DSM-5: ATTENUATED PSYCHOSIS SYNDROME?

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Psychotic syndrome includes several devastating mental disorders characterized by a rupture of higher mental functions. The signs and symptoms of psychosis begin in adolescence or early adulthood and usually begin gradually and progress over time. Attenuated psychosis syndrome is a new DSM-5 diagnostic proposal which deals with identifying people at high-risk mental state (ARMS/UHR) which may be a predictor of conversion to psychosis. The potential benefit would be that if psychotic disorder is treated more effectively in its early stages, it could produce a lasting beneficial effect that probably could not be achieved with later intervention. This syndrome has generated intense discussion in specialized scientific and professional forums, crisscrossing arguments in favor and against its inclusion. HRMS is preferentially evaluated in the adolescent or young adult population. HRMS evolution is associated with a higher rate of transition toward nonaffective psychosis, although it can evolve toward other mental disorders, remain stable or remit over time. Empirical evidence shows that early intervention seems to have a certain beneficial effect, although for now the results are still insufficient and contradictory. The lack of specificity of symptoms in predicting psychosis, presence of certain limitations (e.g., stigmatization), results found in early interventions and lack of empirical evidence, have led to include the attenuated psychosis syndrome in the DSM-5 Appendix III. The main benefits and limitations of including this supposed category, possible lessons learned from this type of study and future lines of action are discussed in the light of these findings.
Key words: Psychos, Risk, Schizophrenia, Vulnerability, Evaluation.

El síndrome psicótico aglutina un conjunto de trastornos mentales devastadores que se caracterizan por una ruptura de las funciones mentales superiores. Los signos y síntomas de psicosis comienzan en la adolescencia o temprana adultez y suelen tener un inicio gradual y progresivo en el tiempo. El Síndrome de psicosis atenuada es una nueva propuesta diagnóstica del DSM-V que trata de identificar a personas con un estado mental de alto riesgo (EMAR) que pueda ser predictor de transición a la psicosis. El beneficio potencial sería que si el trastorno psicótico es tratado con más eficacia en sus fases iniciales se podría producir un efecto beneficioso duradero que probablemente no se alcanzaría con intervenciones más tardías. Dicho síndrome ha generado un intenso debate en los foros científicos y profesionales especializados, esgrimiéndose argumentos a favor y en contra de su inclusión. La evaluación de los EMARs se realiza preferentemente en población de adolescentes o adultos jóvenes. La evolución de los EMARs se asocia a una mayor tasa de transición hacia psicosis no afectivas, si bien puede evolucionar hacia otro trastorno mental, mantenerse estable o remitir con el tiempo. La evidencia empírica indica que una intervención temprana parece tener un cierto efecto beneficioso, aunque los resultados son por el momento insuficientes y contradictorios. La falta de especificidad de los síntomas en la predicción de la psicosis, la presencia de ciertas limitaciones (p. ej., estigmatización), los resultados encontrados en las intervenciones tempranas y la falta de evidencia empírica, han llevado a incluir el Síndrome de psicosis atenuada en el apéndice III del DSM-V. A la luz de los hallazgos encontrados se comentan los principales beneficios y limitaciones de la inclusión de esta supuesta categoría, las posibles lecciones aprendidas de este tipo de estudios así como futuras líneas de actuación.
Palabras clave: Psicosis, Riesgo, Esquizofrenia, Vulnerabilidad, Evaluación.

The psychosis syndrome includes a series of devastating and disabling mental disorders characterized by rupture of higher mental functions. Psychotic disorders, such as schizophrenia, schizoaffective disorder, bipolar disorder and psychotic disorder induced by substances, affect about 2-3% of the population (Perälä et al., 2007). In particular, the prevalence and mean incidence estimated for schizophrenia is four persons per 1000 and 15.2 persons per 100,000, respectively (McGrath, Saha, Chant, and Welham, 2008). The onset of symptoms and signs of psychosis is usually in late adolescence or early adulthood and the disorder seems to be slightly more frequent in men than in women (ratio 1.4:1). The direct and indirect costs generated to both persons affected and their

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families, as well as health and social care are considerable. For example, it could be mentioned that: a) risk of death for any reason is two-to-three times higher in persons with schizophrenia (McGrath, et al., 2008) and die 12 to 15 years sooner than the population mean (Saha, Chant, and McGrath, 2007), and b) the estimated direct and indirect economic cost for schizophrenia and related disorders in Spain was 1,970 million Euros in 2002 (Oliva-Moreno, López-Bastida, Osuna-Guerrero, Montejo-González, and Duque-González, 2006). Based on these findings there is no doubt that any action taken for this syndrome is of the highest relevance. Mental disorders, like psychosis, must be, and in fact are beginning to be, one of the main lines of action within government policies in matters of mental health. Only a more logical comprehension of psychosis considering its complexity and heterogeneity will permit more efficient management of health-care and society resources.

The study of the psychotic phenotype is at a critical moment in the international scientific panorama (Linscott and van Os, 2013). Psychosis and its related disorders have been fully described by several different etiological models (Lemos Giráldez, Vallina Fernández, Fonseca Pedrero, Paino, and Fernández Iglesias, 2012; Tandon, Keshavan, and Nasrallah, 2008). Recently, van Os, Kenis, and Rutten (2010) proposed an interesting psychosis phenotype model which could be summarized in the following points:

a) The psychosis syndrome includes four intercorrelated dimensions: Affective dysregulation, characterized by impairment of affect, and symptoms of depression, mania and anxiety are also found. Psychosis, characterized by hallucinatory experiences and delusional ideation. Negative, characterized, among others, by physical and social anhedonia, avolition, and affective flattening. Cognitive, characterized by information processing deficit such as alterations of memory, attention and/or executive functions. These four dimensions are rather congruent with those formulated in the DSM-5 (Tandon et al., 2013) and with those found in empirical studies of patients with psychosis (Reininghaus, Priebe, and Bentall, 2013) and completely cover the symptomatic heterogeneity found in clinical practice and research. The fact is that other facets could have been considered, such as cognitive disorganization or psychomotor alterations.

b) The psychosis phenotype is distributed over a psychopathological continuum of severity. The symptoms and signs of psychosis may be found in both general and clinical populations. People could be located at some point on this extended psychosis phenotype continuum limited by poles of "normality" and "illness". In this sense, people who are near the severity end (psychosis) would possibly have a higher probability of surpassing the clinical threshold, of coming into contact with the health-care systems, as well as greater associated disability and need for treatment. In this model, attenuated psychotic experiences, below the clinical threshold and distributed normally in the general population, would be considered the behavioral expression of latent vulnerability to psychosis. About 10-20% of the general population would theoretically be at risk of moving toward a psychotic syndrome (Linscott and van Os, 2013; van Os, Linscott, Myin-Germeys, Delespaul, and Krabbendam, 2009). This assumption of continuity is coherent with a dimensional evaluation of psychosis symptoms and signs (Barch et al., 2013) which improves acquisition of evidence of validity and reliability of measures (Markon, Chmielewski, and Miller, 2011). It also enables study of such symptoms in the general population and their relationship with risk and protection factors for implementing early detection and intervention strategies.

c) The extent of comorbidity or overlapping of such dimensions varies depending on the place the person occupies on the continuum. As the psychosis phenotype goes from subclinical to clinical, these facets would overlap more. For example, overlapping of negative affective dysregulation would be greater in the clinical population than in the nonclinical population (or in persons in whom it is more severe but still below the clinical threshold). This is congruent with results found in samples of the general, high-risk and psychotic patient populations (Links and Eynan, 2013; Linscott and van Os, 2010; Salokangas et al., 2012).

d) The configuration and interrelationships of the four dimensions may lead to different nosological entities. For example, see the case of a patient in whom the affective dysregulation (mania) and psychosis were more strongly represented or had more weight, comparatively speaking, than the cognitive or negative dimensions (van Os and Kapur, 2009). In this case, and depending on the severity, the level, the number and duration of symptoms and signs, a bipolar disorder might be diagnosed (Heckers et al., 2013).

e) It gives priority to the interaction between genetic and environmental factors in explaining severity and the probability of becoming clinical disorder. The close connection between genetic and environmental factors,

whether in the form of trauma, stress, use of cannabis, virus during pregnancy or obstetric complications, is known in psychosis vulnerability models (Beards et al., 2013; Myin-Germeys and van Os, 2007; Tandon et al., 2008; van Os et al., 2010; Zubin and Spring, 1977). The interface established between environmental and genetic factors is of the highest transcendence in understanding the etiopathogenesis of the psychosis syndrome. The Gene-x-Environment interaction combined with the presence of other factors, such as for example, the occurrence, intensity and persistence of psychosis experiences, as well as comorbidity or associated social dysfunction would explain the transition to the clinical outcome (Kaymaz et al., 2012).

The psychosis syndrome shows an evolutionary course in a series of differentiated stages. Classic retrospective studies by Hafner and An der Heiden (1999) found that 73% of cases began with unspecific prodromal or negative symptoms, 20% began with positive, negative or unspecific symptoms, and only 7% began only with positive symptoms. It was also observed that most patients had a form of chronic onset, with a prodromal stage lasting five years, and already clearly psychotic evolution of over one year before the first admission. Simply, 18% of cases presented a brusque or acute form of onset, with one month of evolution of symptomology. More recent prospective studies also seem to show the existence of a period of previous progression immediately after the first episode (Fusar-Poli, Bonoldi, et al., 2012; Fusar-Poli, Borgwardt, et al., 2012; Lemos-Giráldez et al., 2009; Ruhrmann, et al., 2010; Woods et al., 2009). This phase seems to be followed by a period of around two to five years in which the patients remain relatively stable. Results seem to suggest that the first three years of the illness (treated or not) provide an extraordinary occasion for being able to impede or limit the usual potential decline of psychoses by intervening early and thus possibly achieving better recovery of the disorder (Vallina, 2003; Vallina, Lemos Giráldez, and Fernández, 2006; Vallina, Lemos Giráldez, and Fernández, 2012).

Before formal diagnosis of the clinical disorder, nonspecific changes to a multitude of spheres may be found that could be considered the entrance or doorway to the psychosis syndrome. It is true that for now there are no specific pathognomonic markers (biological, psychological or clinical) available showing whether frank psychosis is present or not. We mention a few prodromes of psychosis here as examples (Lemos, Giráldez, 2012): reduced attention and concentration, depressed mood, sleep disturbance, anxiety, social withdrawal, suspiciousness, deterioration in role functioning, aggressiveness. Late premorbid changes may also be found before the psychotic episode, such as (Lemos Giraldez, 2012): affective (e.g., depression, anxiety, mood swings, tenseness, distrust, irritability, anger), cognitive (e.g., bizarre ideas, vagueness, concentration, and memory problems), in perception of sense of self, others and the world, and psychophysiological (e.g., sleep disorders, poor appetite, somatic complaints, loss of drive or motivation). At present, and as mentioned below, the concept of the prodrome is being replaced by "At Risk Mental States (ARMS) (Yung and McGorry, 1996; Yung et al., 2012). The first is inevitably associated with a psychotic disorder and is more strongly emphasized in retrospective assessments. On the other hand, the second is considered a risk factor for development of psychosis, and places more emphasis on longitudinal follow-up of signs and symptoms, where manifestations do not necessarily become clinical.

THE PSYCHOTIC PHENOTYPE IN THE GENERAL POPULATION AND CLINICAL-PATHOLOGICAL SIGNIFICANCE OF PSYCHOTIC EXPERIENCES

Symptoms of psychosis, such as magical thinking, hallucinatory experiences and/or delusional ideation, can be found present in the general population, below the clinical threshold, and without being associated necessarily with a mental disorder or need for treatment. Epidemiological studies show that about 5-8% of the general population reports some psychotic experience (Linscott and van Os, 2013; Nuevo et al., 2012; van Os et al., 2009). For example, a recent meta-analysis carried out by Linscott and van Os (2013) found 7.2% prevalence and 2.5% mean annual incidence. This meta-analysis identified risk factors predicting psychotic experience: age, income, education, use of cannabis, use of alcohol, employment, marital status, migrant status or minority, urbanicity, stress, and family history of mental illness. These risk factors are similar to those found in patients with psychosis, and lend validity to this construct, as well as support to the assumed continuity between the subclinical and clinical psychosis phenotype (Kelleher and Cannon, 2011). In the adolescent population, the prevalence rates are slightly higher than in adults, reaching figures of 30% and over (Barragan, Laurens, Navarro, and Obiols, 2011; Fonseca-Pedrero, Santarén-Rosell, Paino, and Lemos Giraldez, 2013; Kelleher, Keeley, et al., 2012; Wigman et al., 2011). For example,

Kelleher et al., (2012) conducted a meta-analysis in this population, finding mean prevalence rates of around 17% in children from 9 to 12 years of age and 7.5% in adolescents from 13 to 18.

Independent longitudinal studies show that the healthy participants who report such experiences have a higher future risk of moving to a psychotic disorder (Dominguez, Wichers, Lieb, Wittchen, and van Os, 2011; Gooding, Tallent, and Matts, 2005; Kaymaz et al., 2012; Poulton et al., 2000; Welham et al., 2009; Werbeloff et al., 2012; Zammit et al., 2013). In a recent meta-analysis done by Kaymaz et al. (2012), it was found that individuals who reported subthreshold psychotic experiences was 3.5 times higher than for individuals without psychotic experiences (0.16%) and there was meta-analytic evidence of dose-response with severity/persistence of psychotic experiences. In another follow-up study done by Zammit et al. (2013), in a sample of 4724 participants and evaluated by structured interviews, they found that adolescents who at 12 years of age had had definitive psychotic experiences, were at greater risk of psychotic disorders at age 18 (Odds Ratio: 12.7; CI 95%: 6.2-26.1). However, it is equally true that new studies show the low specificity of such experiences, and that their evolution not only is circumscribed to the clinical diagnosis of psychosis, but also other mental disorders (e.g., posttraumatic stress syndrome or attempted suicide) (Fisher et al., 2013; Rössler et al., 2011), questioned its usefulness as a clinical predictor (Werbeloff et al., 2012). In this sense, it is postulated that this set of experiences present at early ages could be useful as more general markers of mental health problems as adults (Fisher et al., 2013).

Furthermore, individuals who report this set of experiences also usually show subtle emotional, behavioral, psychophysiological, neurocognitive and/or social impairments (Fonseca-Pedrero, Paino, et al., 2011; Horan, Blanchard, Clark, and Green, 2008; Kwapil, Barrantes Vidal, and Silvia, 2008; Lenzenweger, 2010; Raine, 2006) similar to those found in patients with schizophrenia and schizotypal personality disorder. When a schizophrenic patient's healthy family members were analyzed, attenuated psychotic and schizotypal experiences were also a predictive factor (Shah et al., 2012). In this sense, as mentioned, and considering the data all together, attenuated psychotic experiences would represent latent vulnerability to psychosis and could be considered an exophenotype risk marker for study of this set of syndromes (van Os et al., 2009). Table 1 summarizes some of the main findings in the literature referring to subclinical psychotic experiences.

An interesting question is what if all the psychotic experiences have identical clinical significance or if, on the contrary, some specific set of them could have a different psychopathological meaning, and therefore, different implications for prognosis and intervention. This could also be of interest for drawing possible evolutionary trajectories in a propensity-persistence-disability model (van Os et al., 2009). When considering this set of experiences, not only their number and frequency should be kept in mind, but also other factors, such as the associated degree of worry, conviction and distress, to name a few (Preti, Cella, Raballo, and Vellante, 2012). In this sense, if the associated levels of severity and distress are considered, the architecture of the psychosis phenotype could be sketched in the shape of a pyramid with different degrees (Yung et al., 2007). As may be observed in Figure 1, the first level, Level 0, would be absence of such experiences. In continuation, would be psychotic-like experiences unassociated with any distress or experiences that are not distressful but related to another psychopathological syndrome. On Level 3 would be experiences with clearly psychopathological involvement associated with clinical distress and seeking treatment. Finally, on the last two levels would be the signs and symptoms of psychosis, and therefore, associated with greater severity and distress as well as clinically significant disability.

According to Nelson and Yung (2009), each of these levels of the psychosis phenotype architecture could have a different underlying involvement. On the first level,

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TABLE 1
KEY POINTS IN THE STUDY OF SUBCLINICAL PSYCHOTIC EXPERIENCES

Subclinical psychotic experiences

- ✔ They are distributed among the general population below the clinical threshold, and extend beyond the clinical phenotype.
- ✔ Mean annual prevalence is 7.5%, while mean annual incidence is 2%.
- ✔ More frequent in adolescence (prevalence 7.5-17%) than in adults
- ✔ Persistence rate is about 20-30% of cases
- ✔ They predict onset of later psychotic disorder (rate 0.5 per year), particularly if persistent
- ✔ Confluence of other associated factors (e.g., family members with psychosis, coping strategies, social functioning, affective impairment, etc.) is necessary for conversion to a clinical outcome.
- ✔ They are associated with the same risk factors found in patients with psychosis (e.g., young, low income, use of cannabis, childhood trauma, etc.).
- ✔ They can have different clinical-pathological significance and evolutionary paths

experiences would not be associated with clinical distress or need for care. This would be "happy schizotypy" (McCreery and Claridge, 2002). On a second level would be "incidental" experiences (Yung et al., 2009) in the form of clinical "noise", e.g., a person with attenuated positive symptoms who does not go into psychosis or a patient with depression who admits hearing voices that do not annoy him. On a third level, such experiences would be the expression of an underlying disorder, for example, a patient with a disorder of perception of the self as the agent of his own thoughts, experiences, actions, etc., and of the relationship of the self with the world.

ATTENUATED PSYCHOSIS SYNDROME

The attenuated psychosis syndrome has generated and continues generating a stimulating discussion in specialized scientific forums (Arango, 2011; Carpenter, 2009; Carpenter and van Os, 2011; Corcoran, First, and Cornblatt, 2010; Frances, 2010; Huesco, 2011; Obiols, 2012; Ruhrmann, Schultze-Lutter, and Klosterkötter, 2010; Tsuang et al, 2013; Woods, Walsh, Saksa, and McGlashan, 2010). This proposal is based on: a) certain signs and symptoms indicative of the risk of conversion to psychosis can be identified, and b) their early detection would enable specific intervention to be carried out to prevent conversion or diminish the possible impact of the clinical situation. In this sense, the results show that groups of persons at risk who show a higher probability of transition to psychosis can be identified. However, and as shown further below, these two points are not necessarily entirely true since, for the time being: a) a high percentage of the participants considered at high risk of psychosis do not necessarily develop a psychotic-like

FIGURE 1
ARCHITECTURE OF THE PSYCHOSIS PHENOTYPE, MODIFIED FROM YUNG ET AL. (2007)

disorder, and b) there is not enough empirical evidence related to the supposed beneficial effect of early intervention. In view of the above, at first, the DSM-5 psychotic disorders work group modified the diagnostic label from "psychosis risk syndrome" to "attenuated psychosis syndrome" or "attenuated psychotic symptoms syndrome" (curiously, the name was changed but the diagnostic criteria remained exactly the same), and later included it not in the main DSM-5 document, but in Appendix III (Tsuang et al., 2013).

Diagnostic criteria

The diagnostic criteria proposed by the DSM-5 psychotic disorders work group are discussed below:

A. Characteristic symptoms: 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/perceptual abnormalities
   3. Disorganized speech/communication
B. Duration and frequency: Symptoms in Criterion A must be present at least once per week for the past month.
C. Progression: Symptoms in Criterion A must have begun or worsened in the past year.
D. Clinical distress/dysfunction/seeks treatment: Symptoms of 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 mental disorder, including substance-related disorders.
F. Clinical criteria for a psychotic disorder have never been met.

It may be observed that the attenuated psychosis syndrome would be a polyhedral construct based on the descriptive psychopathology, specifically on the symptomology, frequency, duration, progression, associated distress (dysfunction or seeking treatment) and two exclusion criteria. From our point of view, this set of symptoms would be the intermediate phenotypic expression of a psychopathological continuum, with potential conversion to frank psychosis, although without definite risk of such progression. This entity is also founded on a paradigm shift based on a determinist approach rooted in well-established cause-effect relationships, to another with a probabilistic approach, based on the existence of true and false risk signs (prodromal). Therefore, its function would be rather early detection and would involve estimation of risk probability,
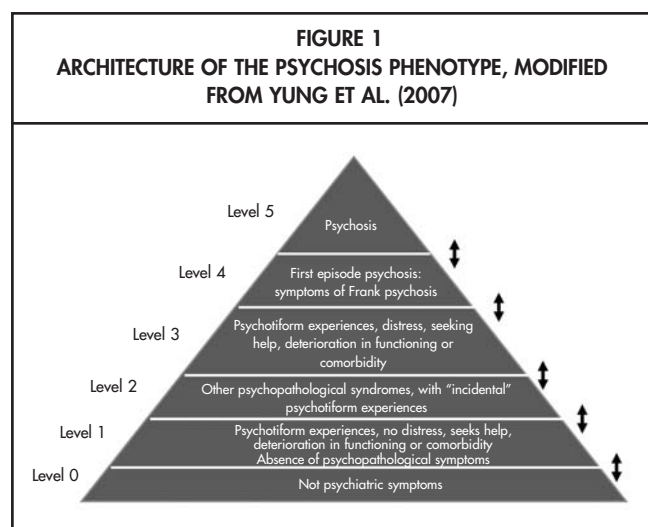
not necessarily an early diagnosis (Lemos Giráldez, 2012). For example, Table 2 presents a hypothetical case of attenuated psychosis syndrome. Such cases could serve, for example, for training clinicians and professionals not assigned to specialized research units.

The debate is served: pros and cons

Logically, the inclusion of such a nosological category in the DSM-V has generated an interesting debate, brandishing arguments in favor and against. Some of the explanations given by experts in the subject are described in continuation. Those who are in favor of developing and including this syndrome in the APA manual point out that: a) it could stimulate research and improve strategies for early identification, prevention and early intervention, b) early prevention could delay, diminish or even prevent possible development of psychosis, c) such signs and symptoms can be evaluated reliably and validly, d) many patients at risk arrive at clinics with cognitive deficiencies, as well as certain distress and disability, so the associated suffering could be reduced, although a clinical condition were not present, and e) the stigma associated with such a diagnosis could be modified and managed.

On the other hand, authors who are against inclusion of this syndrome consider the following limitations or problems, that is: a) lack of empirical evidence and results still inconsistent for now, b) high rates of false positives (about 75%) and low rates of conversion to psychosis; c) lowering of clinical thresholds, which would lead to higher rates of mental disorders and psychopathologization of society and culture, d) sample bias (studies have been done, preferentially in samples from research clinics linked to the university system, but it has not been examined in all cultures and there are not even any studies with representative samples of the population taken by random sampling); e) difficulty in setting cut-off points for diagnosis and fuzzy borders for differentiating clinical and subclinical states, f) this diagnosis can be associated with stigma and discrimination, g) increase in unnecessary treatments, for example, use of psychopharmacology (low doses of antipsychotics) with the consequent collateral effects (e.g., teenage weight gain) and economic and health-care cost, h) different legal-legislative (the role of insurers in some countries) and economic implications (possible benefits to the pharmaceutical industry).

Likewise, many questions remain unanswered, to cite just a few: Can it be diagnosed in adolescence? What is attenuated and what is sufficient severity? Should negative symptoms be considered? Is it the same in all cultures? Are clinicians trained well enough in it? How should professionals be trained in it?

EVALUATION OF THE PSYCHOSIS PHENOTYPE USING MEASUREMENT INSTRUMENTS: HIGH-RISK PARADIGMS

The idea of preventing and intervening early in persons at risk of psychosis to mitigate its possible impact on many levels has pushed the development and validation of a wide variety of measurement instruments (Addington and Heinssen, 2012; Barrantes-Vidal, Obiols, and Zaragoza Domingo, 2006; Fonseca-Pedrero, Lemos-Giráldez, et al., 2011; Fonseca-Pedrero et al., 2008).

The whole evaluation process goes through having psychometric-quality measurement instruments. Without proper evaluation, it would not be possible to make a precise diagnosis and without the right diagnosis, effective intervention cannot be carried out. That is, if evaluation is deficient, it is possible that both the diagnosis and intervention may be erroneous. In the field of psychosis, and any other, there is no doubt that the use of measurement instruments with good metric quality with respect to score reliability and evidence of validity, based on which solid well-founded decisions may be made, is a necessity from both clinical and research viewpoints. Logically, measurement instruments must be correctly translated, adapted, designed and validated in our context, following international guidelines and standards

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**TABLE 2
A PRACTICAL CASE OF ATTENUATED PSYCHOSIS SYNDROME. (JACOBS ET AL.,2011)**

Susana is a 17-year-old girl in her fourth year of secondary education (ESO). Her mother takes her to a psychologist after noticing some "strange" behavior which has caused her concern. Susana has an uncle with schizophrenia. Her mother comments that the girl's "strange" behavior has been occurring for about five months. The teenager comments that once or twice a week she has heard a voice whispering to her when she is alone in her room, but she is not very sure about where it comes from or what it says. Susana says that it might be a hearing problem. During the interview with Susana, she changes the subject of conversation several times and frequently refers to matters unrelated to the main subject. Her mother is worried because lately Susana hardly goes out with her friends, and they have stopped calling the house. Susana thinks her friends talk about her behind her back, but she is not sure about what they say. Susana's mother has also contacted her advisor, who tells her that her school work has deteriorated dramatically in recent months. Both Susana and her mother comment that there is no history of alcohol or drugs. Medical examinations have not shown anything significant.

(Muñiz, Elosua, and Hambleton, 2013). It is also worth mentioning that inferences made based on the scores on a measurement instrument must always be used within a certain context and population. Thus, what might be valid for a certain group of people or population may not be for another, and what may be valid in one evaluation context is not necessarily in another different one (Muñiz and Fonseca-Pedrero, 2008; Zumbo, 2007).

Furthermore, it is important for risk assessment to consider many sources and reporters (e.g., friends, teachers and parents). It is also relevant for information to be collected from interviews and self-reports. Self-report measures tend to overestimate the rates of attenuated psychotic experiences, although this does not mean that interviews provide more accurate measurement (Linscott and van Os, 2010). In a holistic assessment, any moderating factors should be considered, such as traumatic experiences, coping strategies, affective impairment, social functioning, drug use or family history. Cognitive and neuropsychological functioning should also be evaluated, as well as any other neurobiological indicators (e.g., brain impairment). Needless to say, psychotic symptoms are not restricted only to psychosis, but may be present in other medical conditions (e.g., tumors or other neurological problems), so other possible explanations of theses symptoms must always be considered.

Finally, adolescence is an interesting time for assessment, early detection and identification individuals at risk. In view of the above, some reasons that could be given for this would be: a) the signs and symptoms of psychosis begin around three to five years before the first hospitalization (Häfner and An Der Heiden, 1999), b) most psychosis cases debut in late adolescence or early adulthood (van Os and Kapur, 2009), c) adolescence is a developmental stage in which there is a confluence of a wide variety of physical, psychological and social changes (e.g., hormonal, identity or pair group changes) (Harrop and Trower, 2003), d) confusing effects often found in patients with psychosis are avoided (e.g., medication), e) psychotic-like experiences in adolescents predict development of schizophrenic spectrum disorders (Linscott and van Os, 2013; Zammit et al., 2013), and f) it is possible for early intervention in the initial stages of the disorder to avoid becoming clinical and reduce or mitigate its impact in many spheres. In this sense, it is important to have measurement instruments specifically designed and validated for their use in this sector of the population.

Some of the strategies available for evaluating the (extended) psychosis phenotype before the first psychotic episode are briefly and simply presented below (Keshavan, DeLisi, and Seidman, 2011). Assessment strategies may be different depending on the time (early or late) of the focus of evaluation (traits, experiences or basic symptoms) and of the population analyzed (general population, family members of patients with psychosis or individuals seeking treatment). Logically, this classification does not include all the complexity existing when the psychotic phenotype is evaluated, so it should be seen as an approach that has been simplified for educational and explanatory purposes. For example, there could be a case in which an adolescent with attenuated psychotic symptoms, having a family history of schizophrenia and who was seeking treatment is evaluated. In this case we would have a combination of clinical and genetic high-risk psychometric paradigms. It would also not be clear whether evaluation of the attenuated psychotic experiences could be a strategy differentiated from psychometric high-risk evaluation. In this case, due to its affinity with schizotypal experiences, and because schizotypy is a more holistic construct, they have been included in psychometric high-risk studies. The paradigms are:
✔ Psychometric high risk
✔ Genetic high risk
✔ Clinical high risk
✔ Early prodromes: basic symptoms
✔ Late prodromes: ARMS-UHR

Psychometric high-risk paradigm
The use of self-reports and interviews to identify people in the general population with latent vulnerability to psychosis is known in the literature as the "psychometric high-risk" paradigm. At the present time, this method of research is considered a reliable, valid and accurate strategy for the psychometric detection of individuals at risk for schizophrenia (Gooding, et al., 2005; Kelleher, Harley, Murtagh and Cannon, 2011; Kwapil, et al., 2008), and useful for possible later implementation of prophylactic treatments. This research paradigm attempts to assess schizotypal traits and psychotic-like experiences, although it is also true that some of the instruments presented here could be used in ultra-high-risk or clinical populations, (e.g., CAPE-42). Some of the measurement instruments used most in research and clinical practice for both adult and adolescent populations are mentioned below.

✔ Peters et al Delusions Inventory- 21 (Peters, Joseph, Day, and Garety, 2004).

✔ Community Assessment of Psychic Experiences-42 (CAPE-42) (Stefanis et al., 2002).

✔ Wisconsin Schizotypy Scales (WSS) (Kwapil et al., 2008).

✔ Launay-Slade Hallucination Scale, Revised(LSHS-R) (Bentall and Slade, 1985).

✔ Oviedo Schizotypy Assessment Questionnaire (ES-QUIZO-Q) (Fonseca-Pedrero, Muñiz, Lemos-Giráldez, Paino, and Villazón-García, 2010).

✔ Schizotypal Personality Questionnaire for Children (SPQ-C) (Raine, Fung, and Lam, 2011).

✔ Adolescent Psychotic-like Symptom Screener (APSS) (Kelleher et al., 2011).

Genetic high-risk paradigm

This approach attempts to evaluate schizotypal traits and psychotic-like experiences as well as other possible risk markers (e.g., biochemical, brain, neurophysiological, behavioral, motor and psychological) in healthy family members of patients with schizophrenia. This paradigm usually selects participants at the developmental time most distal from clinical debut and follows them longitudinally. Nevertheless, to improve conversion rates, more recent studies have selected older participants, and evaluated schizotypy and HRMS simultaneously ("progressive closing-in strategy) (Keshavan et al., 2011; Shah et al., 2012).

Clinical high-risk paradigm

The clinical high-risk, ultra-high risk or ARMS paradigm is characterized by evaluation of psychotic experiences or basic symptoms at a time theoretically closer to psychotic disorder debut (compared to the psychometric high-risk paradigm). A certain tool is chosen for each stage of the prodromal states, whether early or late, based on participant age. For example, for earlier periods, instruments based on basic symptoms, for example, the Bonn Scale (Gross, Huber, Klosterkötter, and Linz, 1987) or the Schizophrenia Proneness Instrument (Schulze-Lutter, Addington, Rughrmann, and Klosterkötter, 2007; Schultze-Lutter, Marshall, and Koch, 2012) could be selected. On the contrary, for periods theoretically earlier than the first psychotic episode, the SIPS (Miller et al., 2003) or the CAARMS (Yung et al., 2005)could be used. Some of the scales that have been selected for their relevance and their widespread use in this area of study are:

✔ Structured Interview for Prodromal Syndromes (SIPS)/Scale of Prodromal Symptoms (SOPS) (Miller, et al., 2003).

✔ Comprehensive Assessment of At Risk Mental State (CAARMS) (Yung, et al., 2005).

✔ Prodromal Questionnaire (PQ) (Loewy, Bearden, Johnson, Raine, and Cannon, 2005) and its brief version (Loewy, Pearson, Vinogradov, Bearden, and Cannon, 2011)

✔ Youth Psychosis at Risk Questionnaire (Y-PARQ-B) (Ord, Myles-Worsley, Blailes, and Ngiralmau, 2004).

✔ PROD-Screen (Heinimaa et al., 2003).

✔ Prime Screen Revised (Miller, Cicchetti, Markovich, Mc-Glashan, and Woods, 2004)

✔ Bonn Scale for the Assessment of Basic Symptoms (BSABS) (Gross, et al., 1987).

✔ Schizophrenia Proneness Instrument adult version (SPI-A) (Schultze-Lutter, et al., 2007) and youth version (SPI-CY) (Schultze-Lutter, et al., 2012).

The SIPS/SOPS and the CAARMS are perhaps the scales most widely used in research and clinical practice. Both have been used in samples of the Spanish population (Barrantes-Vidal et al., 2013; Lemos-Giráldez et al., 2009; Lemos-Giráldez et al., 2006). The Spanish version of the SIPS may be downloaded from http://www.p3-info.es /view_article.asp?id=17&cat=4. Three risk groups can be established based on the SIPS scores. These three groups, which have been used most often in research, are:

a) State of attenuated positive prodromal symptoms (high-risk mental state).

✔ Score 3, 4 or 5 on the P1-P5 scales of the SOPS (scores vary from 0 to 6, where "0" is absent and "6" severe and psychotic). Furthermore, the symptom either has to have begun in the past year or currently have reached one point higher than 12 months before. Secondly, the symptom has to be present at the current intensity level with an average frequency of at least once a week during the past month.

b) Brief, limited and intermittent psychotic state

✔ The brief intermittent psychotic syndrome is defined by the clear presence of psychotic symptoms that are recent and short. The psychotic intensity of the symptom (SOPS score = 6) has to have begun in the past three months and have been present at least several minutes a day with a frequency of at least once a month.

c) Genetic risk/schizotypal personality disorder and functional decline.

✔ The patient has a first-degree family member and/or meets the criteria for Schizotypal Personality Disorder. Functional decline is defined operatively as a 30% or

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more decrease in the score on the Global Assessment of Functioning Scale during the past month, compared to 12 months ago.

Of the three risk groups, the most prevalent in field studies is attenuated positive prodromal symptoms (Fusar-Poli, Bonoldi, et al., 2012; Fusar-Poli, Borgwardt, et al., 2012; Lemos-Giráldez et al., 2009; Ruhrmann, Schultze-Lutter, Salokangas, et al., 2010; Woods, et al., 2009). This risk group, adding distress and seeking treatment, is the one that led to attenuated psychosis syndrome. Finally, basic symptoms and derived operative criteria COGDIS (Cognitive Disturbances) and COPER (Cognitive-Perceptive Basic Symptoms) should also be considered given the recent interest they have awakened. As an example, Table 3 gives the COGDIS criteria (Ruhrmann, Schultze-Lutter, Salokangas, et al., 2010; Schultze-Lutter, Ruhrmann, Berning, Maier, and Klosterkötter, 2010).

HIGH-RISK MENTAL STATES: PREVALENCE AND VALIDITY

Based on the operative criteria established in the scales, ARMS can be examined in samples of the general population. Kelleher et al. (2012) gave the SIPS and the CAARMS to 212 adolescents for this purpose. These authors found that based on the CAARMS, 0.9-7.7% of the sample would have ARMS, while with the SIPS, it would rise to 8.1% of adolescents. Furthermore, a considerable percentage had a higher probability of a comorbid Axis I disorder. In another study, Zammit et al. (2013), using a sample of 4724 adolescents and the SIPS, found an ARMS prevalence of 0.7%. This study also found that a high percentage of adolescents with ARMS had not sought treatment. Finally, a telephone-interview study carried out by Schimmelmann et al. (2011) in a sample of

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TABLE 3
CRITERIA OF COGDIS
(COGNITIVE DISTURBANCES)* SYMPTOMS

✔ Inability to divide attention

✔ Thought interference

✔ Thought pressure

✔ Thought blockages

✔ Disturbance of receptive speech

✔ Disturbance of expressive speech

✔ Unstable ideas of reference

✔ Disturbances of abstract thinking

✔ Captivation of attention by details of the visual field

*At least TWO of the NINE symptoms several times per week in the past three months and a certain severity (score higher than or equal to three in the scale response system- SPY-A) are required. Regardless of severity, the first appearance at least one year before.

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56 participants (age 16-35 years), found 2% prevalence.

The cornerstone of the ARMS studies is predicting the psychosis conversion rates, that is, their predictive validity. In the literature there are numerous longitudinal studies that show that participants with ARMS have a higher probability of conversion to clinical psychosis (Fusar-Poli, Bonoldi, et al., 2012; Fusar-Poli, Borgwardt, et al., 2012; Lemos-Giráldez, et al., 2009; Ruhrmann, Schultze-Lutter, Salokangas, et al., 2010; Woods, et al., 2009). A recent meta-analysis done by Fusar-Poli et al. (2012), with a sample of 2502 ultra-high risk participants (58% males; $M=19.9$ years), found an overall conversion rate of 29.2% (CI: 27.3-31.1%), with a mean evolution of 31 months. Conversion rates by time interval were the following:

✔ 18% (12-25%) in six months
✔ 22% (17-28%) in one year
✔ 29% (23-36%) in two years
✔ 32% (24-35%) in three years
✔ 36% (30-43%) in over three years

As observed, the conversion rate in individuals with ultra-high risk per year is 22%, which is far above the annual incidence of schizophrenia, which is around 0.015%. On the other hand, results show that conversion rates have tended to go down in recent years, possibly due to interventions being earlier and more active or because there is more detection of false positives (Yung et al., 2007). Conversion to schizophrenia spectrum disorders also seems to predominate over affective psychoses (73% vs. 11%) (Fusar-Poli, Bechdolf, et al., 2013). A considerable percentage of high-risk individuals also shows a comorbid clinical disorder (Fusar-Poli, Nelson, Valmaggia, Yung, and McGuire, 2014; Salokangas, et al., 2012). As mentioned, not all high-risk cases become psychoses, but may evolve toward other psychological conditions (e.g., substance use), remain stable or remit over time (remission rate 15.4% to 54.3%) (Simon et al., 2011). Finally, a high percentage of these individuals shows cognitive deficits (Fusar-Poli, Deste, et al., 2012), structural (Fusar-Poli, Radua, McGuire and Borgwardt, 2012) and/or neurochemical changes (Howes et al., 2011).

EARLY INTERVENTION

Controlled clinical tests done in persons with ARMS in which different types of intervention are tested are still scarce and show certain methodological deficiencies (e.g., small sample sizes). One recent review of seven studies where different therapeutic approaches were used suggested that the experimental treatment was superior to

the standard treatment in preventing progression to psychosis, with an average conversion rate in all studies of 7.6% for the experimental treatment and 23% for the usual treatment (Fusar-Poli, Borgwardt, et al., 2013). Another review of a total of 11 trials and 1246 participants carried out by Stafford et al. (2013), found a certain beneficial effect of early intervention in delaying or preventing psychosis. At this point the randomized, double blind clinical study with placebo control carried out by Amminger et al. (2010) in which they tested the effect of omega-3 fatty acids in ultra-high risk patients should be mentioned. The results showed that after 12 weeks, the intervention with omega-3 fatty acids was higher than the placebo in reducing risk of progression to psychosis. Doubtless such findings can offer a safe, effective strategy for prevention in young people with subclinical psychotic states (Amminger et al., 2010). However, such results should be replicated in later research.

The possible beneficial effect of psychological therapies in ultra-high risk patients has also been the subject of analysis. A study carried out by Morrison et al. (2012) using a sample of 288 patients (144 experimental group and 144 control group) found that intervention with cognitive therapy (six months of treatment) plus monitoring did not significantly reduce transition to psychosis or distress related to the symptoms compared to the control group results (monitoring only); however, cognitive intervention did reduce the severity of the psychotic symptoms. In another study done by van der Gaag et al (2012) using a sample of 201 patients, it was found that cognitive-behavioral therapy (concentrating on normalization and awareness of cognitive bias) showed a favorable effect on conversion to psychosis, as well as a reduction in subclinical psychotic symptoms compared to the conventional treatment group. Thus the results found with regard to the effectiveness of the cognitive-behavioral therapy in preventing conversion to psychosis in ultra-high-risk participants are for now insufficient and contradictory (Morrison et al., 2012; van der Gaag et al., 2012).

SUMMARY

The purpose of this article was to offer a general view of the current state of attenuated psychosis syndrome, concentrating specifically on adolescence and early adulthood. Throughout the study an attempt has been made to deal briefly with the following points: a) the psychosis phenotype and its expression in the general population, b) diagnostic criteria of attenuated psychosis syndrome and its possible benefits and limitations, c) measurement instruments available for evaluating risk of psychosis, d) prevalence of ARMS in the general population, as well as evidence of predictive and concurrent validity available, and e) results of early intervention in ultra-high-risk individuals.

Mental balance in any individual is characterized by a certain order and hierarchy of higher mental functions such as memory, language, thought, attention or executive functions (planning, monitoring, etc.). In some people, this balance and structure ruptures for a variety of reasons and circumstances, which impacts drastically on personal functioning in family, school, and work. At this point is when, in clinical convention, a mental disorder may first be spoken of. Logically, this mental disorder often does not happen suddenly, but develops over time. There are also intermediate mental states which, although they do not reach the clinical threshold, may predict the debut of a future mental disorder and impact on the person's life on many levels. Attenuated psychosis syndrome, or psychotic symptom syndrome, is a new nosological category proposed by the DSM-5 psychotic disorders work group which is included in Appendix III of the APA manual.

The psychosis phenotype is distributed over a psychopathological severity continuum. Psychotic experiences, under the clinical threshold and present in the general population represent the behavioral expression of latent vulnerability to psychotic disorders. Such experiences do not make up a single phenomenon; there are several types, with different clinical implications, evolutionary trajectories and underlying causes. Depending on the point a person is at on this continuum, and his interaction with genetic and environmental factors, he could be more or less vulnerable to schizophrenia spectrum disorders. In samples from the general population, conversion would be about 0.6%, about 10% in samples of patients with anxiety or depression, and around 20% in samples at clinical high risk for psychosis.

Prospective studies carried out in people at high risk show that this type of participant has a greater probability of psychiatric outcome. This has opened the possibility of interventions indicated for preventing or becoming clinical or reducing their possible impact. Based on these results, and due also to the growing interest in a prevention model in health sciences, the DSM-5 psychotic disorders work group has proposed inclusion in the manual of a new nosological category called attenuated psychosis syndrome. This syndrome is a polyhedral construct based

on the frequency, duration and progression of certain symptoms associated with social dysfunction, seeking treatment and/or clinically significant distress. However, for the time being, there is insufficient empirical evidence on identification of this type of person since a high percentage of participants considered high-risk do not necessarily evolve toward a psychotic disorder. At the same time, the results show that early intervention (e.g., cognitive-behavioral therapy) carried out to prevent conversion to psychosis is still insufficient and contradictory. These two points, along with other limitations and problems (e.g., stigmatization, absence of adequate sampling, overdiagnosis, unnecessary treatments, use of antipsychotics, lack of training, etc.), highlight the prematurity of introducing this proposal in the main text, so it was decided to include it in DSM-5 Appendix III.

Diagnosis of psychosis is complicated and heterogeneous, with wide inter and intraindividual variability, where for now there are no pathognomonic markers. At the same time, its dimensions fluctuate over time, arising sequentially and combining interactively and dynamically (McGorry and van Os, 2013). The early stages of incipient mental disorders such as psychosis are hard to define precisely, just as it is to delimit what is considered normal from what is a mental disorder. This attenuated psychosis syndrome could assist in improving prediction of conversion to frank psychosis as well as intervention and prevention strategies. For the moment, for lack of new evidence and considering the absence of specificity of symptoms, its function would rather be early detection and would involve risk probability estimation, and not necessarily an early diagnosis of psychosis. It should not be forgotten that a diagnosis has to be useful. Its usefulness must enable differentiation of people who are ill from those who are not and improve disorder therapeutic decisions and prognosis.

Furthermore, the proposal of this entity could bring with it incorporation into the health-care system of a model based on clinical stages. Such models propose intervention based on chronological development, degree of progression and symptom distress (Yung and McGorry, 2007). There are hybrid models that combine a categorical approach and a dimensional one. Lessons learned based on this set of studies show that it might be more beneficial to move in the direction of a general syndrome of early mental distress, or "increased" risk mental state, for a goal of universal prevention. This is related to a prodromal prevention model (Fusar-Poli, Yung, McGorry, and van Os, 2014) which postulates

how mental disorders emerge from an unspecified state of mental distress, which may evolve little by little over time toward different recognizable syndromes, such as anxiety (Syndrome 1), depression (Syndrome 2) or psychotic disorder (Syndrome 3). In this model, treatment of early mental disorders can effectively prevent conversion to a general mental disorder, compared to the exclusive ARMS approach in which it would only benefit a much smaller set of the population (e.g., psychosis).

If we were to try and see into the future, interesting questions still remain to be solved and improved. There is no doubt that it would be of interest to improve psychosis transition rates using new predictive models. To do this, negative symptoms could be included in diagnostic criteria, ARMS groups could be joined, or different research paradigms combined in a perspective including many levels of analysis (cross-sectionally). Other phenotype factors that seem to have an important role in predicting onset of psychosis could also be identified, such as persistence, intensity, affective dysregulation, maladaptive coping styles, environmental impacts (e.g. trauma), etc., to name only a few. The incorporation of neurosciences in the study of psychopathology (Sanislow et al., 2010), validation of scales in samples representative of the population and multicenter longitudinal studies are extremely promising lines for future research. Finally, it should not be forgotten that the ultimate usefulness of this type of syndrome and nosological proposal is to favor the fullest development of the individual, without losing sight of the Hippocratic aphorism *primum no nocere.*

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