Chapter

Schizophrenia: Early Recognition and Prevention

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Abstract

Schizophrenia is a heterogenous disorder presenting as episodes of psychosis against a background of cognitive, social, and functional impairments. Schizophrenia, a multifaceted neuropsychiatric disorder, is affecting approximately 1% of the population worldwide. Its onset is the result of a complex interplay of genetic predisposition and environmental factors. The clinical staging model of psychotic disorders implies that early successful treatment may improve prognosis and prevent progression to more severe stages of disorder. So, prevention and early intervention of schizophrenia are correlated with the prodromal phase, especially with "at risk mental state" (ARMS) and the prediction of their transition to a full-blown psychotic disorder. The psychosis prodrome includes nonspecific signs and symptoms (such as depressed mood, anxiety, sleep disturbance, and deterioration in role functioning), "basic symptoms" (thought interference, disturbance of receptive language, and visual perception disturbance), attenuated or subthreshold psychotic symptoms, neurocognitive deficits, and neurobiological changes measured via magnetic resonance imaging (MRI). Increasing improvements in the identification of those truly at "high risk" for psychotic disorder have paved the way of early intervention strategies in this population and increased the possibility of minimizing distress and disability and delaying or even preventing the onset of an evident psychotic disorder. The treatment (antipsychotic medication, psychological and social interventions) for young people who meet ARMS criteria should not only focus on the symptoms that constitute the ARMS criteria but also address the broader range of difficulties with which the young person might present. There are some ethical issues to consider when selecting specific treatment options, and the potential risks of treatment have to be balanced against the potential benefits.

Keywords: early recognition, clinical staging model, prodromal phase, at risk mental state, prevention

1. Introduction

Schizophrenia is a heterogenous disorder presenting as episodes of psychosis against a background of cognitive, social, and functional impairments.

Schizophrenia, a multifaceted neuropsychiatric disorder, is affecting approximately 1% of the population worldwide. Its onset is the result of a complex interplay of genetic predisposition and environmental factors.

After more than 100 years of studies and clinical psychiatric practice, passing through numerous conceptualizations of psychosis and schizophrenia, research tries to achieve an evolutionary pattern of psychosis and to establish clear, distinctive diagnostic criteria for every type of psychosis.

Psychosis is unanimously considered essential for understanding the evolution and treatment process and also for estimation of prognosis.

Recently, the area of "prodromal" research in schizophrenia and related disorders has grown considerably. From initial retrospective studies of this phase, dating back to the early twentieth century, the last decade of the century has seen the beginning and expansion of prospective studies aiming to identify the earliest manifestations of psychotic illnesses. From identification of these prodromal or "ultrahigh-risk"(UHR) individuals, the area has also developed to include intervention studies aiming to prevent, delay, or ameliorate the onset of a full-blown psychotic disorder and to investigate underlying processes that cause or contribute to the onset [1].

The fact that psychosis disorders, such as schizophrenia, begin with a prodromal phase prior to the onset of frank psychotic symptoms has been known since the first description of the illness was documented [1].

The pattern of psychosis and of the first episode of psychosis is similar to the pattern of schizophrenia but more complex.

Strauss and Carpenter considered that schizophrenia includes an interactive, developmental, and systematic model [2–6]. By analogy, the model of the first psychotic episode can be considered an interactive, developmental, and systematic model.

The arguments to sustain this theory (hypothesis) are:

1. Variables that interact either sequentially or simultaneously and are nonspecific or partly known.

2. Genetic vulnerability is sometimes well known; in the first psychotic episode, there is a variety of genetic mechanisms with varying degrees of impact and strong expressiveness even from the prodromal or prepsychotic period. But for those with well-known genetic vulnerability, clinical expressivity may be missing, and not everyone with genetic predisposition shows schizophrenia.

3. Perinatal factors may constitute an independent variable that increases the person's vulnerability to develop a psychotic pathology, and when interacting with genetic and environmental factors, the risk increases both in schizophrenia and psychosis [7].

Due to the complexity and heterogeneity of the first psychotic episode, to conceive and to unanimously recognize it like a coherent and unitary model are extremely difficult. The unknowns of this huge puzzle are still numerous despite the scientific efforts.

The model of the first psychotic episode has a medium- or long-term impact on schizophrenia model and can be of particular relevance to both etiopathogenesis and treatment as well as prevention strategies.

Over the last years, the most exciting signs of progress in defining a new conceptualization of psychosis are reported by the genomic studies [8, 9]. Maps of the neurobiological circuits of cognitive functions have been designed and have tried to explain the ways in which these circuits become dysfunctional in various disorders including the psychotic ones.

2. Description of psychosis

Researchers from the National Institute of Mental Health (NIMH) have reported three conclusions:

1. Psychosis is a neurodevelopmental disorder, with onset in adolescence and period when the cortex is still in development.

2. For most disorders related to the cortical functions, the changes of cognitive and comportamental fields appear (occur) later, suggesting the existence of biological dysfunctions long before psychosis.

3. Psychosis like other complex diseases has a multifactorial determinism.

These data have facilitated the explanations of the pattern of psychosis by integrating molecular biology, neuroscience, and behavioral sciences. This new approach tries to discover finally the new treatment strategies including new medications (antipsychotics) and psychological, social, and other potential interventions.

The work group for psychosis within DSM-V proposes distinct clinical domains for each psychotic disorder correlated with the neuronal circuits [10].

In 2009 Jim van Os, one of the members of work group for psychosis, proposed a new syndrome named "salience dysregulation syndrome" as a diagnostic to be used [11].

Jim van Os used the psychotic model of Kapur who considers that hallucinations and delusional ideas appear because the individual has difficulties in recognizing his or her mental experience relevance. Jim van Os used the term syndrome not disease, because a syndrome is a set of symptoms that appear simultaneous without having a common cause. The symptoms described are positive and negative symptoms, disorganization, developmental cognitive deficits, and depressive and maniacal symptoms [11].

The "salience dysregulation syndrome" was divided for diagnosis into:

a. "Salience dysregulation syndrome with developmental cognitive deficits"

b. "Salience dysregulation syndrome with affective expression"

c. "Salience dysregulation syndrome not otherwise specified" [11]

3. Attenuated syndrome

In 2010, Dominguez and collaborators [12] also members of work group for psychosis described two new innovative aspects:

- Deconstructing psychosis/schizophrenia disorganization considered as a syndrome.

- The attenuation of psychotic symptoms is a favorable predictor for the outcome.

In his study [12], Dominguez considered that the association of negative symptoms or of the disorganization with attenuated psychotic symptoms increases the risk of developing a psychotic frank syndrome.

4. The prodrome

Although there is great variability between patients in how their prodromes manifest, certain symptoms and signs have been frequently described. These include depressed mood, anxiety, irritability and aggressive behavior, suicidal ideation and attempts, and substance use. The most commonly occurring prodromal symptoms, according to retrospective studies of patients with schizophrenia and schizophreniform disorder, are reduced concentration and attention, reduced drive and motivation, depression, sleep disturbance, social withdrawal, suspiciousness, deterioration in role functioning, and irritability [1].

Studying these symptoms, we observe two things. First, many of them are nonspecific occurring frequently in the prodromes of nonpsychotic threshold syndromes. Second, a considerable amount of psychiatric symptoms, disability, self-harming, and other health-damaging behaviors, occur during this prodromal phase, even in the earliest stages [1, 19, 22, 39].

Cognitive, affective, and social disturbances known as "basic symptoms" are also commonly described in the early prodromal phases. This concept of "basic symptoms," developed in the 1960s, has significantly influenced the new area of prodromal research [1].

5–10% of the general population experience attenuated or subthreshold form of psychotic symptoms like transient perceptual symptoms; suspiciousness; reference and bizarre delusional ideas (e.g., the beliefs that others may be thinking badly about or laughing at); nonattendance at school, university, or work; and altered behavior toward family and friends [1, 16].

The difference between these phenomena and clear psychotic symptoms is due to their intensity, frequency, duration, and deleterious effects on the individual functionality of the person.

Neurocognitive deficits in particular impaired attention, spatial and verbal memory, and speeded information processing are also evident in the prodromal phase but at a lower degree of severity comparing to those found in first-degree relatives of patients with schizophrenia or in fully affected patients [1].

Specific cognitive deficits may be related more directly to affected brain structures and candidate genes and so may be more directly predictive of psychosis.

5. Treatment

In the prodromal and in the onset phase of psychosis, neurobiological changes can be identified. During the process of transition to psychosis, magnetic resonance imaging (MRI) highlights significant bilateral reduction in gray matter volume in the cingulate region as well as in the left parahippocampal gyrus, left fusiform gyrus, left orbitofrontal cortex, and one region of the left cerebellar cortex [1]. It is important to notify that these brain changes were not present in the UHR group that did not develop psychosis.

The differentiation between normal and abnormal has important implications for defining the prodromal phase of schizophrenia and the therapeutic interventions at this early stage. Atypical antipsychotics has improved the treatment and the outcome of schizophrenia and psychosis due to their low risk for adverse effects like extrapyramidal effects, tardive dyskinesia, sedation, weight gain, metabolic syndrome, amenorrhea, galactorrhea, sexual dysfunctions, etc.

Psychosocial interventions give optimism regarding the prognosis of disease by improving family and social difficulties, stigma avoidance, victimization, isolation, and poverty [13].

If the prodrome can be recognized prospectively and treatment can be provided at this stage, then disability could be minimized, some recovery may be possible before symptoms and poor functioning become obvious, and the possibility of preventing is feasible and realistic. The early intervention aims:

- To slow or possibly to stop further deterioration and even further progression to psychosis.
- To reduce the poor functional outcome characterizing many vulnerable individuals, whether or not psychosis actually develops.
- To evaluate and prevent secondary morbidity in order to decrease morbidity and mortality in the first episode of psychosis.
- To create research opportunities to develop new therapeutic strategies.
- To develop secondary prevention strategies.

Early intervention has to take place in the three important phases of early psychosis:

a. In the phase of risk when the symptoms are subtle and can be confused with particularities and difficulties specific to adolescence.

b. In the period of frank psychosis in which if the symptoms remain untreated, there is a risk of temporal or permanent disability.

c. In the critical period after the onset of the first episode of psychosis, a period which can last up to 5 years after the onset, the length of time that treatment should be comprehensive and specific.

6. Redefining psychosis

The latest attempts redefining the concept of psychosis have focused particularly on the first episode of psychosis and on prodromal stage of schizophrenia.

Arguments for these new concepts can be synthesized as:

- Clinical heterogeneity of patients diagnosed with first psychotic episode.
- The heterogenous outcome of these patients.
- The instability of the diagnosis over time.
- Avoidance of negative prognostic.
- Stigma avoidance.

7. A history of prodrome: benefits of diagnosis of the prodrome

Over 100 years ago, Emil Kraepelin (1896), cited by Patrick McGorry at the beginning of the chapter "A stitch in time" [14], wrote "it is of the greatest medical

importance to diagnose cases of dementia praecox certainly and at an early stage" (Kraepelin, 1896/1987, p. 23).

In 1908, Eugen Bleuler, cited by Patrick McGorry in the same book [14], wrote "the sooner the patients can be recovered and the less they are allowed to withdraw in their own world, the sooner they become socially functional" (Bleuler, 1908/1987, p. 63).

Coming from 1927 [15], we find the same idea "I feel certain that many incipient cases might be arrested before the efficient contact with reality is completely suspended, and a long stay in institutions made necessary" ([15], p. 135). Meares in 1950 wrote "it is not necessary to diagnose early schizophrenia but to diagnose prepsychotic schizophrenia ‚to prevent damage".

These statements can be used not only as the foundation stones for any therapeutic intervention but also as arguments to emphasize the importance of early phases of psychosis.

8. Definition of prodrome

So, the prodrome is a distinct period in the evolution of the first psychotic episode, mostly unknown or minimized as importance. The onset's particularities and the evolution of the first psychotic episode are involved in the short-, medium-, and long-term prognosis. The recovery depends on the early initiation of therapeutic strategies.

The prodrome was originally defined as the prepsychotic period preceding a relapse in patients already diagnosed with psychosis. Subsequently a distinction was made between the initial and the relapse prodrome [16].

Other definitions are [16]:

- "a heterogenous group of behaviors having a temporal relationship with psychosis' onset".
- "the period from the first symptoms noted until the onset of prominent psychotic symptoms".

All definitions of prodrome phase have in common the presence of symptoms and the temporal relationship with the onset of psychosis, with two important practical consequences. The first implication is the person being symptomatic during the prodrome will ask for medical help, so it is possible to establish a diagnosis and a therapeutic strategy. The second implication is the person can develop the disease after the end of the prodromal phase, suggesting that the transition from prodrome to frank psychosis may be detectable.

9. False positives and treatment

However, early attempts at prodromal intervention were hampered, by the problem of "false positives" and their implications for preventive intervention. "False positives" refer to those who are identified as being prodromal, at risk of developing a psychotic disorder in the near future, but who do not do so. Some of these people were in fact never "destined" to develop a psychotic disorder (the "true false positives") [1]. These persons may be harmed by being considered as "prodromal" or "high risk of psychosis" and may receive treatment unnecessarily

[17–19]. In contrast are those individuals who would have developed a psychotic disorder were it not for some alteration in their circumstances,such as a treatment intervention, stress reduction or cessation of illicit drug use, that preventing this form occurring [1]. This latter group has been termed "false false positive" [19]. It is virtually impossible to distinguish between these two groups phenotypically at baseline and follow-up.

10. Description of prodromal phase

The conceptualization of the prodrome phase uses two methods: a retrospective/passive method which involves getting information from the patient and his/her family and a proactive one which includes observation and patient monitoring during psychosis.

Yung and McGorry [16] describe the phenomenology of the prodrome phase, summarizing the data from the literature with those of the Melbourne Personal Assessment and Crisis Evaluation (PACE) approach [20, 21]. The PACE Clinic recruits those patients with a perceived need for psychiatric help.

11. Ultrahigh risk

The PACE ultrahigh-risk (UHR) criteria require that a young person aged between 14 and 30 is referred for health care to the clinic if the criteria for one or more of the following groups are met:

1. Attenuated psychotic symptom (APS) group has experienced subthreshold, attenuated positive psychotic symptoms during the past year.

2. Brief limited intermittent psychotic symptom (BLIPS) group has experienced episodes of frank psychotic symptoms that have not lasted longer than a week and have spontaneously abated.

3. Trait and state risk factor group has a first-degree relative with a psychotic disorder or the identified subject with a schizotypal personality disorder and has experienced a significant decrease in functioning during the previous year [19, 22]

The ultrahigh-risk (UHR) criteria allow the recognition of young people at risk of onset of a psychotic disorder (late adolescence/early adulthood) who also report mental state disorder suggesting an emerging psychotic process or who may have a positive family history of psychosis accompanied by evidence of mental ill health.

Necessarily, criteria have also been developed to define the onset of frank psychosis. These are not identical to DSM-V criteria [22, 23] but are elaborated to define the minimal point at which antipsychotic treatment is indicated. This definition is arbitrary but even has a well-defined treatment implication, applicable equally to "substance-related symptoms, symptoms that have a mood component—either depression or mania—and schizophrenia spectrum disorders." The predictive aim is the first-episode psychosis requiring antipsychotic treatment, arbitrarily defined by the persistence of clear psychotic symptoms, more than 1 week [1, 19].

The intensity of psychotic symptoms characteristic for each of the UHR groups was firstly assessed using the following scales: the "Brief Psychiatric Rating Scale (BPRS) and the Comprehensive Assessment of Symptoms and History (CASH) interview." To specify the frequency and duration of psychotic symptoms, new criteria were needed. So, a new instrument, the Comprehensive Assessment of At Risk Mental States (CAARMS) was designed so that all relevant domains (intensity, frequency, duration, and recency) could be assessed [1, 24].

The PACE UHR criteria have been adopted and adapted in a large number of other settings around the world (USA, UK, Norway, Germany, etc.).

Symptoms associated with prodromal phase.

Yung and McGorry [16] identified eight subtypes of symptoms characteristic of prodromal phase:

- Neurotic symptoms: anxiety, irritability, restlessness.
- Affective symptoms: depression, anhedonia, guilt, suicidal ideas, thymic oscillations.
- Volitional disturbances: apathy, loss of interest, low energy, fatigue.
- Cognitive deficits: attention deficit, rumination, abstraction difficulties, thought blockages, thought interference, thought perseveration, thought pressure.
- Psychotic symptoms: visual and auditory perceptual disturbances, suspiciousness or paranoid ideation, derealization, unstable ideas of reference.
- Physical symptoms: somatic symptoms, weight loss, low appetite, sleeping disorders.
- Behavioral dysfunctions: social withdrawal, impulsivity, aggressivity, bizarre behavior, functional deterioration.
- Other symptoms: sensitivity, odd beliefs or magical thinking, dissociation.

Yung and collaborators [19, 25] have elaborated a set of operational criteria to identify individuals at risk for developing a psychotic disorder over the next 6–24 months as Global Assessment of Functioning (GAF) scale score <51, BPRS score >2, and Hamilton Depression Rating Scale (HRDS) score >18 [19, 25].

12. Risk factors to developing psychosis

During the years, several research teams have identified a number of risk factors for the development of psychosis: Carr and collaborators (2000): family history, perinatal complications, premorbid personality, stressful life events; Mason et al. [26]: schizotypal personality disorder, hallucinations, magic thinking, odd beliefs, anhedonia, withdrawal, functional deterioration [27].

13. Duration of prodrome

Regarding the duration of the prodrome, retrospective studies suggest a variation ranging from a short period to several years [7, 26, 28].

14. Genetic risk programs for psychosis

The development of genetic high-risk (GHR) programs was an important step for early detection and intervention, especially in schizophrenia.

In recent years, genetic research have identified specific genes for schizophrenia, some with early phenotypic expression may be considered important biomarkers, for example, the CHRNA7 gene situated on chromosome 15 with importance in genetic transmission and heredity of schizophrenia [29–32].

The phenotype "schizophrenia" has been characterized by the presence of behavioral abnormalities, the related outcome, and its longitudinal course, but not its fundamental biological substrate. The absence of a neuropathological basis for schizophrenia was one reason that some researchers supported the neurodevelopmental hypothesis of schizophrenia issued by Weinberger [33]. Evidence of obstetrical complications being associated with the risk of schizophrenia supported that developmental abnormalities were involved [34].

The premorbid risk factors associated with schizophrenia as motor and cognitive delay and obstetrical complications are nonspecific; their prevalence in the nonaffected population is important, so their positive predictive value for the development of schizophrenia is limited.

Neuroimaging anomalies found in patients diagnosed with first-episode psychosis have been interpreted as supportive of a static structural abnormality associated with schizophrenia that had originated early in neurodevelopment [35].

Recently, the association of molecular genetics with intermediate phenotypes such as cognitive impairment or abnormal brain functioning, as measured with functional neuroimaging, has generated diverse understanding of major psychosis. The combination of different levels may be of particular importance for longitudinal "at risk" studies. These studies can identify individuals who are at true risk of developing major psychosis prior to its full clinical expression, enabling us to treat "at risk" individuals prior to full manifestation of psychosis and prevent its appearance during critical developmental periods such as late adolescence [1, 36].

The measurement of genetic profiles using groups of candidate genes in combination with psychosocial risk factors such as stress and illicit drug use in samples of patients with clinically significant but subthreshold features of psychosis and mood disorder is a key strategy in enhancing predictive power for transition to more established and severe psychotic disorders, in treatment selection, and in longer-term prognosis [1].

Genetic studies suggest that diagnostic boundaries may be modified based on genetic information and some genes such as NRG1, DTNBP1, DISC1, and BDNF may relate to risk for both schizophrenia and mood disorders [37]. The synergistic use of genotyping with phenotypes characterizing brain functioning will contribute to a better understanding of the mechanisms by which genes interact with other genes and/or environmental risk factors.

15. Disadvantages of "prodromal" identification

Identification by different methods of people at risk of psychosis in the general population has allowed an increase in accuracy from a rate of 1% to a rate of approximately 30% [1]. However, the increase in accuracy has raised some criticism. One is that the screening would not be effective in the general population because of the lower base rate of psychotic illness in that population [38], so screening for UHR criteria would not be supported at this stage [19]. The second criticism is that there is a high false positive rate in all of these studies, the majority

of participants not developing psychotic disorder. Consequently, some persons will be "diagnosed" and treated as if they were at "high risk" of psychosis, when this may not be true. This false identification may have negative consequences on those individuals: they may become anxious or depressed about the possibility of developing schizophrenia or receiving treatment, stigmatized by others or themselves or both [39]. These people may be exposed to drug or other therapies, with potential adverse effects without gaining any benefit [39, 40–43]. This controversy on the risk benefit balance of early intervention strategies must be addressed by future studies.

16. Predictors of psychotic disorder in high-risk groups

Since 2004, many prospective programs focused on early psychoses have been developed.

The term "at risk mental state" (ARMS) is still used today to describe individuals at risk to develop a psychotic disorder [1, 44]. So, different diagnostic systems have been achieved, one of the most known and sophisticated systems being developed by McGorry and his team (1966) in order to reduce the number of "false positive" cases [1, 44]. The diagnostic system accomplished by McGorry et al. has three categories of diagnostic criteria for individuals' "at risk mental state" (ARMS):

1. Attenuated psychotic symptoms (APS).

    a. The presence of at least one of the following: ideas of reference, odd beliefs, magical thinking, perception disturbances, paranoid ideation, formal thought disorder, disturbances of receptive language.

    b. Frequency of symptoms: several times a week.

    c. Duration: have experienced subthreshold, attenuated positive psychotic symptoms during the past year.

    d. Recently: stressful life events during the last year.

2. Brief limited intermittent psychotic symptoms group (BLIPS).

    a. Transient psychotic symptoms: the presence of at least one of the following—ideas of reference, odd beliefs, magical thinking, perception disturbances, paranoid ideation, formal thought disorder, disturbances of receptive language.

    b. Frequency of symptoms: few times a week.

    c. Duration: less than a week and spontaneously abated.

    d. Recently: short intermittent psychotic symptoms were present during the previous year.

3. Trait and state risk factor group.

    a. First-degree relative with a psychotic disorder or the identified individual with a schizotypal personality disorder.

b. Significant decline in functioning during the previous year.

c. Duration: at least 1 month and no more than 5 years [19, 22].

These criteria were criticized for the absence of negative symptoms of schizophrenia.

Cornblatt et al. mentioned, among the diagnostic criteria of the prodrome, negative attenuated symptoms or disorganization, which define clinical high-risk (CHR) group representing the early prodromal stage and CHRT group representing tardive prodromal stage [45]. CHRT group is characterized by negative attenuated symptoms, disorganization, and positive symptoms.

Negative symptoms are impaired concentration and attention, subjectively abnormal emotional experiences, blunted affect, impaired energy, and impaired tolerance to stress [24].

Marked impairment in role functioning, flat or inappropriate affect, anhedonia, and asociality were found at significantly higher levels at baseline in those who went on to develop psychosis than in those who did not [26]. So, negative symptoms have been found to be predictive of psychosis [1].

Positive symptoms like unusual thought content, suspiciousness, perceptual disturbance, conceptual disorganization, and disorganized communication are significant predictors of psychosis [19, 46, 47].

The ultrahigh-risk (UHR) criteria have been used and modified in different countries around the world: USA, UK, Germany, and Finland.

The German Research Network on Schizophrenia (GNRS), Cologne, Bonn, Düsseldorf, and Munich, introduced the basic symptoms into the definition on the prodrome [48, 49].

The basic symptoms included thought interferences, perseveration, pressure or blockages, and disturbances of receptive language; decreased ability to discriminate between ideas and perception or fantasy and true memories; unstable ideas of reference; derealization; and visual or auditory perceptual disturbances. Using these basic symptoms, it should be possible to identify subjects at risk of developing schizophrenia, and so early intervention is possible. Because basic symptoms were frequently found before any subthreshold or attenuated psychotic symptoms, these criteria were thought to be detecting the very beginning of the initial prodromal phase [50].

Unlike McGorry et al., the GNRS distinguishes between the "early initial prodromal state" (EIPS) and the "late initial prodromal state" (LIPS). The EIPS criteria attempt to define a group at incipient but not imminent or immediate risk of psychosis. The criteria consist of the 10 predictive basic symptoms of which one or more is required, plus the PACE trait and state risk UHR criterion.

16.1 The EIPS criteria

One or more of the following basic symptoms:

- Thinking disturbances: perseveration, pressure, blockage, ideas of reference (unstable)
- Disturbances of visual and auditory perception
- Disturbances of receptive language (either heard or read)
- Diminished capacity to discern between ideas and perception, fantasy, and true memory

16.2 Derealization

The onset of the symptoms has occurred at least a year ago, with a frequency of several times a week within the last 3 months.

- Decrease in "the Global Assessment Functioning Score" (DSM-V) of at least 30 points in the past year which add one of the following risk factors: "first-degree relative with a lifetime diagnosis of schizophrenia or a schizophrenia spectrum disorder and/or pre- or perinatal complications".

- The absence of attenuated or transient psychotic symptoms [1].

The LIPS criterion attempts to identify those at more immediate risk and is based on the APS and BLIPS criteria [51].

16.3 The LIPS criteria

- The presence of at least one of the following attenuated positive symptoms (APS) present within the last 3 months, appearing several times per week for a period of at least 1 week, but no longer in the same severity than 1 year: "ideas of reference; odd beliefs or magical thinking; unusual perceptual experiences; odd thinking or speech; suspiciousness or paranoid ideation".

- "Brief limited intermittent psychotic symptoms (BLIPS), defined as appearance of one of the following frank psychotic symptoms for less than 1 week (interval between episodes at least 1 week) and resolving spontaneously: hallucinations; delusions; formal thought disorder; gross disorganized or catatonic behaviour" [1].

This two-stage prodromal state guides the treatment approach, that is, psychological or pharmacological therapy [51–53]. LIPS criteria denote an imminent risk of transition to psychotic disorder within the next 12 months, so an antipsychotic medication—second generation—appeared justified. Psychological interventions were crisis intervention, psychoeducation, family counseling, and assistance with education or work-related difficulties.

In EIPS group the psychological intervention (cognitive behavioral therapy (CBT) or the supportive control condition) appeared successful in preventing further progression of the illness [54].

17. Early intervention and prevention

Early intervention may be able to delay or even prevent onset of psychosis in the UHR or prodromal stage. Both antipsychotic medication (risperidone 1–2 mg/day, olanzapine 5–15 mg/day) and psychological interventions (cognitive behavioral therapy (CBT), case management, supportive therapy, problem-solving strategies) might have a role in treating the difficulties and problems that UHR young people experience, as well as in reducing the rate of transition to psychosis and in reducing symptomatology. Deterioration in psychosocial functioning and persistent disability is also an important treatment goal [1].

Therapeutic strategies must be personalized and correlated with the first psychotic episode stages. Treatment for young people who meet ARMS criteria should

not only focus on the symptoms that constitute the ARMS criteria but also address the range of difficulties which the young person might present.

Side effects associated with all antipsychotic medications are weight gain, diabetes, and sexual dysfunction for olanzapine [55–57] and sexual dysfunction and insomnia for risperidone [1]. Extrapyramidal side effects such as tardive dyskinesia, which is often irreversible, are less common with the newer, atypical antipsychotics [58, 59]. Evidence also suggests that certain antipsychotics (haloperidol) reduced gray matter volume in the brains of patients with a first episode of psychosis [60]. In contrast the newer second-generation antipsychotic medications, in fact, have neuroprotective qualities.

Antipsychotic drugs are potentially useful in the latter phases of the prodromal period when attenuated psychotic symptoms are evident and the individual is on the edge of a conversion to full psychosis.

Psychological interventions are useful in earlier and less symptomatic stages of the prodrome, to manage the stress, depression, anxiety, sleep disturbance, and decline in functioning. CBT should be effective for people with attenuated psychotic symptoms or with brief limited intermittent psychotic symptoms and for individuals who are "false positives" [22].

Psychological treatments may be not only necessary but sufficient for some of these putatively prodromal patients [1].

Further researches are required to determine which treatment strategies are most effective and how long they should be continued.

Ethical considerations associated with treatment of young people who meet ARMS criteria have been widely debated [17, 28, 40, 41, 42, 45, 46]. Concerns about stigma associated with being identified as having a label of ARMS "false positives" and for how long should treatment be provided (in other words, how long is the period of risk) remain unresolved, and even clinical research into ARMS has now been conducted for over a decade.

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