Risk syndromes in psychiatry: a state-of-the-art overview

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Summary

Early identification and timely intervention are crucial issues in contemporary psychiatry, both in terms of improved outcome and optimal treatment delivery as well as service reform. Although the field has advanced substantially in the last 25 years, there is a constant need to revise and ponder the core constructs that have been developed and field-tested. This is even more important given that early identification relies on the timely discernment and recognition of a variety of symptomatic presentations which are typically subclinical in terms of intensity or frequency of signs and symptoms. This overview will offer an updated conceptual map of the field.

psychosis, schizophrenia, prevention, identification, risk

One the major concerns of modern psychiatry remains the implementation of efficient prevention models. Primary and secondary prevention strategies have been addressed in several fields of medicine, but early detection in psychiatry still remains a grey zone. Serious mental illnesses share an early presentation, with a typical beginning during adolescence for the 75% of them [1]. The personal and societal impact of such disorders makes early detection and intervention a crucial issue, in the attempt to prevent significant consequences on individual functioning [2].

Staging models have been developed in order to use a preventative approach, targeted at avoiding the onset and/or progression of serious mental disorders, with treatment regimens selected according to stage and individual profile risk factors [3,4]. Staging allows the introduction of effective treatment in early illness phases, by means of placing individuals on a continuum in the context of the disorder progression. This goes along with the assumption that administering treatments during early illness stages could also modify the individual risk of disease progression [5]. Although the first models were mainly applied to psychosis, the concept of staging has been progressively applied to severe psychiatric disorders, in the attempt to define early clinical phenotypes showing an enhanced risk of progression into chronic and recurrent phases of such disorders. In this overview, current evidence about staging systems will be summarized, with particular focus on at risk mental states for psychosis and bipolar disorder.

A model for the early identification of psychosis: the Ultra-High Risk (UHR) paradigm

The ultra-high risk (UHR) paradigm was developed in order to target psychosis (rather than schizophrenia) at its prodromal phase, improving preventive interventions before the onset of a full-blown disorder [6]. The UHR cri-

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teria require subjects aged 14-30 being referred for mental health problems and possibly being assigned to at least one of the following subgroups: 1 – The attenuated psychotic symptoms (APS) group: those who have experienced subthreshold, positive APS during the past year. 2 – The brief limited intermittent psychotic symptom (BLIPS) group: those who experienced episodes of frank psychotic symptoms for no longer than a week which spontaneously abated (that is, without treatment). 3 – The trait and state risk factor group: subjects with a first-degree relative with a psychotic disorder or those who have a schizotypal personality disorder and a significant decrease in functioning or chronic low functioning during the previous year [6]. The main tools used to assess UHR features are the Comprehensive Assessments of At-Risk Mental States (CAARMS) [7] and the Structured Interview for Prodromal Syndromes (SIPS) [8]. These criteria combined multiple risk factors to concentrate the level of risk in the selected group. The strategy prioritizes specificity over sensitivity, with the possibility that people genuinely at risk may not be identified [6]. Short-term predictors of psychosis onset in UHR samples include long duration of symptoms prior to treatment [9]; basic and negative symptoms [7,10–13]; depression [9,13]; and substance abuse [14]. Subthreshold positive symptoms [7,10,11], poor functioning [7,10,15] and having genetic risk with functional decline [14], turned out to be significant predictors in the large North American Prodrome longitudinal Study [14]. Interventions during the UHR stage demonstrated to be effective both in reducing the risk of transition for at least 1-2 year and improving functional outcomes [16,17]. Early rates of transition from UHR state to psychotic disorder were about 35%-40% within 12 months [6]. However, transition rate has shown a reduction, with estimates between 10% and 18% within 1 year [18–23]. Several UHR studies tried to identify the severity of sub-threshold positive psychotic symptoms at baseline as a predictor of transition to stage 2 (i.e. full psychosis) [4]. Constructs related to thought disorder/disorganization and unusual thought content, such as paranoid thoughts, appear to be particularly associated with psychosis onset. Bizarre thinking and schizotypal personality disorder have also been highlighted as able to predict transition. Negative symptoms that could be considered as predictors of onset of stage 2 psychosis include amotivation as defined by avolition/apathy or anhedonia, alogia and social isolation/withdrawal. Poor functioning is one of the most consistently identified predictors of transition to psychosis. In other recent studies, poor social functioning, particularly social adjustment, have been evaluated as risk factors for transition [24–26]. Other identified clinical risk factors consist of depression and/or anxiety and first rank symptoms, sleep disturbances, higher genetic loading due to family history, early onset of psychiatric symptoms and substance misuse. Finally, a long duration of symptoms before first clinical contact has been identified as a predictor of transition [27].

Despite the huge amount of literature analyzing UHR as a predictor of psychosis development, the heterogeneity of patients meeting these criteria has been demonstrated, with different factor contributing to the overall risk [28]. In the attempt of better identifying subjects at higher risk of psychosis, several biomarkers were studied as possible candidates for adding specificity to UHR criteria, with particular attention to markers of oxidative defense, cortisol and other stress-related molecules, membrane fatty acids [29–31]. In this framework allostatic load, namely a multisystem index associated to metabolic, cardiovascular, immune dysregulation and linked to chronic stress, was hypothesized to be implicated in the physiopathology of psychosis, with a possible connection to the outcome of at-risk subjects [32]. Along with this, further research is still being developed in order to add specificity to UHR, i.e. identifying neuroimaging alterations predicting transition to psychosis. The main findings reported aberrant activation patterns in the prefrontal cortex, medial temporal lobe, caudate and mid-brain, together with a reduction of functional connectivity [33]. Structural abnormalities were also found in the volume of prefrontal cortex, medial temporal lobe and cingulate cortex and changes were reported in glutamate levels in the caudate and dopamine in the striatum [34]. Since peripheral serum biomarkers and brain imaging represent a field of growing research, future acquisition will hopefully add specificity to the UHR model, in a multimodal approach possibly based on individual risk.

Splitting or lumping? Risk syndromes for Bipolar Disorder (BD)

The identification of early stages in bipolar disorder (BD) represents a crucial issue in order to delay the transition from an ultra-high risk state to the full-blown syndrome, similarly to what has been shown for psychotic disorders. The early manifestations of BD lie along a broad spectrum, going from non-specific symptoms until sub-threshold mood episodes. The question if a common staging model could be defined for different diagnostic subgroups still remains to be addressed in the context of an open "splitting" versus "lumping" debate [4]. Introducing a separate stage model for BD raises relevant issues about the possibility of prodromal symptoms overlapping with symptoms of other disorders at later stages. Along with this, non-specific manifestations common to schizophrenia, BD and other affective disorders at early stages could require a trans-diagnostic approach [5].

Despite this still open debate, at-risk states for BD represented an important focus of recent literature, in the attempt of identifying specific prodromes and illness trajectories [35]. This could be related to the frequent early onset of the disorder, with first manifestations during adolescence in up to 70% cases, which makes BD an optimal candidate for early intervention strategies [36]. In addition, a relevant diagnostic delay was demonstrated for BD, estimated about 8-10 years, possibly related to a poorer prognosis [37], also in consideration of the hypothesized degenerative nature of the disease, with progressive changes in some biomarkers [38,39]. Identifying different factors defining at-risk stages of BD has several treatment implications but could be related to unspecificity problems, in consideration of the pleomorphic nature of such conditions [40]. Promising research studied the offspring of individuals affected by BD, but a clear characterization of the population of youth at risk of developing the illness is lacking. Prospective research also requires large cohorts and time for longitudinal follow-up, so the present evidence is still in part connected to the results of retrospective studies.

Less severe manifestations of the illness may present prior to the full-blown disorder, encompassing different psychopathological dimensions such as affective, cognitive and behavioral symptoms which gradually increase until the clear onset represented by the index-episode. These symptoms, recognized as possible prodromes of the illness, may precede the onset of BD by weeks or months, showing some continuity with the main episodes [35]. Prodromes were studied both under a categorical and dimensional point of view. Particularly, the most frequent symptom clusters predicting the onset BD over and above the classical diagnostic categories seemed to be affective lability, subthreshold hypomanic symptoms, anxiety/depression [41]. Despite this, patterns of early symptoms are related to a scarce predictive value, due to the unspecific nature of such presentations, overlapping with the manifestations of other psychiatric disorders. In addition, prodromes were not only studied as predictors of BD onset but also as predictors of relapse in the context of a certainly diagnosed illness and were more frequently identified retrospectively, after the progression towards the threshold of the diagnosis itself. Some adjunctive features during a first depressive episode were proposed as possible markers of bipolarity, with the strongest predictive value demonstrated for psychotic, atypical and mixed features [42,43].

In consideration of the scarce specificity offered by prodromal features, markers of vulnerability such as family history for BD or other psychiatric disorder and early onset of parental BD should be considered, demonstrating the genetic load of the illness [44]. In addition, environmental factors were proposed as possible triggers of BD, with main evidence for childhood trauma and sexual abuse, but unspecific meaning and conflicting results hinder the inclusion of such events as definitive markers of the illness. Thus, the combination of one or more clinical symptoms preceding illness onset and other precursors such as familial markers should be considered, defining a "risk syndrome" increasing the likelihood of the progression to BD [35]. Research on risk syndromes, despite presenting some limitations so far, represents a promising approach, also in the perspective of identifying which components of causal risk factors are modifiable and how interventions could possibly alter them.

Based on the need of assessing individual risk for developing BD, screening instruments were proposed, especially for the detection of prodromal symptoms. Despite increasing research, no clinical scales demonstrated enough reliability for this purpose. As a consequence, clinical assessment remains the first screening method in order to detect cases at risk of BD. For this attempts, clinical criteria were developed in an attempt to increase the specificity of prodromal symptoms, with three groups proposed by Bechdolf et al. [45] in the Bipolar-at-risk (BAR) criteria, including sub-threshold hypo/manic symptoms (group 1), depressive episode with cyclothymic characteristics (group 2) and depressive episode with genetic risk for BD. The BAR criteria represent an instrument with good reliability and predictive value [46], but further examination is required in order to assess their generalizability and clinical validity in larger samples and daily clinical practice [40,43]. Specific risk calculators have also been developed in order to estimate the personal risk of BD onset, i.e. evaluating the possibility of developing the illness within 5 years in youths with positive familial history, on the basis of symptom clusters, social functioning and parental age at onset [47].

In the context of the research on BD at-risk states, biomarkers have been demonstrated to play an important role in adding specificity to early diagnosis, representing brain dysfunction in the context of a patophysiological process of aberrance. Pro-inflammatory serum cytokines seem to be generally increased during acute phases of BD and to predict the onset of hypomanic symptoms, probably related to the altered transcription of inflammatory genes [48]. Similarly, abnormalities in neurotrophic molecules such as BDNF and in factors related to oxidative stress were showed as possible biomarkers of BD, related not only to the brain damage caused by the illness but also to the pathophysiology. During the last years, a bench of neuro-imaging findings were detected. Specific patterns of activation were showed for subjects aged 10-12 who later developed the disorder and a delayed development of the functional network was also detected, although the above-mentioned findings were not specific for BD. In addition, a decrease of the grey matter volume in the regions underpinning emotional processes, such as amygdala and orbito-frontal cortex were shown [49]. Further abnormalities were investigated as possible markers of at-risk states for BD, with encouraging evidence about the increase of gray matter volumes in some areas, i.e. right posterior cingulate cortex and superior frontal gyrus, which could also explain cognitive symptoms in this special at-risk population [50].

At-Risk Mental States (ARMS) and Clinical High At-Risk Mental States (CHARMS): preventing the transition to exit-syndromes

At risk mental states (ARMS) represent open psychopathological frameworks, with possible developments towards other clinical conditions, which could persist as well as fully resolve (51). It has been increasingly acknowledged that ARMS should be considered as a syndrome *per se,* not only a risk condition for disorder progression. They usually present with symptoms which can be detected, albeit below classic diagnostic thresholds, associating with distress, functional impairment and reduced quality of life. In consideration of this, such states appear to be closer to first episode psychosis than to healthy controls [52]. The progression of ARMS into a classically diagnosable mental disorder, with clear-cut and more stable symptoms, defines the *transition* state, defined as a significant event connoting a likely more serious illness requiring a change in treatment, namely the use of antipsychotic medications. Transition is not assumed to be inevitable, since amelioration and remission are possible. Due to its structure, this staging system is also known as a "trunk and branch" model, with the trunk representing the pluripotent risk of symptoms and the branches the particular exit-syndromes in which the former disorder crystallizes over time, such as psychotic or affective disorders [53–55]. This model also allows for so-called comorbid outcomes, for example, emergence of both psychotic and affective syndromes. This conceptual framework can guide the search for risk and protective factors for disease progression.

A more recent conceptualization of ARMS is represented by the Clinical High At-Risk Mental State (CHARMS), a broader definition of a syn-

drome that deserves treatment due to help-seeking and distress associated with presenting symptoms, albeit below threshold for canonical categorical diagnoses. Such criteria were developed on the basis of available evidence and expert clinical experience and are applied using a combination of validated instruments [56]. The CHARMS approach was aimed at identifying the sub-syndromal population at risk of severe psychopathology, providing an operational definition of a broad-spectrum pluripotent state. This requires a broadening of at-risk states for psychosis and their operationalization into a trans-diagnostic ARMS which is also in line with evidence regarding the non-specific nature of emerging psychopathology. In fact, the majority of subjects at risk for psychosis fulfill diagnostic criteria for one or more mood, anxiety, substance use and personality disorders, and the criteria capture markedly elevated risk for exit syndromes other than psychosis [57–59]. This may reflect an "early shared pathway" or a form of pluripotency of the early clinical phenotypes of mental disorders. In consideration of this, observed early signs and symptoms may not indicate a fixed trajectory to particular diagnoses and may evolve into a range of different psychiatric syndromes [60,61]. Noteworthy, subthreshold (stage 1b) states include attenuated psychotic symptoms,

subthreshold bipolar states, mild-moderate depression and borderline personality features of reduced range and shorter duration than full diagnostic threshold (see **Figure 1**). The trait vulnerability is then expanded to include history of serious mental disorders in a first degree relative, in addition to functional decline or chronic low functioning in the young person. Data show about 30% transition rate to stage 2 over a 6-12 month period in young people meeting these criteria and receiving treatment in mental health services, as opposed to <5% transition rate in help-seeking young people below this threshold (stage 1a). Furthermore, since CHARMS target is any stage 2 "exit syndrome" rather than a specific disorder outcome, the observation that evolution of symptoms from stage 1 do not necessarily follow a homotypic course (i.e., sub-threshold psychosis evolving into full threshold psychosis), but possibly heterotypic ones (i.e., attenuated mood spectrum symptoms without psychotic elements evolving into first episode psychosis), gives even more consistency to the CHARMS pluripotent model. Such broader input-output approach can include and detect a wider sample of sub-threshold conditions, allowing researchers to trace trans-diagnostic trajectories of emerging mental disorders and tailoring more efficient preventive interventions.
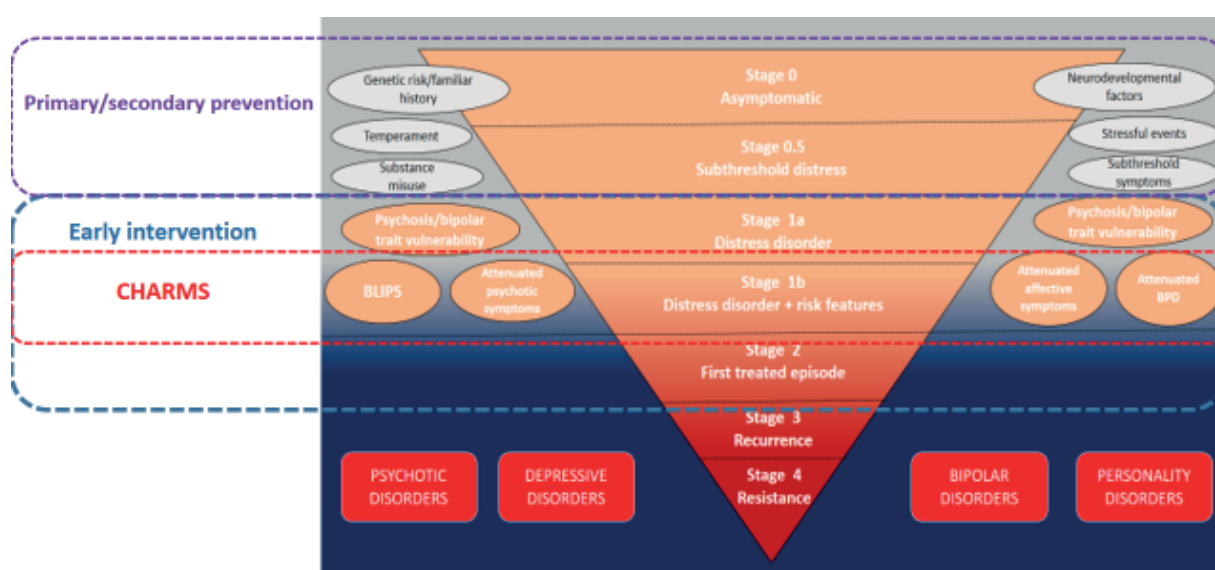

Figure 1. Trans-diagnostic staging model and possible relationship with risk syndromes and CHARMS paradigm. Readapted from Hartmann et al., 2017].

CONCLUSIONS

Risk syndromes for the development of psychosis and bipolar disorder represented a crucial focus of research during the last decades. Despite the huge amount of literature, data about the predictive value of risk criteria are not univocal. Further research on biomarkers could add specificity to such prodromal syndromes, combining multimodal factors with the aim of an individualized precision approach. Along with this possibility, trans-diagnostic models could lead towards a redefinition of staging models, taking into account the pluripotent nature of early clinical phenotypes. This approach encompasses a broader range of disorders, recognizing the complexity of emerging psychopathology and its dynamic evolution, in the attempt of an early intervention model which should be applied in order to facilitate the access to clinical services over and above the presence of a clear-cut clinical diagnosis.

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