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Attenuated psychosis syndrome in DSM-5

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ABSTRACT

Despite advances in the treatment of schizophrenia over the past half-century, the illness is frequently associated with a poor outcome. This is principally related to the late identification and intervention in the course of the illness by which time patients have experienced a substantial amount of socio-occupational decline that can be difficult to reverse. The emphasis has therefore shifted to defining psychosis-risk syndromes and evaluating treatments that can prevent transition to psychosis in these ultra-high risk groups. To consider the appropriateness of adding psychosis risk syndrome to our diagnostic nomenclature, the psychotic disorders work group extensively reviewed all available data, consulted a range of experts, and carefully considered the variety of expert and public comments on the topic. It was clear that reliable methods were available to define a syndrome characterized by sub-threshold psychotic symptoms (in severity or duration) and which was associated with a very significant increase in the risk of development of a full-fledged psychotic disorder (schizophrenia spectrum, psychotic mood disorder, and other psychotic disorders) within the next year. At the same time, the majority of individuals with "attenuated psychotic symptoms" had one or more other current psychiatric comorbid conditions (usually mood or anxiety disorders, substance use disorder; Fusar-Poli 2012) and exhibited a range of psychiatric outcomes other than conversion to psychosis (significant proportions either fully recover or develop some other psychiatric disorder, with a minority developing a psychotic disorder). Although the reliability of the diagnosis is well established in academic and research settings, it was found to be less so in community and other clinical settings. Furthermore, the nosological relationship of attenuated psychosis syndrome (APS) to schizotypal personality disorder and other psychiatric conditions was unclear. Further study will hopefully resolve these questions. The work group decided to recommend the inclusion of attenuated psychosis syndrome as a category in the appendix (Section 3) of DSM-5 as a condition for further study.

1. Introduction

Despite therapeutic advances over the past half-century, schizophrenia continues to be a debilitating disorder with profound lifelong impairments in social and vocational functioning for most of those

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with the condition (Cornblatt et al. 2007). Much of the decline occurs early in the course of the illness, and overall outcome is directly correlated with functional ability prior to onset of psychosis and inversely correlated with duration of untreated psychosis (Carpenter, 2009; Woods et al., 2010; Boonstra et al., 2012). These facts have provided the impetus to early intervention efforts. Reducing treatment delay from the onset of the initial psychotic episode by early diagnosis and effective treatment has yielded only modest improvements in outcome for individuals with schizophrenia, however, leading to interest in possibilities for intervention even earlier in the course of the illness (i.e., before onset of psychosis; Fusar-Poli et al., 2013). This knowledge has led to interest from several centers, including the North American Prodromal Longitudinal Study (NAPLS, Cannon et al. 2007; Addington et al., 2007), in developing early psychosis detection, intervention, and treatment programs.

In order to address this need and in light of improvements in outcome observed in various early psychosis intervention programs, the psychotic disorders work group considered the addition in DSM-5 of a new category of "psychosis risk syndrome" or "attenuated psychosis syndrome" to describe a condition with recent onset of modest, psychotic-like symptoms and clinically relevant distress and disability. These patients also are at significantly increased risk of conversion to a full-blown psychotic disorder (Fusar-Poli et al., 2012a, 2012b, 2012c, 2012d, 2012e). Based on a review of the data relatively early in the process, it was realized that it may be premature to recommend a new category primarily based on future risk (i.e., "psychosis risk syndrome") and not on current clinical need (Carpenter and van Os, 2011; Tandon and Carpenter, 2012). Data revealed that a majority of individuals with this condition did *not* go on to develop a psychotic disorder and that most individuals with this condition had additional relevant clinical needs other than the risk of conversion to psychosis. Consequently, a condition that described current clinical need – attenuated psychosis syndrome (APS) – was considered instead. In contrast to "psychosis risk syndrome," APS describes a currently relevant clinical condition leading to help seeking, with many more clinical outcomes other than conversion to psychosis. The main considerations with respect to APS involved matters of reliability of diagnosis in routine clinical settings and whether it had more validity and provided greater clinical utility than current classification systems (Woods et al. 2009; Carpenter and van Os, 2011; Tandon and Carpenter, 2012). The relationship of APS to related diagnostic categories such as schizotypal personality disorder was also evaluated. In addition to reviewing all available data, the psychotic disorders work group consulted a range of experts and considered a variety of public and expert comments on the topic.

2. Proposed clinical criteria for APS

A. At least one of the following symptoms is present in attenuated form with sufficient severity and/or frequency to warrant clinical attention:

1. delusions/delusional ideas
2. hallucinations/perceptional abnormalities
3. disorganized speech/communication

B. Symptoms in Criterion A must be present at least once per week for the past month.
C. Symptoms in Criterion A must have begun or worsened in the past year.
D. Symptoms in Criterion A are sufficiently distressing and disabling to the individual and/or legal guardian to lead them to seek help.
E. Symptoms in Criterion A are not better explained by any other DSM-5 diagnosis, including substance-related disorders.
F. Clinical criteria for a psychotic disorder have never been met (McGlashan et al., 2010).

3. Rationale

3.1. Does the new diagnosis address a current unmet clinical need?

A vast majority of individuals who go on to develop schizophrenia or other psychotic disorder exhibit a range of psychiatric symptoms in the period prior to their initial psychotic episode. During this period, many such individuals experience decline in their academic-occupational and other aspects of social functioning that are difficult to reverse when they seek treatment after onset of the psychotic disorder (Tandon and Maj, 2008). Currently, there is no diagnostic category to define individuals who are experiencing such psychopathology and are at significantly higher risk for developing schizophrenia or other psychotic disorders. This proposed disorder category is intended for use when there is no existing diagnostic category to better define individuals who are experiencing such psychopathology and are at significantly higher risk for developing schizophrenia or other psychotic disorders. For example, the recent onset and transitory criteria preclude a diagnosis of schizotypal personality diagnosis, and the sub-threshold manifestations of psychosis-like symptoms do not meet criteria for a full psychotic disorder. The current lack of an appropriate diagnosis in DSM-5 prevents such individuals from obtaining appropriate clinical attention that might provide current relief and possibly prevent future adverse psychiatric outcomes. Several groups around the world have devised diagnostic criteria and assessment tools (Miller et al., 2002, 2003; Yung et al., 2005) to reliably identify such "ultra-high risk" individuals who have a significantly greater likelihood than the general population of developing a psychotic disorder over the next two and a half years (Cannon et al., 2008). In general, it appears that about 1/3 of ultra high risk (UHR) cases convert to psychosis (Gee and Cannon, 2011; Fusar-Poli et al., 2012a). Although a range of interventions (including careful observation and monitoring) appear to be effective in reducing rates of conversion to psychosis, they are as yet inadequately differentiated. Close follow-up is important and should include assessment for conversion to psychosis as also assessment for development or persistence of other psychiatric conditions and provision of appropriate treatment.

3.2. Prevalence in epidemiological samples

Relatively little is known about the prevalence of individuals with attenuated psychotic symptoms in the general population. Meta-analyses suggest that the prevalence of individuals with attenuated psychotic symptoms (which is not the same as APS where help seeking behaviors are sought) in the general population is around 5% (Linscott and van Os, 2012); only a small proportion of these seek help with mental health services and would be eligible for a diagnosis of APS, which is defined in terms of help-seeking and clinically relevant distress and dysfunction.

3.3. Information about reliability of proposed criteria

In research settings, the reliability of the proposed criteria is moderate before training (Cohen's kappa ranging from 0.3 to 0.5) and high after training (Cohen's kappa ranging from 0.75 to 0.90). Reliability data in general clinical settings are limited. The DSM-5 field trial provided too small a sample for an informative test of reliability (Regier et al., 2013).

4. Data on validity

4.1. Antecedent validity

Limited information is available in the published literature.

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4.2. Concurrent validity

4.2.1. Cognition

Two meta-analyses by Giuliano et al. (2012) and Fusar-Poli et al. (2012b) have been published. The latter (19 studies, 1188 high risk [HR] and 1029 controls) showed that HR subjects were impaired on tests of general intelligence, executive functions, verbal/visual memory, verbal fluency, attention and working memory and social cognition. Transition to psychosis was associated with deficits in the verbal fluency and memory domains.

4.2.2. Imaging

4.2.2.1. Neuroanatomy. Recent meta-analysis of voxel-based morphometry (VBM) studies (Pantelis et al., 2003; Fusar-Poli et al., 2012c) are consistent with findings of the largest multicenter VBM structural study by Mechelli et al. (2011) in 182 HR and 167 controls, showing that the HR group as a whole had less gray matter volume than did controls in the frontal regions. The HR who later developed psychosis had less gray matter volume in the parahippocampal cortex than the HR subgroup who did not convert.

4.2.2.2. Neurochemistry. Howes et al. (2009, 2011) showed an association between elevation of pre-synaptic dopamine synthesis capacity and transition to psychosis. Multimodal fMRI-PET and fMRI-MRS data also provide support for the validity of an HR diagnosis (Fusar-Poli et al., 2010, 2011).

5. Predictive validity

5.1. Outcomes

5.1.1. Transition risks

A meta-analysis in 27 high risk [HR (at-risk mental states, APS)] studies (Fusar-Poli et al., 2012a), relating to 2502 HR subjects showed the following rates of conversion to psychosis:

18% [95% confidence interval (CI), 12.3%–24.9%] after 6 months of follow-up,
22% (95% CI, 16.6%–27.8%) after 1 year,
29% (95% CI, 23.3%–35.7%) after 2 years, and
36% (95% CI, 29.6%–42.5%) after 3 years.

These risks of developing a psychotic disorder summed across available studies are substantially greater than in the general population—22% at 1 year follow-up compared to a 0.015% annual incidence of schizophrenia (Tandon et al., 2008; Fusar-Poli et al., 2012a). The risk is moderated by increasing the age of HR subjects, a modest but significant effect towards declining transition risks in the most recent published papers and the effects of treatment (Yung et al., 2007).

5.1.2. Diagnostic outcomes

In a meta-analysis of studies in which specific diagnostic outcomes were noted for HR individuals who transitioned to psychosis [$n = 560$ high risk for psychosis (HRP) with transition to psychosis], 73% converted to schizophrenia spectrum disorders (schizophrenia, schizophreniform, schizoaffective) and 11% psychotic mood disorders affective (psychotic depression, bipolar psychosis) (Relative Risk = 5.4) (Fusar-Poli et al., 2012d).

5.1.3. Remission

A systematic review (Simon et al., 2011) uncovering six studies reported remission rates from initial HR status (proportion of remissions ranged from 15.4% to 54.3%).

5.2. Interventions

Controlled clinical trials testing efficacy of various interventions are sparse and of small sample size, with control groups frequently receiving treatment that may be effective. A recent review of seven studies with several different therapeutic approaches suggested that the experimental treatment was superior to usual treatment in prevention of progression to full psychosis, with a transition rate average across studies of 7.6% for experimental treatment and 23% for usual treatment (Fusar-Poli et al., 2013). The most provocative individual study was a random assignment placebo controlled study in which 12 weeks of omega-3 fatty acids was robustly superior to placebo in preventing psychosis over the next 40 weeks, though this single study requires replication (Amminger et al., 2010). There are mixed results with regard to the effectiveness of CBT in preventing transition of the HR state to psychosis (Morrison et al., 2012; van der Gaag et al., 2012).

6. Recommendations of work group

Based on the evidence above, several experts advocated inclusion of APS in the main body of the DSM-5 diagnostic manual (Woods et al., 2010), whereas others suggested that it should be broadened to a general early syndrome of significant psychopathology in line with the staging model of psychopathology (McGorry and van Os, 2013). There was a uniform consensus among the experts that attenuated psychosis syndrome is a condition that warrants systematic attention (Yung et al., 2012), although experts disagreed as to whether this diagnosis should be placed in the main body of the diagnostic manual or whether it should be placed in the appendix (Section 3) as a condition for further systematic study (Corcoran et al., 2010; Drake and Lewis, 2010; Woods et al., 2010; Carpenter and van Os, 2011; Tandon et al., 2012). The work group believed that one fundamental question was whether APS would be reliably diagnosed by non-experts in ordinary clinical settings. Without field trial data supporting reliability (Regier et al., 2013), it was clear that APS would not be considered further for the main text (Tandon and Carpenter, 2013). If the field trials had been adequate and supportive of reliability, an interesting debate would have commenced as to whether to recommend that APS be included in the main text, Section 3, or to make no recommendation for inclusion. Five principal areas of debates put forth by the experts who recommend inclusion of APS in the appendix instead of the main body of the diagnostic manual were:

- A majority of individuals with current APS have some other current psychiatric comorbidity (frequently depressive, anxiety, or substance use disorder; Fusar-Poli et al., 2012a, 2012b, 2012c, 2012d, 2012e), which warrants appropriate treatment at the current time. The alternative view is that these symptoms are common in many disorders including psychotic disorders, merit clinical attention, but are not established as the basic disorder in research to date relevant to APS.
- A substantial proportion of individuals with APS do not go on to develop major psychopathology. Whereas conversion to schizophrenia or other full-blown psychosis is one possible outcome of APS, this occurs in a minority of persons. The alternative view is that many of the patients continue to have symptoms and functional impairments that merit attention (Addington et al., 2011), and that the value of identifying APS is not only determined by subsequent transition to psychosis, although secondary prevention of full psychosis is a desirable effect as well.
- It is unclear if APS represents a trait or state vulnerability (for ncreased risk of development of a psychotic disorder) and its relationship to schizotypal personality disorder is not clear. This is countered by noting that the criteria for APS focus on state phenomena, and that individual for whom APS is an appropriate diagnosis do not meet trait requirements for a diagnosis of schizotypal

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personality disorder. Further, many individuals with schizotypal personality disorder do not progress to schizophrenia or a related full psychosis, though rates of progression may be higher in young persons with schizotypal personality disorder.

- ➢ It is unclear if the distress and/or disability resulting in help-seeking behavior by this group of individuals is related to APS or the "comorbid" mental disorder; help seeking is part of its definition in DSM-5. The counter-argument is that the APS criteria require that distress, dysfunction, and/or impairment be related to the symptom criteria. This does not exclude anxiety or depression from contributing to help seeking, but these would be judged to be associated or secondary features, not a disorder that accounts for the full clinical presentation. If anxiety, for example, is considered co-morbid, the question remains as to co-morbid with what? APS would be the proposed answer.
- ➢ There was concern about potential stigma and inappropriate antipsychotic utilization in individuals with APS (Woods et al., 2012). The counter-argument was that a new APS category will educate clinicians about the relative lack of utility of antipsychotic medications in this population (Stafford et al., 2013) and may actually reduce inappropriate antipsychotic use among youth. Furthermore, any stigma is principally related to behaviors associated with a diagnosis of APS rather than the diagnosis itself; thus, an APS category might lead to a reduction in traumatic experiences (Addington et al., 2013).

Despite the validating evidence in research to date (Fusar-Poli et al., 2013), the failed reliability field trials precluded further consideration for inclusion as a new disorder in the main text. Studies to date have been organized around the concept of the schizophrenia prodrome and results support APS as currently defined to be part of a schizophrenia spectrum disorder. It is expected that future studies that include risk or prodromal features of other disorders associated with psychosis may broaden the definition and change the proportion of transition cases that belong in the schizophrenia spectrum.

The work group determined that more work was necessary before APS could be considered for inclusion in the main body of DSM (Yung et al., 2012). From a clinical point of view, immediate needs include the following:

(i) knowledge on how APS works in ordinary clinical settings in terms of reliability and predictive utility;
(ii) at what stage in the development of APS related pathology is it optimal to define a disorder; and
(iii) whether a disorder, so defined, enhances the acquisition of therapeutic knowledge.

The work group concluded that there were strong reasons to continue to evaluate this clinical entity and provision of specific criteria and description would help in this effort. Furthermore, it was also recognized that early detection and intervention is a high value throughout medicine, and that secondary prevention of full psychosis may offer substantial life course benefits. It seems likely that psychiatry will move in this direction with a number of disorders in the future. For reasons reviewed above, APS is being assigned to Section 3 for further study.

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COI statement

The authors have declared all relevant conflicts of interest regarding their work on the DSM-5 psychotic disorders work group to the APA on an annual basis. The complete details are posted on the public Web site http://www.dsm5.org/MeetUs/Pages/PsychoticDisorders.aspx.

We will provide an update of this detailed statement to the editor when all of the manuscripts submitted for a special section on DSM-5 in *Schizophrenia Research* are complete.

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