inhibition of the acoustic startle response FEP < late PRS < early PRS < HC almost = medicated SCZ (Quednow et al 2008)
		- habituation PRS + SCZ = HC (Quednow et al 2008)
Cognition	Social Cognition	- ↓ social cognition in PRS patients = SCZ patients (Niendam 2009)
	Processing speed	- FEP < PRS < HC, PRS-P=PRS-NP (Eastvold et al 2007)
		- PRS < HC (Keefe et al 2006)
		- PRS-P < PRS-NP (also after Bonferroni-Holmes adjustment) (Pukrop et al 2007)
		- PRS < HC (Niendam et al 2006)
		- UHRPRS < HC (Niendam et al 2007)
		- motor speed PRS < HC (Niendam et al 2006, 2007)
		-↑ in processing speed associated w/ ↑ in attenuated positive sxs + social functioning (Niendam et al 2007)
		- PRS and FEP < HC (ns) (Ozgürdal et al 2009a)
		- PRS < HC (Hawkins et al 2004)
Cognition	Working memory / short-term memory Working memory / short-term memory cont'd	- FEP < PRS < HC, PRS-P=PRS-NP=FEP (Eastvold et al 2007)
		- PRS < HC, among best discriminating factors (logistic regression) (******Pflueger et al 2007)
		- PRS < HC, PRS-P < PRS-NP (ns) (Wood et al 2003)
		- verbal working memory FEP < PRS < BS+HC (Simon et al 2007)
		- spatial working memory PRS < HC (Smith et al 2006)
		- PRS < HC (Lencz et al 2006)
		- PRS-P < PRS-NP (also after Bonferroni-Holmes adjustment) (Pukrop et al 2007)
		- PRS=HC (Niendam et al 2006)
		- PRS < HC (ns), FEP < HC (sign) (Ozgürdal et al 2009a)
		- (digit span) PRS-P+PRS-NP show decline over f/u (Wood et al 2007)
		- PRS < HC (Hawkins et al 2004)
	Verbal episodic memory	- FEP < PRS < HC, PRS-P=FEP (Eastvold et al 2007)
		- ↓ verbal memory in PRS-P (Brewer et al 2005)
		- verbal learning + memory: immediate recall FEP < PRS+BS, delayed recall FEP=PRS+BS (Simon et al 2007)
		- verbal memory PRS < HC (Lencz et al 2006)
		- verbal memory scores at baseline PRS-P < PRS-NP (Lencz et al 2006)
		- verbal memory PRS-P < PRS-NP (Pukrop et al 2007)
		- verbal learning and memory PRS < HC, associated w/ ↓ social functioning (Niendam et al 2006)
		- verbal learning + memory PRS < HC (trend) (Niendam et al 2007)
		- verbal memory PRS and FEP < HC (ns) (Ozgürdal et al 2009)
		- PRS < HC (Hawkins et al 2004)
	Visual memory	- PRS-P show decline over f/u (Wood et al 2007)
		- ↓ visual reproduction in PRS-P (Brewer et al 2005)

Domains	Findings in Prodromal Patients	
Cognition		↑ in visual learning memory associated w/ ↑ in attenuated positive sxs + social functioning (Niendam et al 2007)
		- visual learning +memory PRS=HC (Niendam et al 2006)
		- PRS=HC (Hawkins et al 2004)
	Visual-spatial functioning	- PRS < HC (trend) (Lencz et al 2006)
		- (perceptual organization + spatial working memory) PRS < HC (Myles-Worsley et al 2007)
	Executive functioning / Cognitive Flexibility / Reasoning + Problem Solving	- FEP < PRS < HC, PRS-P=PRS-NP (Eastvold et al 2007)
		- PRS < HC, among best discriminating factors (logistic regression) (Pflueger et al 2007)
		- PRS < HC (Lencz et al 2006)
		- verbal executive functions PRS-P < PRS-NP (Pukrop et al 2007)
		- PRS and FEP < HC (ns) (Ozgürdal et al 2009a)
		- PRS and FEP ns different from HC (TMT+Stroop, Ozgürdal et al 2009a)
		- FEP=PRS=BS=HC (TMT A&B, Simon et al 2007)
		- PRS=HC, ↓ reasoning + problem solving associated w/ ↓ social functioning (trend) (Niendam et al 2006)
		- PRS < HC (Hawkins et al 2004)
	Attention / Vigilance	- PRS < HC (Pflueger et al 2007)
		- attention (SANS subscale) at baseline PRS-P < PRS-NP (Yung et al 2004)
		- sustained attention: FEP = PRS < HC, PRS-P = PRS-NP (Francey et al 2005)
		- sustained attention FEP+PRS < BS+HC (ns) (Simon et al 2007)
	Attention / Vigilance cont'd	- attentional set-shifting: PRS-P show decline over f/u (Wood et al 2007)
		- set-shifting (perseverative errors in WCST): FEP>PRS>BS>HC (ns) (Simon et al 2007)
		- sustained attention PRS < HC (ns), FEP < HC (sign) (Ozgürdal et al 2009a)
		- vigilance in PRS < HC (Keefe et al 2006)
		- PRS compared to HC: conflicting results (Hawkins et al 2004)
	General intelligence	- FEP < PRS < HC, PRS-P=FEP (Eastvold et al 2007)
		- PRS < HC (Pflueger et al 2007)
	Verbal	- PRS < HC, among best discriminating factors (logistic regression) (Pflueger et al 2007)
		- PRS and FEP within higher average level (ns) (Ozgürdal et al 2009a)
		- PRS < HC (Hawkins et al 2004)
	Nonverbal-abstract Performance	- PRS-P=FEP rather due to vocabulary than block subtest (Eastvold et al 2007)
		- PRS-P < PRS-NP (also after Bonferroni-Holmes adjustment) (Pukrop et al 2007)
		- PRS > HC and FEP (premorbid) > HC (Ozgürdal et al 2009a)
		- performance IQ PRS < HC (Brewer et al 2005)
		- PRS= HC (Hawkins et al 2004)
	General cognition / Composite Scores	- FEP < PRS < HC across all domains (Eastvold et al 2007)
		- global cognitive performance PRS < HC and PRS relative to estimates of their own prior intellectual functioning (Lencz et al 2006)
		- PRS-P < PRS-NP, PRS-NP=HC (Keefe et al 2006)
		- time to development of FEP was not related to severity of neurocognitive deficits (Keefe et al 2006)

Domains	Findings in Prodromal Patients
	- ↑ neurocognitive function in UPRS-NP but not PRS-P (Keefe et al 2006) - poor global cognitive functioning (CPT) + better short-term visual learning and attentional abilities (WAIS-R digit symbol subtest) predicted conversion to FEP (K-M estimated survival analysis) (Keefe et al 2006) - PRS-P < PRS-NP (Pukrop et al 2007) - PRS = HC (Ozgürdal et al 2009a)
Visual Saccades	- Antisaccade error rate: recent-onset SCZ > PRS > HC - Antisaccade error rate: -PRSP > PRSNP (at baseline, trend) -↓ spatial working memory function related to ↑ antisaccade errors in PRS - Abnormal antisaccade task performance in PRS (Nieman et al 2007)
Binocular depth inversion	- PRS, SCZ (treatment-naive and short-term treatment) > HC - ROC analysis for PRS-P revealed an AUC of 0.70 (Koethe et al. 2009)
Olfactory deficits	- olfactory identification: PRSP < PRSNP = HC (Brewer et al 2003) - FEP + PRS < HC (Brewer 1996); - PRS < HC (Brewer et al 1998)
Metabolic / Proteomic Profiles	- Proteomic profile: 36% of PRS = FEP (drug-naïve) - Metabolic profile: 29% of PRS = FEP (drug-naiv) -> changes in levels of glucose, lactate, VGF-derived peptide (VGF23-62) and transthyretin protein (Huang et al. 2007)
Cortisol	Thompson et al 2007: Significant positive correlations in PRS patients between: - Plasma cortisol levels + experience of 'hassles' - Plasma cortisol levels + level of depression and anxiety No significant correlations between: - Plasma cortisol levels + experience of stressful life events - Plasma cortisol levels + global psychopathology, psychotic symptomatology, functioning or pituitary and hippocampal volumes
Genes	- SNP8NRG243177 allel of the NRG1 gene: ↑ conversions in PRS with risk genotype (Keri 2008)

FEP= First-Episode Psychosis, PRS Psychosis Risk SyndromePRS; PRS-P= Psychosis Risk Syndrome patients converted to Psychosis, PRS-NP= Psychosis Risk Syndrome patients not converted to Psychosis, GHR= Genetic High Risk, HC= Healthy Controls, ROC=Receiver-Operating Characteristics, AUC=Area Under Curve, NRG1= Neuregulin 1

Table 5

Medications With Putative Neuroprotective Properties

Medication	Putative Mechanisms (preclinical studies)	Supportive/Preliminary Evidence (clinical studies)
Mood Stabilizers (Carbamazepine, Lamotrigine, Levetiracetam, Lithium, Phenytoine, Topiramate, Valproate)	-mechanisms still speculative -sodium channel blockers (lamotrigine, phenytoine) -potent neurotrophic+neuroprotective properties (Manji et al 2000) activation of extracellular signal-regulated kinase signaling cascade + activation of anti-apoptotic cytoprotective substances (e.g. bcl-2) in CNS + cells of human neuronal origin (valproate + lithium) (Greay et al 2003, Yuang et al 2001; Chen et al 1999) -inhibition of pro-apoptopic protein (GSK-3β) (Frey et al 2007) ↑ in anti-apoptopic factors bcl-2 -> inhibition of free radical accumulation (Chen et al 1999) -inhibit intracellular free calcium concentration, lipid peroxidation, protein oxidation, DNA fragmentation, cell death (Shao et al 2005) and ↓ marker of oxidative stress (Frey et al 2006) -chronic Rx w/ valproate protects neurons from oxidative stress (Wang et al 2003) + ↑ endoplasmatic reticulum stress protein (GRP 78) (Wang et al 1999) -neuroprotective effects in frontal cortex, hippocampus, striatum at subtherapeutic doses in rats (Manji et al 2000) -↓ PKC (Manji et al 1999) ↑-↓ NMDA-mediated excitotoxicity (Hashimoto et al 2002; Nonaka et al 1998)	-**PRS patients** treated w/ low-dose Lithium > improvement in sxs + less progressive brain changes than PRS w/ supportive counseling (Berger et al 2007) -↓aggressive behavior in children at-risk for BD w/ divalproex sodium (Saxena et al 2006) -↑ in overall N-acetyl-aspartate concentrations (Moore et al 2000) + grey matter (Moore et al 2000) in frontal, temporal, parietal, occipital lobes in stable patients w/ bipolar d/o + HC following 4-weel Lithium Rx (>0.7 mmol L^{-1}) -improvement of psychotic sxs w/ lamotrigine in treatment-resistant SCZ (open-label and DBPCT, Dursun et al 1999, 2001), and w/ topiramate in SCZ to a small degree (DBRPCT, Tiihonen et al 2005)
Antidepressants	-modulation of cAMP signal transduction + protection against ↓ BDNF levels (Chen et al 2001) -↑ hippocampal neurogenesis (D'Sa et al 2002, Santarelli et al 2003, Duman et al 2001, Malberg et al 2000) -putative protection against stress-related loss of glial or neuronal cells (Duman et al 2001) -Also potential for pro-apoptotic properties (Serafeim et al 2003) -**1** gene expression of superoxide dismutase (Li et al 2000) -↓ ecstasy-ind. degen. of 5HT synapses (Sanchez et al 2001) -↓ spinal trauma (Salzman et al 1994) -↑ BDNF (Rantamaki et al 2007, De Foubert et al 2004, Calabrese et al 2007)	-naturalistic studies **in PRS patients** (Cornblatt et al 2007, Fusar-Poli et al 2007) -longer duration of naturalistic AD Rx associated w/ full recovery of any syndromal or subthreshold sxs in psychosis NOS (Correll et al 2008), -↓ relapse of depression as well as of psychosis in SCZ patients w/ postpsychotic depression (Siris et al 1994) -↓ negative sxs AD > PBO across 5 RCTs in patients with predominant negative sx SCZ (Rummel et al 2005)
Second-Generation Antipsychotics	-prevention of cell death (Qing et al 2003; Bai et al 2002; Wei et al 2003; Cosi et al 2005; Xu et al 2002; Okamura et al 2003) -↑ NGF (hippocampus) (Angelucci et al 2005) - BDNF (Bai et al 2003), ↓ BDNF (hippocampus) (Angelucci et al 2000)	-sx reduction+at least delayed progression to FEP **in PRS patients** (see table RCTs) -↑ cognitive function in FEP w/ RIS > haloperidol (Harvey et al 2005) -lack of atrophic brain changes w/ OLZ compared to atrophic changes w/ haloperidol in a

Medication	Putative Mechanisms (preclinical studies)	Supportive/Preliminary Evidence (clinical studies)
	-↑ neurogenesis (Wakade et al 2003; Kodama et al 2004; Wang et al 2004) -↑ SOD1 (Bai et al 2002, Li et al 1999) (no change: Parikh et al 2003) -↓ bcl-2 (Li et al 1999; Bai et al 2004) -↓ in neurotrophin receptor P75 (Li et al 1999; Bai et al 2002) - effects of stress-induced ↓BDNF w/ QTP (Xu et al 2002) -mediation of effects of pro-apoptopic stimulus on PC 12 cells by pre-Rx w/ OLZ (Wei et al 2003) -CLZ, OLZ, QTP + RIS, but not HAL: Protection against H2O2-induced oxidative stress (Wei et al 2003) -OLZ: Protection against MPP+-induced apoptosis (Qing et al 2003) and ↑ gene expression of superoxide dismutase (Li et al 2000) -glutamatergic activity (Banerjee et al 1995)	longitudinal MRI study in FEP SCZ patients (Lieberman et al 2005) -prevention of ventricular enlargement in SCZ (Cahn et al 2002)
Omega-3 fatty acids	-mechanisms still speculative, range of anti-apoptopic mechanisms -several preclinical studies indicate neuroprotective properties (Lonergan et al 2002; Martin et al 2002; Martin et al 2002) -neuroprotection in rodent infants against excitotoxic injury when mother rats are given omega-3-fatty acids (Hogyes et al 2003) -↓ PKC (Seung 2001; Padma 1999) -↓ Behavioral abnormalities (Wainwright 1999) ↓- seizure threshold (Yehuda et al 1994) -↓ Ischemia in animal models (Lauritzen et al 2000)	-↓positive+global sxs and↑ functioning **in PRS patients** (DBRPCT, Amminger et al 2007, 2008) -↓ in peripheral+central membrane tissues in SCZ (for references see Fenton et al 2000; Berger et al 2006) -EPA (eicosapentaenoic acid) can ↑ membrane arachidonic acid+EPA concentrations in SCZ (Horrobin et al 2002) -↑ in grey matter volume+N-acetyl-aspertate levels in SCZ w/ E-EPA monotherapy (case report, Puri et al 2002) -SCZ: negative results: Fenton et al 2001 SCZ: positive results: Peet et al 2001; Fenton et al. 2000; Puri et al. 1998 -First episode psychosis: quicker response, ↓ medication+extrapyramidal side-effects in first wks of Rx w/ SGA+EPA vs. SGA+PBO (Berger et al 2007); negative sx improvement correlated with metabolic brain changes, particularly glutathione (r=-0.57) (Berger et al 2008)
Glycine, D-cycloserine, Modafinil (as glutamate receptor agonist)	-glutamate receptor agonists -mediation of some tardive dyskinesia sxs w/ glycine and high-dose D-cycloserine (ns w/ low-dose D-cycloserine) (preclinical study) (Shoham et al 2004) -neuroprotective effects of glycine transporter-1 (GlyT1) inhibitors via revesal of PCP-induced changes+selective inhibition of glycine uptake (without being substrates of transporter protein) in rodents (Harsing et al 2006) -modafinil: neuroprotective effect in model of glutamate excitotoxicity (Antonelli et al 1998)	-ongoing DBRPCTs **in PRS patients** w/ glycine (Woods), D-serine (Javitt) and sarcosine (N-methyl derivative of glycine) (Hereco-Levy & Lerer) -sign clinical improvement in SCZ w/ glycine and D-cycloserine (glycine > D-cycloserine) (Heresco-Levy et al 2004), D-serine (Heresco-Levy et al 2005) and D-alanine (Tsai et al 2006) No significant effects w/ D-serine and -↓ negative+cognitive sxs in AP+glycine (Heresco-Levy et al 1999) -Modafinil did not improve fatigue, positive +negative sxs or cognition (DBPCT, Sevy et al 2005)
Donezil, Galantamine, Rivastigmine	Acetylcholinesterase inhibitors	-moderate cognitive improvement in SCZ w/ adjunct rx w/ donezepil (PBO-controlled + open-

Medication	Putative Mechanisms (preclinical studies)	Supportive/Preliminary Evidence (clinical studies)
		label studies, Erickson et al 2005) – no effects (e.g., Freudenreich et al 2005) -galantamine improved cognition + negative syndrome in SCZ and BPD (Bora et al 2005, Allen et al 2002) -rivastigmine only limited positive effects on SCZ (Kumari et al 2006)
Acamprosate	Glutamate receptor modulator -neuroprotective effects (De Witte et al 2005) -may interact w/ excitatory glutamatergic neurotransmission in general+as an antagonist of metabotropic glutamate receptor subtype 5 (mGluR5) Harris et al 2003)	- trials w/ acamprosate as adjunct Rx in non-alcoholic patients w/ BPD ongoing (see Krebs et al 2006)
Ampakines (CX516, aniracetem, cyclothiazide) 2,3Benzodiazepines (tofisopam, girisopam, nerisopam)	AMPA antagonists	-↑ cognition in augmentation trials w/ CX516 in chronic SCZ (Marenco et al 2002, Johnson et al 2002) -CLZ+ ampakine compound CX516 beneficial in SCZ (Goff et al 2001)
Memantine, Riluzole	-NMDA antagonists	Memantine: -positive effects on cognition + prevented functional decline in Alzheimer's disease (review of DBRPCTs, Areosa & Sherriff 2003)
	Memantine: -Group I glutamate metabotropic receptor antagonists -↓neuronal loss in rodents w/ memantine when exposed to beta-amyloid-induced neurotoxicity (Miguel-Hidalgoet al 2002)	Riluzole: -beneficial in patients w/ sporadic amyotrophic lateral sclerosis (Killestein et al 2005)
	Riluzole: -neuroprotective in models of neuronal injury (Farber et al 2002)	
Benzodiazepines	GABA receptor potentiators	-↓ agitation and anxiety in acute psychosis (Thomas et al 2009) -short term sedation (Volz et al 2007)
Neurotrophines and growth factors (BDNF, erythropoietin)	Erythropoietin: -supporting anti-apoptotic mechanisms -haloperidol-induced neuronal damage mediated by peripherally applied erythropoietin (in vitro) + ↑cognitive performance of aversion tasks in rodents (Ehrenreich et al 2004)	Erythropoietin: -↑ expression of erythropoitetin receptors in hippocampus + cortex SCZ > HC (Ehrenreich et al 2001) -↑ cognitive functioning in chronic SCZ (Ehrenreich et al 2007)
PAF antagonists, Free radical scavengers and antioxidants (Ginkgolide B (BN52021), Vitamin E, N-acetylcysteine)	Antioxidants (vitamin E, ginkgo biloba): -neuroprotective effects (Ahlenmeyer & Krieglstein 2003)	Antioxidants (vitamin E, ginkgo biloba): -↓positive + negative sxs and extrapyramidal side-effects in haloperidol+ginko biloba vs. haloperidol+PBO (DBPT, Zhang et al 2001) -improved/assisted recovery in SCZ+other psychiatric d/o w/ dietary supplementation of antioxidants (Ranjekar et al 2003)

Medication	Putative Mechanisms (preclinical studies)	Supportive/Preliminary Evidence (clinical studies)
	N-acetylcysteine: -modification of oxidative processes via modulation of glutathione	N-acetylcysteine: -↓glutathione (in cerebro-spinal fluid in drug-free patients vs. HC + in prefrontal cortex in SCZ vs. HC) and related antioxidant enzyme activities dysfuntional in SCZ + BPD (Do et al 2000) -↓ mismatch negativity in SCZ (Lavoie et al 2008) -↓ in PANSS total, negative and general psychophathology scores, and with N-ACC+AP compared to PBO+AP (DBPCT, Berk et al 2008)
COX-2 inhibitors (celecoxib)	COX-2 inhibitors: -modulate inflammation -neuroprotective in animal models (Klivenyi et al 2004, Chu et al 2004)	COX-2: -↓in overall psychopathology in RIS+celecoxib (Muller et al 2002) -no differences in FGA+Hydrochloroquine in SCZ (Desta et al 2002)
Estrogen	-asscociated w/ neurodevelopmental processes in Alzheimer's and SCZ (Kolsch & Rao, 2002)	-↓ sxs in SCZ women more rapidly w/ Estrogen (Kulkarni et al 1996) -↓ positive and general psychopathology sxs compared to PBO in SCZ women (Kulkarni et al 2008) -mixed results in meta-analysis (Chua et al 2005)
Magnesium	- altering PKC response to anoxic insult (Libien et al 2005)	-↓ Ischemia (Sameshima et al 2001, Yang et al 2000); -↓ TBI (Saatman et al. 2001, Bareyre et al 2000), but not if given post-injury (Galvin et al 1998)
Inflammatory cytokine antagonists	Blocking the inflammatory response	-some evidence for an imbalance in inflammatory cytokines in schizophrenia, role of stress + weight gain not definite (Potvin et al, 2008, quantitative review) -↑ anti-inflammatory capacity w/ atypical antipsychotics (Maes et al 2000, 2002)

5HT= 5-hydroxytryptamine, AD= antidepressants, AMPA= α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, AP= antipsychotic, bcl 2= B cell lymphoma 2 cells, BDNF= Brain-derived neurotrophic factor, BPD= bipolar disorder, cAMP= cyclic adenosine monophosphate, CLZ= clozapine, CNS= central nervous system, COX-2= Cyclooxygenase 2, DBPT= double blind placebo trial, DBPCT= double blind placebo controlled trial, DBRPCT= double blind randomized placebo controlled trial, DNA= Deoxyribonucleic acid, EPA= eicosapentaenoic acid, E-EPA= ethyl- eicosapentaenoic acid, FEP= first-episode psychosis, FGA= first-generation antipsychotic, GABA= gamma-aminobutyric acid, GSK-3β= Glycogen synthase kinase 3 beta, HC= healthy controls, MPP= 1-methyl-4-phenylpyridinium, MRI= magnet resonance imaging, N-ACC= N-acetylcysteine, NGF= nerve growth factor, NMDA= N-methyl-D-aspartic acid, NOS= not otherwise specified, OLZ= olanzapine, PANSS=Positive and Negative Sydrom Scale, PBO= placebo, PC12 cells= pheochromocytoma 12 cells PCP= phenylcyclidine, PKC= protein kinase c, PRS= Psychosis Risk Syndrome, QTP= quetiapine, RCT= randomized controlled trial, RIS= risperidone, SCZ= schizophrenia, SGA= second-generation antipsychotic, SOD1= Superoxide dismutase 1, TBI= traumatic brain injuryPRS

Table 6

Published and Presented Intervention Studies

Study	Design	N	Blinding	Sites	Mean Age (Range)	Sex (% Male)	Active Rx Duration	Active Rx	Mean Dose/ Schedule	Control	Transition to Psychosis – Definition	Follo w-Up Off Rx	% Psychosis Rx vs CTRL	Other Outcomes (Rx)	Other Outcomes (F/U)
McGorry et al. 2002	DBRCT	59	Single	1	20 (14-28)	58	6 mo	RIS+CBT	1.3 mg/d	Usual care	≥ 1 of these sxs: ideas of reference, odd beliefs or magical thinking, perceptual disturbance, paranoid ideation, unusual thoughts or disorganised speech; Frequency: ≥ daily Duration: > one week.	6 mo	Rx: 9.7 vs 35.7 * Off:19.4 vs 35.7 ns	↓ All sxs (active+control), → functional measures (both groups) between group differences ns	↓ All sxs (both groups) → functional measures (both groups) Group differences ns
Phillips et al. 2007												30-40 mo	Off: 32.3 vs 42.9 ns	-	↓ YMRS + ↑ QLS (both groups) → all other between group differences ns
Woods et al. 2003	DBRPCT	60	Double	4	17.7 (12-45)	68	2 mo	OLZ+SFT	8 mg/d	PBO+ SFT	On Presence of Psychosis Scale: ≥ 1 of these sxs: a) unusual thought content, suspiciousness/ persecution, grandiosity with delusional conviction, and/or b) perceptual abnormality of hallucinatory intensity, and/or c) unintelligible speech; present for ≥1 hr/d at average of ≥4 d/wk for ≥1 mo, or sxs are seriously disorganizing or dangerous	-	-	↓ SOPS (total, negative, disorganized) OLZ > PBO MMRM* (LOCF ns) ↑ GAF (OLZ+PBO), → PANSS, MADRS, YMRS (OLZ+PBO)	
McGlashan et al. 2006							12 mo					12 mo	Rx: 16.1 vs 37.9 ns Off: 25.8 vs 44.8 ns	↓ positive sxs OLZ > PBO (tendency) ↑GAF OLZ+PBO → PANSS, MADRS, YMRS (OLZ+PBO)	↑ positive sxs (OLZ: sign PBO: ns)
Morrison et al. 2004	SBRCT	58	Single	1	22 (16-36)	67	6 mo	CBT	26 sessions/6 mo	Monitoring	1) PANSS cut-off: ≥ 4 on hallucinations and delusions and ≥ 5 on conceptual disorganization 2) DSM psychotic d/o criteria 3) AP drugs from independent clinician	6 mo	Off: 5.7 vs 21.7*	↓ PANSS (positive sxs) CBT>Control* GAF+GHQ ns	-
Morrison et al. 2007												30 mo	Off: 20.0 vs 21.7 ns	-	NR

Study	Design	N	Blinding	Sites	Mean Age (Range)	Sex (% Male)	Active Rx Duration	Active Rx	Mean Dose/ Schedule	Control	Transition to Psychosis – Definition	Follo w-Up Off Rx	% Psychosis Rx vs CTRL	Other Outcomes (Rx)	Other Outcomes (F/U)
Bechdolf et al. 2006, 2008	OLRCT	128	Open, masked rater	4	NR (17-35)	NR	12 mo	CBT	60 sessions?? /12 mo	SC	PANSS cut-off: P3 (hallucinations) or P1, P5 or P6 (delusions) or PANSS P2 (formal thought disorder) > 4, duration > 1 week ??	12 mo	Rx: 1.6 vs 13.8* Off: pending	→sxs + ↑ functioning (CBT=SC)	NR
Amminger et al. 2007, 2008	DBRPCT	81	Double	1	16.4 (13-24)	82	3 mo	Ethyl EPA	1.5 g/d	PBO	PANSS cut-off: ≥ 4 on hallucinations and delusions and ≥ 5 on conceptual disorganization, frequency: ≥ several times/week, duration: > 1 week	9 mo	Rx: 2.6 vs 21.1* Off: 4.6 vs 27.5*	↓ PANSS (positive, global), GAF Ethyl EPA>PBO	NR
RPRSmann et al. 2007,	OLRCT	114	Double	4	NR (16-35)	56.5	12 mo	AMI+NFI	50-800mg	NFI	NR	-	-	↓ ERI-BAPPSS, ERI-PPS, ERI-BS, ↓ PANSS (positive, negative, general), ↓ GAF, MADRS (AMI+NFI=NFI)	pending
RPRSmann et al. SIRS meeting 2008	DBRCT	102				NR			100 mg/d			12 mo	**6 Mo:** Rx: 5.3 vs 21.0* Off: pending	Pending	
Yung et al. SIRS meeting 2008	DBRPCT	115	Double	1	NR (14-30)	NR	12 mo	CT+RIS / CT+PBO/ ST+PBO	RIS: 0.5-2 mg/d CT: 1h/week or 2 wks/12 mo	PBO/SC SC: 1h/week or month/12 mo	frank psychotic symptoms occurring ≥ daily for ≥ 1 week (CAARMS)	12 and 24 mo	**6 Mo:** Rx: 4.7 vs 9.1 vs 7.1	↓ BPRS, SANS, HRSD (all groups) ↑ GAF+QLS (all groups)	pending

ns= not significant

*=significant

RIS=Risperidone; AMI=Amisulpride; OLZ=Olanzapine; Ethyl EPA=Ethyl Eicosapentaenoic Acid; NFI=needs-focused-intervention, SC=Supportive Counselling; SFT=Supportive Family Therapy; ST=Supportive Therapy; C (B)T=cognitive (behavioural) therapy; PBO=Placebo; SOPS= Scale of Prodromal Symptoms, QLS= Quality of Life Scale, PANSS= Positive And Negative Syndrome Scale, GAF= Global Assessment of Functioning, YMRS= Young Mania Rating Scale, MADRS= Montgomery-Åsberg Depression Rating Scale, GHQ= General Health Questionnaire, SANS= Scale for the Assessment of Negative Symptoms, BPRS= Brief Psychiatric Rating Scale, HRSD= Hamilton Rating Scale for Depression; SX= symptom, ERI-BAPPS= Basic and Positive Psychotic Spectrum Symptoms score, ERI-PPS= Attenuated and Full-Blown Psychotic Positive Symptoms Score, ERI-BS= Basic Symptoms Score , OLRCT: open label randomized controlled trial

Table 7

Ongoing* Randomized Controlled Intervention Studies in Individuals Considered At High Risk for Psychosis

Author	Design	Intended N /Enrollment	Blinding	Sites	Age range (years)	Active Rx	Follow-up off Rx	Active Rx	Drug dose	Control	Primary outcome measures
Bechdolf PREVENT	RPCT	126	Masked raters	9	17-36	12 mo	No f/u	Aripiprazole+CM / CBT	2-15mg/d	PBO+CM	Transition to psychosis
Nelson / McGorry NEURAPRO 1	RPCT	?	Double	?	? 14-30	3mo	6 mo	CBCM+EPA/DHA	?	PBO	Transition to psychosis
Nelson / McGorry NEURAPRO 2	RPCT	?	Double	?	? 14-30	6 mo	6 mo	CBCM+Quetiapine	?	PBO	Transition to psychosis
Javitt	DBRPCT	72	Double	3	13-35	4 mo / optional cross-over trial	4 mo	D-Serine	60 mg/kg/d	PBO	Prodromal symptoms, neuropsychological measures
Woods	DBRPCT	80	Double	11	16-40	6 mo	6 mo	Ziprasidone	20-160 mg/d	PBO	Transition to Psychosis
Hereco-Levy & Lerer	DBRPCT	60	Double	1	12-45	4 mo / optional+ 2 mo open label	4 mo	Sarcosine	2 g/d	PBO	Positive + negative prodromal symptoms, neurocognition
Vinogradov	DBRCT	100	Double	2	16-25	4 mo / optional + 2-4 mo	2 mo	Neuroadaptive Cognitive Training	60 min session d, 5/week	Active: computer games	Cognitive performance

Ethyl EPA= ethyl eicosapentaenoic acid; SC= counselling; CBT= cognitive behavioral therapy; PBO= Placebo; CBCM= cognitive behavioral case management; CM=Clinical Management; RPCT= Randomized Placebo Controlled Trial; DBRPCT= Double Blind Randomized Placebo Controlled Trial; DBRCT= Double Blind Randomized Controlled Trial

Table 8

Open Questions for Psychosis Risk Syndrome (PRS) Research (± data equivocal; *data absent)

Patient Population
± How can PRS samples enriched for conversion best be ascertained?
± How can PRS samples enriched for conversion best be retained for long periods of time?
Prodrome Characterization
± How can the sensitivity and specificity of the psychosis risk syndrome and of individual symptoms be increased?
± How can the predictive power of the psychosis risk syndrome and of individual symptoms be increased?
± What is the particular diagnostic outcome of those who convert to psychosis? What kind of psychosis risk syndrome are we defining?
± What is the diagnostic outcome of those who do not convert to psychosis, i.e. the false-positives?
Interventions
±Can early interventions improve psychosis risk syndrome states more than a control condition or placebo?
± Can the rate of disease manifestation be reduced?
± Can the disease manifestation be delayed?
± What are the most appropriate interventions?
* Do interventions differ for symptom reduction vs. prevention?
± Are interventions phase-specific (early vs. late psychosis risk syndrome)?
± For how long should interventions for the psychosis risk syndrome be continued?
* Can interventions during the psychosis risk syndrome modify the symptomatic outcome if the full disease develops?
* Can interventions during the psychosis risk syndrome modify the illness course/responsiveness if the full disease develops?
Predictors
* What predicts symptom response, conversion and outcome?
* Is there a relationship between the presence/absence of individual psychosis risk syndrome symptoms or clusters and progression or remission of the psychosis risk syndrome?
* Is there a relationship between the duration of the psychosis risk syndrome and progression or remission of the syndrome?
* Does speed or completeness of psychosis risk syndrome response relate to illness prevention?
* Does speed or completeness of psychosis risk syndrome response relate to illness course and outcome if the full illness develops?
Mechanisms
* What are the mechanisms of psychosis risk syndrome development and reduction/remission?
* What are the mechanisms of progression from the psychosis risk syndrome to full blown psychosis or schizophrenia?
* What are trait markers and what are state markers of conversion to psychosis?
* What are fixed and what are malleable risk factors and mechanisms of conversion to psychosis and functional outcome?
Clinical Application
± At which point of research knowledge can/should the psychosis risk syndrome be incorporated into the DSM or ICD system?
* How can research findings be transferred and implemented into clinical settings?