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The psychosis risk syndrome and its proposed inclusion in the DSM-V: A risk–benefit analysis

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ABSTRACT

The inclusion of a psychosis risk syndrome has been proposed for the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders. The appropriateness of inclusion of this new risk syndrome in the DSM depends on a careful analysis of both anticipated benefits and risks. Purported benefits include early recognition and case identification, and the hypothetical benefit of preventive intervention of psychotic disorders, for which there is as yet no clear evidence base. However, there is a potential for high rates of false positives particularly at the community level given the difficulty in discriminating mild symptoms from normal variants and low base rates of the syndrome in the general population. High false-positive rates in and of themselves are not necessarily problematic if the risk–benefit ratio is significantly favorable, as with screening for cardiovascular risk factors. For the psychosis risk syndrome, by contrast, there are substantial risks, for both stigma and discrimination, and for unnecessary exposure to antipsychotic medications, which make the high false-positive rate associated with the psychosis risk designation particularly problematic. More research is needed to improve the positive predictive value of the psychosis risk syndrome so that it can be considered for inclusion in future editions of the DSM.

1. Introduction

Each revision of the Diagnostic and Statistical Manual of Mental Disorders (DSM) brings forth proposals for the inclusion of new syndromes and disorders. All suggestions for new disorders inevitably present benefits and risks to those who would be identified as having the condition as well as to the system of psychiatric care at large. Historically, proposals for new disorders have typically emphasized the advantages of recognition and case identification in order to facilitate appropriate management with the goal of reducing patient suffering. However, hand-in-hand with these purported benefits go the risks associated with being labeled as having a mental disorder (e.g., stigma, denial of future insurability) and risks associated with treatment (e.g., medication side effects). For example, when it was proposed that Premenstrual Dysphoric Disorder (PMDD) be included in the DSM-III-R (Spitzer et al., 1989) and again in DSM-IV (Severino, 1996), purported benefits included that recurrent premenstrual mood symptoms would be recognized by clinicians in women as psychiatric symptoms and appropriately treated, and not dismissed as "moodiness." However, concerns were raised as to the risk of stigmatizing women especially in the workplace, where they have been historically discriminated against. In weighing these benefits and risks, the DSM-IV Task Force decided that on balance it would be premature to add PMDD to the main body of DSM-IV, and instead included it in the appendix for "criteria sets and axes provided for future study" to encourage future research (Gold, 1998).

For DSM-V, the inclusion of a psychosis risk syndrome has been proposed. Given that psychotic disorders such as schizophrenia are chronic illnesses largely refractory to cure

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which cause immense suffering to patients and families, the hope is that with early identification and intervention, we might be able to forestall or prevent the onset of psychosis in vulnerable individuals and mitigate the long-term course and outcome. Whether it makes sense to actually include such a risk syndrome in DSM-V requires a careful consideration of both its benefits and risks and should only seriously be considered if the benefits clearly outweigh the risks.

2. History and rationale

The impetus for early identification and preventive intervention for schizophrenia and other psychotic disorders comes from their associated disability and refractoriness to cure. As schizophrenia is a developmental disorder with antecedents in childhood and adolescence, a strategy to identify young people at risk for developing schizophrenia is plausible. For example, individuals who go on to develop schizophrenia have a history of developmental delays, isolated play and speech problems, and some clumsiness, as compared with normal controls (Done et al., 1994; Fish et al., 1992; Jones et al., 1994; Tarrant and Jones, 1999). As children, they are rated by teachers as having comparably worse attention spans and more hyperactivity, shyness, and withdrawal (Olin et al., 1998). However, given that most children with these subtle motor, social and cognitive deficits in childhood do not go on to develop schizophrenia, these characteristics lack the specificity needed to prospectively identify those at risk for developing psychosis.

A more promising strategy comes from "prodromal", or "clinical high risk" (CHR) research (these terms are used interchangeably), which focuses on the period of time immediately preceding an index episode of psychosis. Such research aims to identify teens and young adults who are help-seeking and who endorse psychotic symptoms which are in attenuated form. Evidence suggests that this "prodromal" period is a reasonable window of risk to try to identify, as retrospective studies with first-episode schizophrenia patients have shown that a prodrome occurs in ~75% of first-episode patients, has a duration of 3–4 years and is characterized by functional decline and attenuated psychotic symptoms (Hafner et al., 1998). In pioneering studies in both Australia and the United States, young people with "subthreshold" psychotic symptoms and/or functional decline in the context of genetic risk for schizophrenia were ascertained and followed longitudinally for development of psychosis (Miller et al., 2003; Yung et al., 2003). In these earliest studies, prodromal status was associated with a 40 to 50% rate of "conversion" to psychosis within 1 to 2 years (Miller et al., 2003; Yung et al., 2003). A consortium of research groups in North America reported a more modest rate of transition to psychosis; for example 35% within 2.5 years (Cannon et al., 2008). In Australia, one-year transition rates for patients ascertained in successive years have steadily decreased over time: 50% in 1995 → 32% in 1997 → 21% in 1999 → 12% in 2000 (Yung et al., 2007).

The need to assess attenuated psychotic symptoms formed the basis for the development of two measures, the Comprehensive Assessment of At-Risk Mental States (CAARMS) (Yung et al., 2005); and the Structured Interview for Prodromal Syndromes/Scale of Prodromal Symptoms (SIPS/SOPS) (Miller et al., 2003; Woods et al., 2009) which have been utilized in the various prodromal studies. These instruments define attenuated psychotic symptoms and provide operationalized criteria for the prodromal categorization in terms of recency of onset, frequency, associated distress of such symptoms, including that they cannot be better explained by other DSM diagnoses, and that they have never surpassed the threshold of a frank psychotic disorder. Both the CAARMS and SIPS/SOPS are reported to have good to excellent interrater reliability among clinical researchers receiving rigorous training (Yung et al., 2005; Addington et al., 2007).

It should be noted that since DSM-III, the diagnostic criteria for schizophrenia have included a prodromal phase which is used in the determination of the total duration of illness and which closely resembles the psychosis risk syndrome. What makes the proposed psychosis risk syndrome novel, however, is that the syndrome stands apart from the diagnosis of schizophrenia and must be identified prospectively in the absence of any psychotic periods, as opposed to the schizophrenia prodrome, which can only be identified in retrospect after the active phase symptoms have emerged.

3. The proposed psychosis risk syndrome criteria: what are they?

There are six criteria for the proposed psychosis risk syndrome (Table 1). Criterion A for the psychosis risk syndrome is derived explicitly from Criterion A for schizophrenia, which describes the active phase symptoms. Specifically, any of the first three "active phase" symptoms (i.e., hallucinations, delusions or disorganized speech) must be present in an "attenuated form", specific language that is identical to that used in the DSM-IV definition of the prodromal phase of schizophrenia, i.e., "symptoms listed in Criterion A present in an attenuated form" (DSM-IV-TR, p. 312). To distinguish these from threshold psychotic symptoms, Criterion A clearly specifies that reality testing must be retained for a psychotic symptom to be considered "attenuated", and this is supported by examples in the proposed text for attenuated hallucinations and delusions (for example, emphasis on the person retaining a

Table 1
Proposed criteria for the risk syndrome for first psychosis.

a) Characteristic symptoms: at least one of the following in attenuated form with intact reality testing, but of sufficient severity and/or frequency so as to be beyond normal variation;
  (i) delusions
  (ii) hallucinations
  (iii) disorganized speech
b) Frequency/Currency: symptoms meeting criterion A must be present in the past month and occur at an average frequency of at least once per week in past month
c) Progression: symptoms meeting criterion A must have begun in or significantly worsened in the past year;
d) Distress/Disability/Treatment seeking: symptoms are sufficiently distressing and/or disabling to the patient and/or others to lead to help-seeking
e) Characteristic attenuated psychotic symptoms are not better explained by another DSM-V diagnosis
f) Clinical criteria for any DSM-V psychotic disorder have never been met
* As described by the official website on March 15, 2010: http://www.dsm5.org/ProposedRevisions/Pages/proposedrevision.aspx?rid=412

level of skepticism and doubt about his or her symptoms). Criteria B and C specify the frequency and progression of attenuated psychotic symptoms. Criterion D notes that they must cause distress or impairment, as a way of distinguishing attenuated symptoms from normal experience, which is echoed in language in the proposed accompanying text, which states that: "mild psychotic experiences which are not compromising or distressing occur not infrequently in persons in the community, and that such phenomena do not necessarily confer increased risk for a psychotic disorder." Criterion E specifies that the symptoms are not better explained by other diagnoses. Criterion F lists prior psychotic disorder diagnosis as an exclusion, which aims to distinguish putatively prodromal symptoms from residual psychotic symptoms.

4. Potential benefits of inclusion in DSM-V

The main benefit of inclusion of the psychosis risk syndrome in DSM-V is that it would encourage attention and resources to be directed to an important clinical problem — namely, a constellation of symptoms seen in teens and young adults which can confer considerable morbidity (and risk) but which do not fit neatly into any known diagnostic entity. Therefore, the popularization of the psychosis risk syndrome concept may hypothetically lead to the identification and treatment of young people who are suffering. Although there is as yet no clear evidence base for treatment of the psychosis risk syndrome, the various associated symptoms and morbidity may be amenable to intervention, including anxiety, depressive symptoms, social withdrawal, and academic impairment. Also, the identification of the psychosis risk syndrome may reduce the potential for misdiagnosis and consequent unnecessary or inappropriate treatment. For example, associated features of the risk syndrome, such as attentional problems, might lead clinicians to initiate treatment with stimulants that could have the potential to exacerbate attenuated positive symptoms. The availability of a more salient diagnostic alternative in the DSM would improve the process of differential diagnosis and promote better management.

An additional potential benefit of inclusion of a psychosis risk syndrome is that it highlights important epidemiological work that demonstrates that attenuated psychotic symptoms are prevalent in the general population, and may be associated with both current morbidity and risk for illness (Poulton et al., 2000; Van Os et al., 2001; Verdoux and Van Os, 2002; Yung et al., 2009). The conceptualization of typically stigmatized phenomena as existing across a spectrum within the general population suggests the possibility that liability to psychosis, as with liability to depression, is simply a human vulnerability. This may have the positive effect of reducing the stigma of psychosis, if such symptoms cannot be ascribed simply to being different or "other". Furthermore, the inclusion of a psychosis risk syndrome in the DSM would also bring psychiatry in line with other fields of medicine that identify risk factors for the purposes of instituting preventative interventions. For example, it is well-recognized that gradations of blood pressure or cholesterol confer quantified risk for cardiovascular disease, and hence preventive efforts can be undertaken to promote or preserve good cardiovascular health.

5. Potential risks of inclusion in DSM-V

5.1. False positives

By far, the most significant risk associated with the inclusion of a psychotic risk syndrome in DSM-V is its potential for high rates of "false positives" i.e. individuals diagnosed with the syndrome who will never develop a psychotic disorder in the future. There are two types of "false positives" associated with this proposal. The first type, which is part-and-parcel of the concept of a risk syndrome, is that the syndrome identifies a group of *at risk* individuals only a fraction of whom will ultimately develop a psychotic disorder. Using the development of a psychotic disorder within a fixed period of time as the "gold standard," sensitivity and specificity statistics for the risk syndrome diagnosed by expert raters using well-validated instruments such as the SIPS/SOPS (Woods et al., 2009) or the CAARMS (Yung et al., 2005), have been determined. In published studies, the rate of these "false positives" (i.e., those identified as having the risk syndrome based on the presence of attenuated psychotic symptoms who do not develop a psychotic disorder within 2–3 years) ranges from 50% to 84% (Table 2).

The second type of false positive reflects the fact that when the diagnostic criteria for this syndrome are applied in community settings by clinicians of various backgrounds and levels of experience, there are high rates of misdiagnosis using expert-applied diagnoses as the standard of diagnostic

Table 2
Transition rates to psychosis in psychosis risk cohorts.

Authors/location	Cohort	"False positives"	Duration of study (in months)
Larsen (2007) (Norway)	Research clinic	57% (8 of 14)	12
Miller et al. (2003) (US)	Research clinic	57% (8 of 14)	6
Yung et al. (2003) (AUST)	Research clinic	59% (29 of 49)	12
Mason et al. (2004) (UK)	Research clinic	50% (37 of 74)	12
Morrison et al. (2002) (UK)	Research clinic	78% (18 of 23)	12
Cannon et al. (2008), Woods et al. (2009) (US multisite)	Research clinics	65% (189 of 291)	30
Yung et al. (2007) (AUST) — cohorts ascertained in successive years	Research clinic	Year 1995: 50%	12
		Year 1996: 67%	12
		Year 1997: 68%	12
		Year 1998: 71%	12
		Year 1999: 79%	12
		Year 2000: 82%	12
Yung et al. (2008) (AUST)	Clinical sample	84% (245/292)	24

accuracy. One study suggests that this "community" false-positive rate may be at least as high as 47%: among 143 young people identified as at risk for psychosis by non-experts, only 76 met research criteria for the risk syndrome when evaluated by researchers (Yung et al., 2008). Moreover, given that the "non-experts" in this study were not drawn from the community at large but instead were part of an outpatient program housed alongside two specialty psychosis research programs in Melbourne, they were more likely than the average clinician to have experience assessing individuals with psychotic disorders. Consequently, this false-positive rate of 47% is almost certainly lower than what would be obtained by clinicians in general community settings, although this remains an empirical question to be tested. Combining this 47% false-positive rate of individuals diagnosed by clinicians as compared to the experts *with* the baseline expert-diagnosed false-positive rate of 84% in this sample yields a total false-positive rate for the psychosis risk syndrome diagnosed by clinicians of 91% in this one study i.e. 47% plus 84% of the remaining 53% yields 91%. This is an illustrative example of the potential combined effects of the two false-positive rates, though these actual numbers are study-specific and should not be generalized to the issue at large.

It is likely that this high false-positive rate is due largely to the inherent difficulty in distinguishing between attenuated positive symptoms and the normal range of thoughts, speech, and behavior characteristic of adolescents and young adults transitioning through a challenging phase of life. The examples of "mild" but yet still qualifying attenuated positive symptoms presented in the proposed accompanying descriptive text illustrate the challenges inherent to making this distinction. For attenuated hallucinations, examples include unformed altered perceptions "e.g., shadows, trails, halos, murmurs, rumbling". Attenuated delusions are described in the text as including unusual ideas and overvalued beliefs which can have a range of content, including perplexity, nihilism, philosophy, magic, suspiciousness and grandiosity. The text goes on to describe mild suspiciousness as "notions that people are untrustworthy" and mild grandiosity as "notions of being gifted, influential or special." Similarly, in its discussion of mild forms of thought disorder, the text offers the following illustrative example: "the patient frequently gets into irrelevant topics but responds easily to occasional clarifying questions." The only provision in the proposed criteria set for distinguishing normal variations from prodromal symptoms is the requirement that the symptoms must be "of sufficient severity and/or frequency as to be beyond normal variation" (Criterion A) and that they "are sufficiently distressing and/or disabling to the patient and/or others to lead to help-seeking" (Criterion D). The problem is that neither of these requirements actually serves to differentiate "normal" from "abnormal." Although being "distressing" to the person is likely an indicator of abnormality in that it suggests that the phenomenon is ego-dystonic and thus similar to typical symptomatic presentations, the offered alternative of being distressing to others opens the door to pathologizing eccentric or creative behavior that is not understood or appreciated by parents, teachers and others who may be more conventional or strait-laced based on transgenerational or cultural differences.

Another contributing factor to the false-positive rate in the community, beyond the challenges involved in making an accurate and reliable diagnosis on the boundary with normality, are differences in the nature of the base population from which patients are ascertained. The false-positive rates in research settings come from assessments of clinical populations in which patients are referred for evaluation because of a suspicion that they might be at risk for psychosis and thus would be expected to have relatively high base rates of a risk for psychosis. Outside of these research settings, however, it can be expected that the base rate is going to be considerably lower, closer to community prevalence rates estimated to be less than 1%. For example, in the Melbourne study discussed above, only 16% of those individuals designated at risk by experts actually went on to develop the disorder, which the authors attribute to low prevalence of the psychosis risk syndrome in a general adolescent clinical population (Yung et al., 2008).

High false-positive rates in and of themselves are not necessarily problematic if the risk–benefit ratio is significantly favorable. For example, although the Framingham Heart Study showed that most individuals with mild hypertension or elevated total cholesterol do not develop coronary heart disease (Wilson et al., 1998), screening for these risk factors is widely accepted and promoted given that the potential benefits of early intervention are high and there is relatively little risk associated with the recommended interventions, in this case instituting lifestyle changes and administration of statins and/or antihypertensive agents. However, as we will discuss in the following sections, the risk–benefit ratio for the psychosis risk syndrome is far from favorable given the high risks for stigma (and potential resultant discrimination) and for unnecessary exposure to antipsychotic medications, and the low benefits resulting from case identification given the lack of a clear evidence base for effective interventions.

5.2. Stigma

For serious mental illness, the label of mental disorder is typically associated with undesirable characteristics, such that individuals with this label are stereotyped in a negative way (Link et al., 1989). When these associated characteristics are particularly alien or frightening, as with the labels of psychosis or schizophrenia, the labeled individuals are then seen as "not us". The consequences for individuals with a particularly stigmatizing label include internalized stigma (individuals see themselves as bad, defective, or unworthy), identity engulfment (individuals see the illness as a defining aspect of who they are, instead of as something they have), shame (the label is kept secret and concealed from others), and discrimination on the part of others, expressed as devaluation or unfair treatment (Link and Phelan, 2001).

It is an empirical question as to whether this same dynamic will exist for the psychosis risk syndrome (Corcoran et al., 2005; Yang et al., 2010-this issue). Although research has shown that families of "prodromal" patients endorse minimal "associative" stigma, and attribute this stigma more to symptoms and behaviors than to the label of risk (Wong et al., 2009), there are no corresponding data regarding the experience of stigma by patients themselves. However, it is likely that knowing that one is at risk to develop a disabling and incurable psychotic disorder would have an impact on how the person views himself and plans for the future, including career and family. Similarly,

based on current practices by the insurance industry with other disorders and risk syndromes, the impact of the identification of a risk for psychosis on future insurability (especially for life or disability insurance) is likely to be negative.

5.3. Unnecessary exposure to antipsychotics

Prescribing patterns of psychiatrists worldwide suggest that antipsychotics will be used to treat the psychosis risk syndrome, despite the absence of a clear evidence base to do so and the prevalent adverse effects of weight gain (up to 8.8 kg) (McGlashan et al., 2006) and motor abnormalities (i.e. treatment-emergent akathisia in 8/15 patients receiving aripiprazole) (Woods et al., 2007) documented in clinical trials of putatively prodromal cohorts. The push to do so may come not only from the pharmaceutical industry but also from a fear of liability were a patient with the risk syndrome to develop psychosis and incur or cause injury, especially in the absence of any known alternative treatments. Further, as little or nothing is known about the long-term outcomes in individuals identified as at risk for psychosis, these young people may be prescribed antipsychotics indefinitely. This is particularly concerning, given that antipsychotic medications can pose significant risk to cardiovascular and general health.

6. What we propose

Given the likely high false-positive rate combined with the unfavorable risk–benefit ratio, our view is that it would be premature to include the psychosis risk syndrome as an official category in the DSM-V, either as a disorder or as part of a new risk syndrome section. We recommend instead that the psychosis risk syndrome be considered for inclusion within the appendix for "Criteria sets and axes provided for further study." This would further the main potential benefit of its inclusion in DSM-V, namely the encouragement of attention to an important clinical problem and the provision of a standardized definition for research. Below, we outline a research agenda which we believe will advance our understanding of the psychosis risk syndrome, with the expectation that it may be considered for inclusion in a future edition of the DSM if supported by additional findings.

6.1. Improve the predictive value of the psychosis risk designation through identifying biomarkers

The main problem with the current psychosis risk designation is that it as yet remains poorly defined, with unclear validity, and limited specificity, which is not surprising as it has been the focus of research for only a decade or so. We do not know yet how to determine different levels or quantity of risk, or how to differentiate risk for psychosis broadly from that for schizophrenia spectrum disorders. As it stands, the identification of individuals as at risk for psychosis depends solely on behavioral indices of signs, symptoms and clinical history. There is a need to identify and better characterize other predictors of psychosis, including neuropsychological deficits (Brewer et al., 2005; Lencz et al., 2006), impaired social skills and early role functioning (Cornblatt et al., 2003) and putative biomarkers of psychosis risk from neuroimaging (Schobel et al., 2009), studied separately and in combination (Lieberman & Corcoran, 2007).

6.2. Develop safe and effective interventions to prevent psychosis and improve current morbidity

Another focus of research efforts should concentrate on intervention for the psychosis risk syndrome, both in terms of treatment of current morbidity and functional impairment, and preventive intervention to forestall the onset of psychotic disorder. As yet there is no clear evidence base, and there have been only a handful of clinical trials which are promising but not conclusive, comprising not only antipsychotics (McGorry et al., 2002), which are sometimes associated with significant side effects (McGlashan et al., 2006; Woods et al., 2007), but also general neuroprotective strategies with antidepressants (Cornblatt et al., 2007), omega fatty acids (Amminger et al., 2007, 2010) and psychological treatments such as cognitive behavioral therapy (McGorry et al., 2002; Morrison et al., 2004). Treatments evaluated in clinical trials should be guided by advances in our understanding of the pathophysiological mechanisms of evolution of psychosis in a developmental context, informed by the identification of biological markers of risk and illness progression which can themselves also enhance predictive value of the risk designation.

6.3. Develop appropriate services for the identification and treatment of individuals at risk

Finally, much remains to be learned about the optimal delivery of services such that individuals can be ascertained and receive appropriate treatment, with minimization of adverse effects related to stigma and structural discrimination, including forensic issues, insurability, housing and employment (Lieberman & Corcoran, 2007).

7. Conclusion

In summary, the nascent field of prodromal or clinical high risk research offers great promise in terms of our understanding of the risk for developing psychotic disorders such as schizophrenia, and much work remains to be done to characterize and improve the positive predictive value of this risk syndrome, and to develop effective interventions and services. We believe that it is premature to include the psychosis risk syndrome in the main body of the DSM given the expected high false-positive rate and the unfavorable risk–benefit ratio associated with this syndrome. Our recommendation is that the syndrome be listed in an appendix of DSM-V as a provisional syndrome in need of further research.

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Contributors

Cheryl Corcoran, with significant input from Michael First, wrote the first and subsequent drafts of this manuscript. Barbara Cornblatt provided conceptual input, feedback and editing of the manuscript.

Conflict of interest

Dr. Corcoran and Dr. Cornblatt do not have any actual or potential conflicts of interest. Dr. First consults with pharmaceutical companies to provide diagnostic training for clinical trials and receives book royalties from APPI and Wiley-Blackwell. In the past 12 months, he has consulted with Cephalon, GlaxoSmithKline, Memory Pharmaceuticals, Worldwide Clinical Trials, and i3 research.

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