Psychosis at the Beginning: Detecting, Understanding, and Treating: Focus on the Clinical High Risk concept

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Focus on the Clinical High Risk concept"

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ABBREVIATIONS

APS: Attenuated Psychosis Syndrome

ARMS: At Risk Mental State

BLIPS: Brief Limited Intermittent Psychotic Syndrome

CAARMS: Comprehensive Assessment of At Risk Mental States

CBD: Cannabidiol

CBT: Cognitive Behavioral Therapy

CHR : Clinical High Risk

CHR-P: Clinical High Risk for Psychosis

COGDIS: Cognitive Disturbances basic symptoms

COPER: Cognitive-Perception basic symptoms

COPS: Criteria for Prodromal States

DSM: Diagnostic and Statistical Manual of mental disorder

DUP: Duration of Untreated Psychosis

FACT: Family-aided Assertive Community Care

FEP: First Episode Psychosis

FFT: Family-Focused Therapy

fMRI: functional Magnetic Resonance Imaging

GAF: Global Assessment of Function

GRD: Genetic Risk and Deterioration

MRI: Magnetic Resonance Imaging

RANZCP: Royal Australian and New Zealand College of Psychiatrists

PRS: Polygenic Risk Score

SIPS: Structured Interview for Prodromal States

SOPS: Scale of Prodromal States

SPI-A: Schizophrenia Proneness Instrument – Adult

UHR: Ultra High Risk

SUMMARY

Psychoses are one of the main groups of mental disorders. They are complex and often debilitating illnesses that have historically been very challenging to treat. Almost 25 years ago, based in part on the observation that initial treatment delay for psychoses often led to poor prognosis, a sustained interest was born in identifying and defining early psychotic stages, with the hope of allowing for effective early detection and intervention. Based on retrospective observation of the psychotic prodrome, the Clinical High Risk (CHR) concept was developed. Representing early stages of psychosis with a risk of progressing to more advanced stages, different types of risk groups were defined: APS: Attenuated Psychosis Syndrome, BLIPS: Brief Limited Intermittent Psychotic Syndrome, and GRD: Genetic Risk and Deterioration to which the notion of "basic symptoms" was added as a risk factor. The CHR concept also allowed for the proposal and development of a staging concept as applied to psychotic disorders. Psychometric instruments developed to identify CHR states (CAARMS and SIPS instruments notably) have allowed more precise detection and evaluation. Currently it is estimated that a little over 20% of individuals detected as CHR will transition to a full psychosis within 3 years, which is less than half the rates initially reported 20 years ago. This evolution may represent more refined evaluation but also likely improved treatment. The CHR concept, particularly through the staging system, has also enhanced our biological understanding of psychosis as biological processes altered in psychosis, such as striatal dopamine or cortical thinning, which can in many cases be shown to progress across stages. This may in turn allow for better identification of biological treatment opportunities, and also facilitate the development of reliable biomarkers for psychosis. Finally, the CHR concept has allowed the investigation of preventive therapeutic possibilities for early psychosis. The most promising results are currently for cognitive behavioral therapies and omega-3 fatty acid supplementation.

INTRODUCTION

This paper aims to give an overview of what has come to be known as the clinical high risk for psychosis (CHR) concept. It has been proposed to represent an initial phase of the psychotic disorder, and the concept is linked to the notion that psychotic disorders evolve in stages. The concept has been largely in its current form for over two decades, with a wealth of research and experience to enrich it. In light of this experience, the following pages will aim to address, from a mostly clinical and slightly historical perspective, the challenges of the CHR concept: defining it in a useful manner, understanding the pathology and proposing effective treatments

Psychosis

To address defining an early phase of psychosis, attempting a definition of psychosis itself is a start. Psychosis is a term that has seen a large number of meanings, both historically and still currently. It is a widely used concept which arguably still suffers from quite a degree of ambiguity in meaning which contributes to the challenges in communicating about it and studying it.

In popular understanding the term psychosis is, and often has been, synonymous with insanity (1). Popular current definitions often focus on an abnormal contact with reality such as Merriam-Webster's:

"*Psychosis: a serious mental illness (such as schizophrenia) characterized by defective or lost contact with reality often with hallucinations or delusions"* (2)

The references to psychosis in the DSM-5 (3) relate to the definition of psychotic disorders as disorders presenting with one or more of the five following domains (symptoms): hallucinations, delusions, disorganized thoughts, disorganized behavior, and negative symptoms. Hallucinations, delusions, and disorganized thoughts and behaviors are considered "positive symptoms", termed positive because of the presence (rather than absence) of a pathopsychological process. Negative symptoms are so termed because of representing the absence of a psychophysiological process (4). The suggestion and subsequent adoption of this separation of psychotic symptoms between positive and negative symptoms in the early 1980s has been debated from the start (5). In particular a number of more recent studies pertaining to a factor analysis of psychotic symptoms strongly suggest that disorganized thoughts and behavior should be considered dimensionally separate from both other positive and negative symptoms (6). As it stands the DSM-5 classification still retains this (perhaps oversimplified) distinction and, as can be surmised, the current definitions give greater weight to positive than negative symptoms, these symptoms being briefly defined as followed:

Hallucinations: According to the DSM-5, "hallucinations are perception-like experiences that occur without an external stimulus. They are vivid and clear, with the full force and impact of normal perceptions, and not under voluntary control. They may occur in any sensory modality, but auditory hallucinations are the most common in schizophrenia and related disorders".

Delusions: The DSM-5 definition of delusions focuses on belief inflexibility: "delusions are fixed beliefs that are not amenable to change in light of conflicting evidence".

Disorganized thoughts: Disorganized thought is usually evaluated through speech and can present as various thought disorders that impede comprehension, such as circumstantiality (including irrelevant details in speech), derailment (a breakdown in the logical connection between ideas), thought blocking (disruption of thought process), or flight of ides (successions of multiple associations)(7)

Disorganized behavior: These symptoms are observed in patient's inability to complete goal-directed activities with typically inappropriate or illogical behavior. This symptoms domain includes catatonia (a condition including bizarre posturing, mutism and stupor) as an extreme form

Negative symptoms: Negative symptoms are so-named because they present the absence of a normal mental function. Negative symptoms include, affective flattening (reduced emotional expression or reaction), alogia (reduced speech), anhedonia (lack of pleasure), avolition (lack of motivation), and social withdrawal. Currently, it is generally accepted that negative symptoms include these five mentioned key constructs, which can be further categorized into two main and independent factors (8):

1. Diminished expression, including affective flattening and alogia
2. An avolition/apathy factor, including anhedonia, avolition, and social withdrawal.

Psychotic diagnoses

The DSM-5 discriminates between different psychotic diagnoses based essentially on cause (medical condition, substance, other mental disorder, or otherwise idiopathic), specific psychotic and associated symptoms, and duration. The psychotic and "schizophrenia spectrum" disorders are summarized in Table 1

Table 1: Psychiatric Diagnoses

DSM-5 Schizophrenia Spectrum and Other Psychotic Disorders
Schizotypal (personality) disorder
Delusional disorder
Brief psychotic disorder
Schizophreniform disorder
Schizophrenia
Schizoaffective disorder
Substance/medication-induced psychotic disorder
Psychotic disorder due to another medical condition
Catatonia associated with another mental disorder (catatonia specifier)
Catatonic disorder due to another medical condition
Unspecified catatonia
Other specified schizophrenia spectrum and other psychotic disorder
Unspecified schizophrenia spectrum and other psychotic disorder

Reference: (3)

Psychosis – historically

Early clinical descriptions compatible with modern psychosis are numerous. Early Greek physicians addressed and categorized mental illness with an accent on what are now called psychoses: Hippocrates first proposed classification of mental disorders included many terms still in use today such as insanity, paranoia, mania and melancholy (9).

The first use of the term "psychosis" in medical literature is usually ascribed to Austrian medical doctor Ernst von Feuchtersleben in 1845 (10). Von Feuchtersleben, like many of his contemporaries, sought to emphasize such disorders as a disease of mind *and* brain (as opposed to only the mind), which would set a first block towards the understanding of these disorders from a biological perspective. The evolution of the term "psychosis "would however be quite intricate and rich (11), laying the groundwork for over a century of confusing literature.

Emil Kraeplin is often credited with the first clinical definition of the major psychotic disorder that would later be known as schizophrenia. In his 1899 “”Lehrbuch des Psychiatrie”, Kreaplin included the psychotic disorder he termed “dementia praecox”. Kraeplin’s work solidified a medical model for the psychoses but also, as the term suggests, insinuated these psychoses were a chronic neurodegenerative disease (11).

The term schizophrenia was first coined by Swiss psychiatrist Eugen Bleuler in the early 20th century (12). In his seminal “Dementia Praecox or the Group of Schizophrenias” (1911), Bleuler renamed Kreaplin’s dementia praecox and nuanced its clinical description, but still considered it a generally deteriorating disease.

Both the notions of psychosis and schizophrenia would continue to evolve throughout the 20th century, and starting in 1952 these concepts could be followed in the succeeding editions of the Diagnostic and Statistical Manual of Mental Disorders (1st edition 1952, 2nd edition 1968, 3rd edition 1980, 4th edition 1994, 5th edition 2013). Of note, while the notion of psychoses being a brain disease remained, the definitions of the psychoses and schizophrenia were progressively descriptive and symptom based, with no etiological basis.

Focusing on more recent conceptual evolution, compared to the 4th edition of the DSM, the DSM-5 would bring some minor changes to the categorizing and descriptions of the psychoses; however a major addition in the annex (Section III under “conditions for further study”) would be the Attenuated Psychosis Syndrome. This concept (according to the DSM-5 this concept is not intended for clinical use but for research purposes) represented a first conclusion of research in the field of the beginning phases of psychosis that will be summarized below:

Why the beginning?

Towards the end of the 20th century, the psychoses, and in particular schizophrenia, were recognized as one of the major mental disorders, often presenting as a chronic debilitating disease with a poor prognosis. Despite something of a revolution in the treatment of psychoses in the 1950s with the introduction of antipsychotic medications, the severity of these diseases was often frustrating for clinicians who still had limited options to curb the poor prognosis in many patients.

This was elegantly formulated by Tom McGlashan, a leading clinical psychiatrist and researcher and pioneering proponent of early intervention in psychosis, by the following observation he made concerning his patients with schizophrenia treated in his clinic (Chestnut Lodge) (13):

“With (my patients at Chestnut Lodge) I came upon the scene too late; most of the damage was already done. I remain convinced that with schizophrenia in its moderate to severe form, our current treatment efforts amount to palliation and damage control. There is no doubt that our efforts make a difference, but they effect little if any restitution of what has been lost. For many vulnerable to schizophrenia, the ultimate answer lies in early detection and preventive intervention.”

Despite progress that had been made in the field of treatment of the psychoses and schizophrenia, McGlashan’s proposal represented a growing conviction that early intervention would be a, if not the, most effective treatment. One important observation that contributed considerably to this notion of the importance of early intervention was strong correlation of “DUP” with prognosis.

DUP

DUP (Duration of Untreated Psychosis) is defined as the duration for an individual suffering from psychosis between the first manifestations of psychotic symptoms to the first adequate treatment. Already in the 1980s it was becoming apparent that longer DUP was related to overall worse outcome (14), and a increasing number of studies would confirm this. An often cited 1991 overview by Richard Wyatt would base a recommendation for early intervention based on these observations (15).

A 2005 meta-analysis of 43 studies (including over 2500 study subjects) focusing on the relationship between DUP and outcome in first episode schizophrenia (16), clearly confirmed this association:

Longer DUP was significantly associated a poorer response to treatment: As measured by the size of effect DUP had a small to moderate magnitude effect on global psychopathology (Effect size 0.51, 95% CI 0.33-0.69), positive symptoms (Effect size 0.41, 95% CI 0.22-0.59), negative symptoms (Effect size 0.3, 95% CI 0.14-0.46), as well a global function as measured by GAF (Effect size 0.6, 95% CI 0.4-0.8). Notably, longer DUP was not significantly associated with a more severe initial presentation of global psychopathology, positive symptoms, or function, although initial presentation of negative symptoms was slightly worse (a significant but small effect size of 0.28, 95% CI 0.1-0.45). Patients with longer DUPs usually had similar first presentations (usually a hospital admission) than those with shorter DUPs, but the long DUP would indicate a less likely positive response to treatment.

There was however from the first discussions concerning the importance of DUP already debate as to the significance of the relationship between long DUP and poor outcome: One initial and main question was whether long DUP, meaning delay to treatment, was a direct cause of poor outcome, or rather a marker of more severe schizophrenia, particularly characterized by a more insidious and difficult to detect onset (17). Other hypothesis as to the relevance of long DUP and poor outcome included the implication of reduced social support or even neurotoxicity of untreated psychosis leading to poorer outcome (18).

While these considerations and more recent results (reviewed in (18)) supported the notion that DUP is not a sole and simple contributor to poor outcome, nevertheless, near the turn of the century, the psychoses and schizophrenia remained difficult to treat conditions in many cases, with growing evidence that early intervention might hold a key to improved outcomes.

DETECTING

Towards the end of the 20th century, many groups were increasingly interested in the potential benefits of early intervention in psychosis (some initial discussions brought by Max Birchwood and Pat McGorry (19) (20)). This was related to the evolving understanding of the psychotic disease as well as the direct observation of generally improved outcome for those who had benefitted from treatment earlier rather than later in the course of their psychosis (notably as observed through DUP). This would lead to a focus on the early phases of psychosis, in particular those preceding a clear-cut "first episode", when patients met clear diagnostic criteria (such as those for a DSM-5 psychotic disorder), which was usually the first presentation of these patients in a clinical setting. The idea was to define a clinical state that could identify individuals risking a later development of psychosis (21).

This preceding phase had historically been called "prodrome" (a term first coined in 1932 by Mayer-Gross (22)) by analogy with other medical disorders, but this was a retrospective (related to the psychosis phase) concept. Prospectively this would be considered a "risk state" for developing psychosis. By different authors, this risk state has been referred to as "at risk mental state" (ARMS), "ultra high risk" (UHR), somewhat confusingly still "prodrome", "high risk" or "clinical high risk" (CHR). Although each of these denominations has been attributed with specific characteristics depending on authors, recently the later denomination (CHR) is the more generally used in the field. Specifying CHR-P relates to clinical high risk for psychosis (In this review CHR is considered CHR-P)

Prodrome

The notion of psychosis prodrome was well established as the phase preceding a first episode of psychosis. As studied by Häfner and colleagues (23), the prodrome is described as a period preceding a first episode by months and sometimes years, with retrospectively observed symptoms. These symptoms include most often what are considered negative symptoms, such as reduced concentration, reduced motivation, anergia and depressed mood; less often general psychopathology symptoms such sleep disturbances, anxiety, irritability and overall deterioration in function; and even less often prodromal symptoms of suspiciousness. These retrospectively observed symptoms were generally considered nonspecific, often related to other mental disorders and as such not immediately usable for identifying individuals at risk (see below).

The Australian school ARMS, UHR and CAARMS

An Australian team led by Allison Yung and Patrick McGorry is often credited with the initial sustained attempts at defining the pre-psychosis risk state, with a first suggestion of ARMS ("at risk mental state") (21). Based on their own cohorts of young patients with emerging psychosis, Yung and McGorry observed that while most patients presented with many of the previously described "prodromal" symptoms in the years preceding a first psychosis, these symptoms were common in young adults and not readily usable to define a specific risk state. What they did observe was, often closer to a first psychosis episode (by months), variations of psychotic symptoms that were either mild or of short duration. Coupled with an overall observation of frequently reduced social function preceding psychosis and the known importance of genetic risk (see "Understanding" below), this led to the proposal of three defined risk groups:

Group 1: Individuals with a combination of trait and state risk factors, defined as relatives (1st or 2nd degree) with a psychotic disorder, or schizotypal personality disorder, combined with a change in functioning "indicative of the development of a probable prodromal state"

Group 2: Individuals having developed attenuated psychotic symptoms (defined by the authors as markedly peculiar behavior; digressive, vague, overelaborate, or metaphorical speech; odd or bizarre ideation or magical thinking; or unusual perceptual experiences).

Group 3: Individuals with a history of fleeting psychotic experiences, limited to one week, which the authors termed BLIPS: brief limited intermittent psychotic symptoms

This initial proposal of three types of risk groups at risk for developing psychosis set the groundwork for the next 20 years of research in the field.

The same group would over the years refine the definition and detection of these three risk groups.

In particular they would develop and introduce an instrument designed to identify ARMS, the Comprehensive Assessment of At-Risk Mental States (CAARMS) (24), and concomitantly define as "Ultra high risk" (UHR) (25) those individuals determined at risk of imminent transition to psychosis as determined by criteria within the CAARMS. These presented slight modifications of the criteria defining the groups already identified in their 1996 work: Group 1 was the Vulnerability group, Group 2 the Attenuated Psychosis group, and Group 3 the BLIPS group.

The CAARMS explores seven symptom domains: Positive symptoms (comprising 3 types of symptoms), cognitive symptoms (2 types of symptoms), emotional disturbance symptoms (3 types of symptoms), negative symptoms (3 types of symptoms), behavioral change symptoms (4 types of symptoms), motor/physical symptoms (4 types of symptoms), and general psychopathology symptoms (8 types of symptoms). Each symptom is rated on an intensity (0-6) and frequency (0-6) subscale. Only positive symptoms (intensity and frequency) are used to determine UHR risk status (Table 2). The CAARMS positive symptoms comprise "unusual thought content" (related to delusions), "perceptual abnormalities" (related to hallucinations), and disorganized speech

In their initial study evaluating the validity of the CAARMS as a predictive instrument, the authors noted that non-psychotic patients presenting at their clinic who were determined to be UHR using the CAARMS ("CAAMRS-positive") were over 12x more likely to develop a psychotic disorder within 6 months compared to CAAMRS-negative patients (relative risk 12.4, 95% CI 1.5-103.4). They concluded that the CAARMS had sufficient discriminate and predictive validity, as well as inter-rater reliability, to be a valid instrument for identifying at risk states for psychosis. Over the following years, this instrument would become perhaps the most widely used in the field of emerging psychosis.

The American school, Prodrome, CHR and SIPS

During the same period, American groups, led notably by Barbara Cornblatt, Tandy Miller and Tom McGlashan, were doing similar studies on young patients in an effort to also define reliable criteria for a risk state. With one of the first uses of the term "Clinical high risk" (CHR) in the psychosis setting, B. Cornblatt (26), inspired by a neurodevelopment model of psychosis, initially suggested 3 risk stages preceding a first episode psychosis, each with increasing levels of risk. An initial "attenuated negative symptoms" state characterized by negative and nonspecific symptoms (e.g., social isolation, school failures), a "moderate attenuated positive symptoms" state characterized by emerging attenuated positive symptoms of moderate intensity, and a "severe attenuated positive symptoms" state characterized by severe attenuated (but subpsychotic) positive symptoms. Of interest in this initial small (48 patients) study, transition to full-blown psychosis over a 6 month period was observed for almost half (7 out of 15) patients initially in the "severe attenuated positive symptoms" group but very rarely for the other groups (1 of 33 patients). This seemed to confirm the observations from the Australian groups that comparatively important attenuated positive symptoms were most useful for prediction risk for later transition to psychosis. This would lead American groups to progressively adopt 3 risk groups (termed syndromes) very similar to those proposed by Yung and McGorry: A Genetic Risk and Deterioration Syndrome (equivalent to the Australian vulnerability group), an Attenuated Positive

Symptom Syndrome (equivalent to the Attenuated Psychosis group), and a Brief Intermittent Psychotic Symptom Syndrome (equivalent to BLIPS).

The American groups had been developing instruments similar to the CAARMS for detecting Clinical High Risk patients: notably the SIPS (Structured Interview for Prodromal Symptoms), including its psychometric scale, the SOPS (Scale of Prodromal Symptoms), and the diagnostic criteria for attributing a risk group, the COPS (Criteria for Prodromal States) (27, 28).

The SIPS (/SOPS) differs slightly from the CAARMS in its more pronounced focus on psychotic symptoms. The SIPS/SOPS explores four symptom domains: Positive symptoms (comprising 5 types of symptoms), negative symptoms (6 types of symptoms), disorganization symptoms (4 types of symptoms), and general symptoms (4 types of symptoms). Each symptom of rated simply on an intensity (0-6) subscale. As for the CAARMS, only positive symptoms are used to determine UHR risk status (Table 1). The SIPS/SOPS positive symptoms comprise "unusual thought content" (related to delusions), "suspiciousness" (related to persecutory delusions), "grandiosity "(related to megalomaniacal delusions), "perceptual abnormalities" (related to hallucinations), and conceptual disorganization. Criteria for the 3 risk groups are compared between CAARMS and SIPS/COPS in Table 2.

Table 2: UHR Criteria CAARMS vs. SIPS(COPS)

	CAARMS	SIPS(COPS)
Vulnerability Group Or Genetic Risk and Deterioration Syndrome	1st-degree biological relative with a history of psychotic disorder OR Schizotypal personality disorder in patient AND At least a 30% drop in function (GAF score) compared to premorbid function over at least one month during last year	1st-degree biological relative with a history of psychotic disorder OR Schizotypal personality disorder in patient AND At least a 30% drop in function (GAF score) over the last month as compared to 1 year ago
Attenuated Psychotic Symptoms' Or Attenuated Positive Symptom Syndrome (APS)	For at least 1 week, score of 3-5 on unusual thought content scale, 3-4 on perceptual abnormalities scale or 4-5 on disorganized speech scale with a frequency score of 3-6 OR Score of 6 on unusual thought content scale, 5-6 on perceptual abnormalities scale, or 6 on disorganized speech scale with a frequency score of 3 AND Symptoms present in last year and for less than five years	Score of 3-5 for at least 1 of 5 symptoms (unusual thought content, suspiciousness, grandiosity, perceptual abnormalities, conceptual disorganization) AND First occurring or worsening within past 12 months AND At least once a week within past month
'Brief Limited Intermittent Psychotic Symptoms" or "Brief Intermittent Psychotic Symptom Syndrome (BLIPS/BIPS)	Score of 6 on unusual thought content scale, 5-6 on perceptual abnormalities scale or 6 on disorganized speech scale with a frequency score of 4-6 AND Each episode of symptoms is present for less than one week AND Symptoms present in last year and for less than five years	Within past 3 months score of 6 for at least 1 of 5 symptoms (unusual thought content, suspiciousness, grandiosity, perceptual abnormalities, conceptual disorganization) AND At least present for several minutes per day at a frequency of at least once per month

From (24)(CAARMS) and (28) (SIPS)

As for the CAARMS, the initial studies evaluating the validity of the SIPS were encouraging. Miller et al. determined that in their small study cohort 43% of SIPS-positive (6 of 14) non-psychotic patients transitioned to psychosis within 6 months, whereas none (0/20) of the SIPS-negative did (28).

Basic symptoms

First described by Gerd Huber (29), "basic symptoms" as related to psychosis were regarded as the earliest subjectively experienced symptoms of psychosis and could concern domains of drive, volition, affect, concentration, memory, thinking and speech (30).

Given their early presence in the psychopathological process, basic symptoms were suggested as useful for identifying psychosis risk states, notably by Frauke Schultze-Lutter (31). Her 2007 study used an instrument that had been developed to measure basic symptoms, the SPI-A (Schizophrenia Proneness Instrument – Adult) to measure Basic Symptoms in 146 putatively prodromal patients. Patients were categorized into two risk groups: a basic risk "cognitive-perception basic symptoms (COPER) group, and a high-risk "cognitive disturbances" (COGDIS) group. The high risk COGDIS group differed from the low risk COPER group by the type and number of basic symptoms present (COGDIS criteria summarized in Table 3)

Table 3

Basic symptom criterion 'Cognitive Disturbances' (COGDIS) – high risk
At least 2 of the following 9 basic symptoms • Unstable ideas of reference • Disturbances of abstract thinking • Inability to divide attention • Thought interference • Thought pressure • Disturbance of receptive speech • Disturbance of expressive speech • Thought blockages • Captivation of attention by details of the visual field AND Occurrence repetitively within the past3 months

References (30, 32)

In the initial Schultze-Lutter study (31), 23.9% of patients identified as COGDIS transitioned to psychosis within 1 year.

Although basic symptoms were subsequently comparatively less studied as opposed to UHR criteria concerning clinical high risk studies, it was suggested that basic symptoms and UHR criteria could be assessed concomitantly (33). This was done in one study combining UHR criteria (obtained with SIPS instruments) and COGDIS criteria (32). In a naturalistic 2 year study, conversion rates to psychosis were observed for 246 patients of an early intervention center who presented a UHR and/or COGDIS risk. Of the 246 patients, 194 presented risk criteria: 127 both UHR and COGDIS criteria, 37 only UHR and 30 only COGDIS. Transition to first episode psychosis was frequent for patients with combined UHR and COGDIS risk criteria (Hazard Ratio 0.66), which was a high rate for any CHR study. However, transition rates were significantly smaller within 48 months for patients with only one risk criteria set (Hazard Ratio 0.28 for only UHR and 0.26 for only COGDIS). These results suggested a clear benefit to combining risk criteria, allowing for a more precise identification of at risk individuals. In particular it led many authors to consider the CHR high risk state to be best defined as this combination of the UHR and COGDIS risk criteria.

Clinical staging

As the UHR paradigm was emerging as the dominant model for Clinical High Risk studies, with the possible concomitant use of basic symptoms criteria, the concept of clinical staging began to be suggested as a complementary framework

The theoretical proposition was introduced already in the early 1990s by Giovanni Fava, who proposed that "The phenomenological development of schizophrenia, unipolar depression, bipolar disorder and panic disorder may be categorized according to stages" (34). However , the proposition was brought to the forefront almost 15 years later when one of the main actors in the field, Patrick McGorry, suggested that "*defining discrete stages according to progression of disease creates a prevention-oriented framework for understanding pathogenesis and evaluation of interventions.*" (35). Directly inspired by other fields of clinical medicine where categorizing diseases and their progression guided appropriate treatments, the application to psychiatry was suggested as a useful tool, particularly in the field of emerging disorders. Using staging, interventions could be evaluated not only in terms of improvement, but also preventing or delaying progression from earlier to later stages. Furthermore, it was suggested that this staging framework could provide a basis for more precisely studying biological and risk variables across stages.

As did Fava et al., McGorry et al. proposed a 4 stage model (0 to 4), elaborating more on criteria for each stage. Stage 1 was equivalent to prodromes or clinical risk states, stage 2 represented a first-episode of full threshold disorder, and stages 3 and 4 represented chronic evolutions (relapses, and severe persistent, respectively) of the disorder. As applied to psychotic disorders, the application of the four stages is defined in Table 4:

Table 4

Stages of psychosis according to McGorry et al., 2007(35)
Stage 0: Increased risk of psychotic disorder but no current symptoms
Stage 1a: Mild or non-specific symptoms of psychosis. Mild functional change or decline
Stage 1b: Ultra-high risk: moderate but subthreshold symptoms with functional decline
Stage 2: First episode of psychotic disorder: Full threshold disorder with moderate to severe symptoms
Stage 3: Incomplete remission after first episode psychosis, or psychotic recurrence(s) or relapse(s)
Stage 4: Severe, persistent or unremitting psychosis

The staging paradigm for schizophrenia quickly gained ground, at least theoretically, and was notably used (although in somewhat different form from McGorry's proposition) in the influential 2010 perspective paper by National Institute of Mental Health director Thomas Insel, "Rethinking Schizophrenia" (36). Insel saw the staging model as effective in linking the clinical progression of schizophrenia with putative biological progression, largely linked to a neurodevelopmental understanding of schizophrenia.

The validity of a staging model was somewhat supported by studies of Australian teams, applying staging criteria to patients presenting for mental health care in a clinic specialized for young adults (37). Patients were assigned to stages according to presenting symptoms (psychotic for the majority of patients, but also with anxiety and/or depressive symptoms for some) and categorized into stage 1a, 1b, 2 or 3. Out of 209 patients, with a mean age of 19.9 years, over a one year period 10% presented as stage 1a, 54% stage 1b, 25% stage 2 and 11% stage 3. The interrater reliability for stage attribution was considered acceptable (at k=0.71). Furthermore over a period of approximately 1 year, 11% of 1a, 19% of 1b and 33% of stage 2 patients progressed to a later stage. This study supported the notion of staging as a reliable diagnostic approach, with validity and usefulness in a clinical setting. Further studies would

also demonstrate usefulness for the staging approach to psychosis for biological measures (see "Understanding" below).

Summarizing staging and risk states in Table 5, in particular their temporal relationship, stage 0 represents essentially a genetic risk present from birth with no apparent symptoms, Stage 1a is an early (prodromal) risk state present years to months before a possible first episode of psychosis, which would putatively present essentially as basic symptoms. Stage 1b is a late (prodromal) risk state more proximal to a possible first episode (weeks to months preceding), consisting essentially of attenuated psychosis syndrome, BLIPS, and/or functional decline related to genetic risk.

Table 5: Phases of Clinical Risk and High Risk for Psychosis in relation to FEP

	Premorbid	Prodromal (Early)	Prodromal (Late)	FEP
Staging Model	**Stage 0**	**Stage 1a**	**Stage 1b**	**Stage 2**
Basic Symptoms		Present early, with tendency to increase over time		
GRD	Genetic risk present from birth, deterioration months to year before FEP			
APS				
BLIPS				
Time frame (before FEP)	Lifetime	Months-years	Weeks-months	

Grayed boxes represent usual timeframe of presence of symptoms of given risk state

GRD: Genetic Risk and Deterioration APS: Attenuated Psychosis Syndrome BLIPS: Brief Intermittent Limited Psychosis Syndrome FEP: First Episode Psychosis

Psychosis Clinical High Risk and the DSM-5: "Condition for further study"

Beginning in the second decade of the 21st century, experts were reviewing various data in view of revising the DSM for a fifth edition. At this point, the field of CHR had already over a decade of experience, and the inclusion of its various concepts was debated (overview in (38)). Firstly, despite the accumulated evidence, there was still considerable doubt as to the reliability of the various risk states as defined and also the usefulness in predicting actual risk to transition to FEP. APS was the most frequently reported risk state in the literature (compared to GRD, BLIPS, and the basic symptoms risk states) and considered the most reliable. At that time for APS, the risk of transition to psychosis at 3 years was estimated at 36% based on available data (38). As the inclusion of specifically APS as a DSM-5 diagnostic category was hotly debated, arguments against inclusion included: 1.New psychosis diagnoses (even attenuated) would be stigmatizing; 2. It would lead to unnecessary antipsychotic treatment; 3. The majority of individuals with APS would be expected to not develop psychosis; 4. A new diagnostic category would be poorly justified because no effective treatment was validated; and 5. The diagnostic reliability of APS could be in itself poor. Rebuttals to these arguments included that sufficient education and support (for both patients and mental health care professionals) could limit 1 and 2; and for 3 and 4 prevention of psychosis was argued to be only one (if an important) objective of the diagnostic inclusion, it was argued that most APS patients are help-seeking and deserve treatments, which were already being investigated at the time (see below "Treating")(39). As for the diagnostic reliability of APS, initial field trial results were inconclusive. The overall estimate of reliability was in the good range (kappa of 0.46, similar to schizophrenia), but the 95% confidence interval surrounding this estimate was very wide and considered of unacceptable precision,(40).
Finally, the emerging consensus, at least among the involved experts, was that individuals with CHR, in particular APS, did require and deserve treatment (especially when help-seeking), and were at significant risk for ulterior psychosis (and possible other psychiatric disorders, see below). The strongest

consensus seemed to be that CHR and APS were still insufficiently understood and merited further research. Thus a compromise was reached and the proposed criteria for APS "Attenuated Psychosis Syndrome" were included in the section "Conditions for further study", with the specification that these criteria were "not intended for clinical use" but as facilitating further research. The proposed criteria were essentially a fusion of CAARMS and SIPS criteria for APS (see Table 1) and are given in Table 6.

Table 6

DSM-5 Criteria of Attenuated Psychosis Syndrome
At least one of the following symptoms is present in attenuated form, with relatively intact reality testing, and is of sufficient severity or frequency to warrant clinical attention: delusions, hallucinations, disorganized speech
AND
At least once a week within past month
AND
First occurring or worsening within past 12 months
AND
Symptoms are sufficient to warrant clinical attention
AND
Symptoms are not better explained by another disorder
AND
Criteria for any psychotic disorder have not been met

Reference: (3)

Transition to psychosis and validity

20 years on, the base criteria for three main CHR states (GRD, APS and BLIPS) have changed little since the initial propositions of the 1990s. The most significant additions would be the concept of basic symptoms (however very inconsistently used), and the superposition of the staging concept to the CHR states.

Concerning the actual use of the CHR concept, one important factor evaluating validity was the transition rate, indicating how much of a risk a positive CHR "diagnosis" was. Although initially reported transition rates for the UHR states were comparatively high (37 % transition to psychosis within 12 months), an intriguing observation was a progressive decline in reported transition rates the successive studies over the years. An initial Australian study by Yung et al. in 2007 (41) estimated a yearly decline by 80% in published transition rates. This was confirmed in a review by the same group in 2015 which elaborated on possible explanations (42). While the authors attributed the declining rate in part to increased awareness of CHR in professionals and health care users (leading notably to faster referrals and better outcome), this trend underlines methodological issues concerning the validity of the CHR concept and contributed to criticisms already evoked during the DSM-5 debate.

A recent large review (a PRISMA-compliant systematic review of meta-analyses) concerning most data on transition and transition rates in CHR was presented in early 2020 (43). This presents the most comprehensive review of the data to date and includes results from 42 meta-analyses covering 81 independent studies, including measures from over 10'000 individuals, using UHR criteria from

CAARMS or SIPS or DSM-5 (of note there were no meta-analyses of basic symptoms meeting inclusion criteria for this review). Including data from numerous primary and secondary health care centers around the world, an initial review of data revealed that 85% of CHR (testing positive on a CHR instrument) individuals met APS criteria, 10% BLIPS criteria and 5% GRD criteria, clearly confirming earlier appreciations that the APS CHR state was the most frequently encountered in clinical settings (and validating the DSM-5 decision to focus on this category).

Concerning transition rates, it was found that overall, 22% of CHR positive individuals transitioned to psychosis within 3 years. When looking individually at each risk group, APS-positive individuals transitioned at 24% at 3 years, BLIPS at 38% at 3 years, and GRD at 8% at 3 years. The authors noted that CHR-negative controls from the analyzed studies had a transition risk to psychosis at three years that was not significantly different than that of the GRD group.

Concerning instrument validity (CAARMS and SIPS), the authors conclude that these instruments have high sensitivity (95% for SIPS and 86% for CAARMS), but low specificity (47%). This translates to these tools being deemed useful for screening "enriched "populations, such as help-seeking individuals at clinics where the proportion of individuals with risk for developing psychosis is inherently high, but not valid for screening the general population.

This generally confirms a transition rate to psychosis that remains clearly significant with valid instruments, but that is also significantly lower in recent studies compared to the initial analyses of the last century. One critical factor seems to be recruitment of patients, as all studies are based on voluntary help seeking individuals. Another factor that has been mentioned is poor control for treatment effect in most studies, as there is very little data for CHR positive individuals receiving no care (44).

Transition to non-psychosis

Finally an important and more recent observation of the outcomes from long term CHR studies has been that transition to non-psychotic disorders and more generally functionally impaired states is considerably higher than transition to solely a psychotic disorder. This has led to the suggestion that the currently used psychosis CHR more accurately represents a general pluripotent risk state and not simply a marker of psychosis risk (45).

In a 6-year study of 74 UHR patients (46), patients in this risk group overall presented a transition to psychosis of 28.4%, consistent with previous and subsequent findings in other studies. However, an additional 28.3% reported persistent APS, 45.3% were significantly functionally impaired, and 56.8% had at least one non-psychotic comorbid disorder.

These results largely corroborated a previous study from the Australian group of McGorry and Yung (47) of 226 participants who had between 2 to 14 years before the study been identified as UHR patients and had not transitioned to psychosis. Of these patients 28% reported persistent APS and 68% experienced a nonpsychotic disorder, including mood disorder in 49%, anxiety disorder in 35%, and substance use disorder in 29%.

UNDERSTANDING

One of the hopes of the CHR and in particular staging model was that it could aid in the understanding of the pathogenesis of the psychoses, and in turn, a better understanding of the psychotic disease could help refine defining criteria for CHR and improve patient detection and treatment. The CHR paradigm has added to an already large field and evolution of our comprehension of the disease. Heavily influenced by the Kraeplinian concept of dementia praecox, for much of its history, schizophrenia and the chronic psychoses were considered essentially neurodegenerative diseases. Towards the mid 1980s, the neurodevelopment model began to be more in favor, particularly in light of growing studies associating the development of schizophrenia with the interplay of hereditary and environmental factors (48). A prevailing current biological model posits a neurodevelopmental disease characterized by abnormal cortical and subcortical development, with notably consequent dysfunctional striatal dopamine function. The developmental dysregulation seems influenced significantly by genetic factors, but also environmental factors such as pre or perinatal complications, chemical insults, and also sociodevelopmental factors such as adverse life events, migration or urbanicity (48). Of interest to the CHR paradigm can thus be its interplay with hereditary and non-hereditary risk factors, and also its relationship to the pathogenesis of psychosis and finally possible identification of biomarkers that could aid in refining the CHR criteria.

Risk factors

With the caveat that correlation is not necessarily causation, much of what has been posited concerning the pathophysiology of schizophrenia and the psychoses is based on risk factors; factors associated with the development of psychosis. Although several hundred numerous and varied factors have been described to associate with the development of schizophrenia (heeled footwear is a bizarre favorite for introducing conferences (49)), only a few have been shown to have consistent and robust associations

Hereditary risk factors

The most significant risk factor for the development of schizophrenia is hereditary: the monozygotic twin of an individual with schizophrenia has a 50 fold increase in risk of developing schizophrenia compared to controls, and having a first degree relative with schizophrenia confers an approximate 10 fold risk (50). This strong association spurred an avalanche of research into the genetics of schizophrenia starting in the 1980s. After decades of research, the emerging genetic understanding is that of schizophrenia mediated by a large number of common genetic variants, each with small effect associated with a small number of variants with comparatively large effect (48). Of note, some genetic variants seems to confer risk for several psychiatric disorders such as psychosis, bipolar disorder, depression or autism (51, 52). Furthermore, advances in the field of psychosis genetics has allowed the development of a polygenic risk score for schizophrenia (53), although this score has been calculated to explain only 9% of the variance for schizophrenia, suggesting it is not useful for clinical routine.

Non-hereditary risk factors

As alluded to, a large number of factors have been associated with the later development of schizophrenia or psychosis. Of these a recent Radua et al. review determined that a relatively small number of factors showed consistent associations with a strong level of evidence (54). These included immigrant or ethnicity status (relative risk of developing psychosis compared to controls approximately 2-5), urbanicity (growing up in an urban environment, relative risk 2.19), winter birth (relative risk 1.09), childhood trauma (relative risk 2.87), and olfactory abnormalities.

Both immigrant and urban status have been the subject of numerous studies and have been posited to exert effect through socio-environmental adversities, similar to directly measured childhood adversity. Although there is considerably evidence overall for contributions of perinatal and obstetrical complications to the development of psychosis (55), Radua et al. suggest that the evidence is comparatively weak even though ample, with the exception of a small but significant effect of winter birth. The interesting and strong association with olfaction was reviewed by Moberg et al.(56): A meta-analysis of 67 studies of olfaction in schizophrenia patients revealed significant although heterogeneous deficits in olfaction in patients and the authors suggested olfactory measures could be used as markers for schizophrenia.

A further well studied but debated risk factor for schizophrenia is cannabis use. Radua et al. concluded that overall evidence for association was not strong. In a review of the subject, it is concluded that there is an overall moderate direct association of use and later development of schizophrenia (57).

Risk factors and CHR

One would suspect that if the CHR was an early stage of a disease that could progress to psychosis and schizophrenia, it would share similar risk factors. A simple comprehension could be that risk factors predisposing to CHR predispose to schizophrenia by virtue of CHR itself. Although risk factors have generally been less studied in CHR cohorts, and usually limited to checking if they are present in CHR patients, many of the important risk factors observed for schizophrenia are described in CHR (summarized in Table 7).

Table 7: Selected risk factors in schizophrenia and CHR

Risk Factor	Association with schizophrenia	Association with CHR
Heredity	Very strong	Yes (limited studies)
Urbanicity	Strong	No (not investigated)
Migration	Strong	No (58)
Childhood trauma	Strong	Yes
Olfaction	Strong	Yes
Drugs – Cannabis	Moderate	Yes
Obstetrical Complications	Moderate	Yes

References: (43, 54, 59)

The direct association of genetic factors with CHR has been studied in a somewhat limited manner for the moment, and no meta-analyses have addressed this question. However a recent report from the Singapore based LYRIKS study, including 108 CHR patients and 102 controls, found that the schizophrenia polygenic risk score (PRS) associated with CHR patients compared to controls (OR = 1.82) (59). Another recent study suggested that genetic risk as determined by the PRS could be used as a tool to improve predictive accuracy in CHR (60). In their study of 764 CHR patients, Perkins et al. observed an overall transition to psychosis rate of 16%. Including PRS scores modestly improved accuracy of prediction of transition to psychosis (calculated information contributed was estimated at 15% for patients of European descent, and 7% for non-Europeans). While the results of these studies were perhaps not spectacular, they represent a first significant foray into combining genetic with clinical CHR information in an effort to improve validity of the model.

Other associated risk factors with CHR include childhood trauma (more likely in CHP patients than controls, Cohen d=0.62-0.98 depending on type of trauma), obstetric complications (Cohen d= 0.62), and olfactory anomalies (Cohen d= 0.71) (43)

In CHR patients' cannabis use is more prevalent compared to controls (27% vs. 17%). Furthermore, cannabis use at time of CHR diagnosis was associated with an increased risk of future psychosis (Cohen d= 0.31) (43)

Dopamine

Based on the importance of the dopamine theory in psychosis (in particular the notion that excessive dopamine function in ventral striatum leads to psychotic symptoms, (61)), early studies investigated dopamine function according to psychosis stage. Howes et al. (62) observed in a study of brain dopamine that brain striatal dopaminergic function, as measured by (18)F-dopa uptake, was increased in schizophrenia patients (7 patients) compared to healthy controls (12). Of interest in this study, Howes included 24 CHR patients (psychosis stage 1b), who showed striatal dopamine function at intermediate levels between those observed for controls and schizophrenia patients (stages 2-3), suggesting that dopamine dysfunction started already in the risk phases.

Brain imaging and structure

Soon after the proposal of clinical staging models, small but significant brain imaging studies seemed to confirm the validity of staging: in a general brain structure study comparing brain volumes in patients with stage 1b, 2 and 3 psychosis, the gray matter decrease generally seen in schizophrenia was more pronounced in advanced stage patients, particularly in frontal regions, compared to early stage patients (63). Furthermore, other brain volumetric abnormalities tended to increase across stages, in particular the lateral ventricles, the brain structures most often observed to be abnormal in schizophrenia, which were on average less enlarged in stage 2 patients compared to stage 3, and even less so in stage 1a patients.

Brain imaging and machine learning

Based on the notion that both in (stage 2) psychosis, as well as clinical high risk population (stage 1b), structural brain abnormalities could be observed compared to normal controls, several groups set out to use brain imaging as biomarkers for early psychosis.

Using a machine learning approach, MRI-based classification methods were developed allowing the prediction of transition to psychosis CHR subjects. As reported by Zarogianni et al. (64), these approaches have achieved between 75% and 85% accuracy in prediction transitions in small cohorts. The neurostructural abnormalities used in the classification methods are, depending on the group, distributed to different cortical and subcortical regions, but tended to agree with findings from voxel-based meta-analyses of structural brain abnormalities in CHR patients (65)

Other biomarker candidates

Some of the more promising biomarker candidates to aid in identifying and classifying CHR states include those mentioned such as polygenic risk score, or brain structure or chemistry markers. Further possible candidates (reviewed in Liebermann et al., 2019 (66)) that have been investigated include altered sleep spindles (67), salivary cortisol (68), decreased mismatch negativity (68), and blood-based markers (in particular markers of inflammation, oxidative stress, and the hypothalamic-pituitary axis) (69).

TREATING

Defining the CHR paradigm gave the opportunity to develop phase specific treatments. Several approaches have been studied, often taking with slight adjustments treatments used in later phases of psychosis. One of the treatment goals most often aimed for is and measured is limiting transition to psychosis, with secondary goals of alleviating symptoms and burden of the early stage disease. For many authors recently, there have as yet not been any treatments that have been shown to be clearly effective (66). As detailed below, after the initial proposals and definitions of criteria for CHR, several therapeutic approaches were studied. Initial studies focused on antipsychotic medication, cognitive behavioral therapies (CBT), and omega-3 fatty acids. Some subsequently suggested approaches investigated amino acids, family interventions, or cannabidiol.

Antipsychotic medication (olanzapine or risperidone)

Amongst the first therapies proposed to treat the CHR state were antipsychotics, given this approach has for decades been the mainstay of treatment for most psychotic disorders.

An initial study by the Australian group having defined the UHR paradigm compared CHR patients receiving low dose risperidone combined with CBT, to patients receiving only CBT, or only supportive therapy (70). This initial 2002 study with 59 patients was followed up by a 2013 study with 115 patients, concluding that there were no significant differences between groups, and in particular that risperidone had no significant effect on transition rates to psychosis at 12 months.

An American study investigated the effects of another antipsychotic, olanzapine (5 to 15 mg/d) over a 1 year period in 31 CHR patients compared to 29 CHR patients receiving placebo (71). At 12 months, 16.1% of olanzapine treated patients had transitioned to psychosis whereas the rate was 37.9% in the placebo group. However, this difference was not statistically significant. Furthermore, and not surprisingly, the olanzapine group experienced significantly more side effects, in particular weight gain.

A recent Cochrane meta-analysis (72) concluded that based on these studies, antipsychotics do not provide any significant advantage over control treatments, with significantly worse side effects.

After these initial studies of medication with unenthusiastic results, most authors concluded that antipsychotic medication was not a warranted therapy for CHR patients and no consequential further studies were done.

Cognitive Behavioral Therapy (CBT)

Initial CBT approaches for CHR suggested psychotherapies often focused on attenuating symptoms or improving function. Several groups published results on their approaches with initial mixed results but overall more encouraging than for antipsychotic medication.

A Canadian study randomized 51 CHR patients to receive CBT or supportive therapy for up to 6 months and measured transitions and symptoms over an 18 month period (73). Although more patients from the supportive therapy group transitioned, the results were not statistically significant, which was also the case for other clinical measure results.

In a large Dutch study of 201 CHR patients, a CBT-based therapy particularly targeting cognitive biases (related to the formation of delusions), was proposed to one group, while the control group received treatment as usual (74). CBT was provided for 6 months and patients followed for 18 months. Over that period, twice as many control group patients transitioned to psychosis compared to the CBT group (22 vs. 10), which was a significant difference ($p=0.03$): Furthermore, CBT benefitting patients were also significantly less symptomatic at 18 months.

A 2012 German study recruited 128 outpatients presenting a CHR determined using basic symptoms as criteria (75). 63 received an integrated psychological intervention including CBT, and 65 supportive counseling. CBT receiving patients presented less transitions to psychosis at 12 months of study than the control group (3.2% v. 16.9%; p = 0.008) and at 24-month follow-up (6.3% v. 20.0%; p = 0.019).

Finally, an English group performed two successive studies for patients receiving CBT therapies vs. treatment as usual, initially for 58 CHR patients (76), and then another group of 288 patients (77). For the first study CBT showed superiority to control for transitions at 1 year, but this did not persist at a follow up of 3 years. For the second larger study, CBT did not seem to offer a benefit for transition rates evaluated between 12 to 24 months of the study. However the authors noted that CBT reduced symptom severity and furthermore that most participants in both CBT and control groups improved.

In the Kuharic 2019 Cochrane review (72), a meta-analysis of the above CBT studies concluded that overall CBT significantly reduced transition rates. The calculated relative risk for transitioning to psychosis for CBT receiving patients compared to controls was 0.47 (95% CI 0.29-0.76) at 12 months (368 included CBT patients, 360 controls), 0.45 (95% CI 0.29-0.89) at 18 months (124 included CBT patients, 128 controls), and 0.32 (95% CI 0.11-0.92) at 24 months (63 included CBT patients, 65 controls). Overall, authors suggested that CBT could tentatively be considered an effective treatment for reducing transition to psychosis in CHR patients, although the evidence was considered of poor quality, in particular given the heterogeneity of therapeutic approaches and patient characteristics across studies.

Omega-3 fatty acids

Omega-3 fatty acids have been postulated to modulate cell signaling and affect dopaminergic and serotonergic pathways in the central nervous system and have been suggested as therapeutic in a number of psychiatric disorders (reviewed in Bozzatello et al. (78)). In the field of CHR, initial results, notably from the Amminger group, led to omega-3 fatty acids being considered one of the more encouraging options.

A G. Paul Amminger group study recruited 81 patients with CHR (79). Half received 1.2 g/d of omega-3 polyunsaturated fatty acid over a 12-week period, and the other half received placebo. The treatment phase of the study was followed by a 40 week observation phase with outcome measures at 1 year. Main measured outcome was transition to psychosis and secondary measures included symptoms and function. At 1 year 2 (4.9%) of the omega-3 group had transitioned, whereas a highly significantly greater 11 (27.5%) of the control group had (p=0.007). The omega-3 group also showed significantly better improvement of symptoms (p=0.01) and functioning (p=0.002). Adverse effects did not differ between groups and were low for both groups. This group would go on to publish further follow up studies for these patients, but already the strength of the initial results led many clinicians in the CHR field to start offering this treatment to at risk patients (personal observation).

Somewhat anticlimactically, a subsequent larger 2017 replication study led by Pat McGorry did not reproduce the same results (80). This study was about four times larger than the Amminger study (153 CHR patients in omega-3 group, 151 in placebo group). At 12 months, transition rates to psychosis were almost identical at 11.2% (95% CI 5.5%-16.7%) for the control group vs. 11.5% (95% CI 5.8%-16.9%) for the omega-3 group. Given the apparent non-effectiveness of omega-3 treatment in this study, the authors noted that all patients had shown substantial improvement over the 12 month study period and concluded that "omega-3 polyunsaturated fatty acids are not effective under conditions where good quality, evidence-based psychosocial treatment is available".

In Kuharic's Cochrane review (72), a meta-analysis of the two omega-3 studies concluded that overall omega-3 treatment did not significantly reduced transition rates at 12 months. The calculated relative risk for transitioning to psychosis at 12 months for patients receiving omega-3 compared to placebo was not significant at 0.5 (95% CI 0.08-3.08) at 12 months (194 included omega-3 patients, 191 placebo patients). Taking the data from each of the two omega-3 studies individually, the relative risk for

transition for omega-3 receiving patients was calculated at 0.18 (95% CI 0.04-0.74, 81 study patients) for the Amminger study and 1.12 (95% CI 0.58-2.16, 304 study patients) for the McGorry study at 12 months for both studies. The Kuharic review also included data from a 7 year follow-up study of 81 patients from the Amminger study. The relative risk of transition (omega-3 vs. placebo) calculated at this time point was significantly low at 0.24 (95% CI 0.09-0.67). Despite this therapeutic effect being from only one study, Kuharic et al. considered it the most promising and significant of the entire review (and by extension the omega-3 effect at 7 years the most significant studied to date for CHR patients).

Amino acids (glycine / serine)

Two comparatively small but interesting studies analyzed therapeutic effects of amino acid treatments for CHR patients: Woods et al. (81) performed a 12 week placebo controlled trial of glycine treatment in a total of 8 patients and found glycine treatment improved symptoms. Kantrowitz et al. (82), with a slightly larger placebo controlled trial of 35 patients found that D-Serine had beneficial effects on the improvement of negative symptoms. Neither of these studies however reported significant effects on transition rates.

Family interventions

Two studies on family interventions for CHR patients did not demonstrate measurable effects on transition rates to psychosis, but did suggest other benefits:

A 2014 study by O'Brien et al. (83) investigated the effect of family-focused therapy (FFT), an 18 session intervention including psychoeducation and training in communication and problem solving. 66 CHR patients and their families or significant others were involved and for those receiving FFT, measurable and significant improvement in family communication was observed. The authors suggested further study to investigate whether improved family communication could influence transition to psychosis.

In a non-randomized 2015 study by McFarlane et al. (84), 337 patients presenting at an early detection and intervention program were offered treatment based on their estimated risk level for developing later psychosis. High risk patients received FACT (Family-aided assertive community care), and those at a lower estimated risk received standard community care. Although given the study structure interpretation was difficult, FACT seemed to have a comparatively beneficial effect on symptom evolution but not a significant effect on transition rates (6.3 % at two years for the high risk patients receiving FACT, 2.3% at two years for the low risk patients receiving standard community care).

Cannabidiol (CBD)

Cannabidiol, one of the major cannbinoids found in cannabis, has been studied as a possible therapy for psychosis (85). A recent study of CBD use in CHR, while not strictly a therapeutic investigation, sought to determine the effect of CBD on brain function measured by fMRI (86). This study measured brain activation in brain areas after a cognitive task and found that a single dose of CBD improved activation of parahippocampal, striatal and midbrain structures (regions implicated in psychosis and cognitive function) compared to placebo receiving CHR controls. The authors suggested that improved activation of these areas could underlie therapeutic effects.

Therapeutic guidelines - Stage specific treatment

Taking into consideration the studies performed, some authors and groups have been recommending certain therapeutic approaches for CHR patients, despite not very strong evidence for any particular intervention so far. One of the currently most cited guidelines for CHR treatment and the only national

guidelines to clearly incorporate a staging model into treatment recommendations, are the 2016 clinical practice guidelines for the treatment of schizophrenia and related psychotic disorders from the Royal Australian and New Zealand College of Psychiatrists (87). The RANZCP guidelines identify several potential benefits of intervening in CHR (termed "pre-psychotic" stages). These include that intervention may lessen social disability, favor engagement with mental health professionals, lessen trauma and stigma, and reduce duration of DUP and delay or prevent transition to psychosis.

For patients diagnosed with CHR with proper assessment, regular monitoring is recommended (every 2-4 weeks), and CBT is proposed as a preferred intervention. Also recommended is appropriate management of co-occurring syndromes such as depression and substance abuse, and information about level of risk should be given.

Finally, the RANZCP guidelines do not recommend antipsychotic treatment for CHR patients unless they present frank psychotic symptoms or unremitting subthreshold symptoms unresponsive to other approaches. Of note, the RANZCP guidelines do not recommend using omega-3 fatty acids ("fish oil supplementation"), stating that results are so far inconclusive.

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CONCLUSION

Early detection and intervention as it pertains to CHR is now well within its third decade. One of the main initial clinical justifications for introducing this concept and allocating health care resources to it was to nip psychotic diseases in the bud by detecting them early and treating them when they were ostensibly more easily (or effectively) treated. It is difficult to ascertain precisely how well this goal has been achieved.

The initially proposed criteria for early stages of psychosis, conceptualized as "risk states", or CHR, have changed little from their first introduction, with still three defined risk groups (APS, BLIPS and GRD), with the addition of the concept of basic symptoms as a fourth group (or more accurately fourth and fifth with COPER and COGDIS groups), and superposition of a staging concept, which relabels two risk groups: Stage 1a (which can roughly be understood to encompass the early GRD group, and early basic symptoms such as COPER), and Stage 1b (roughly APS, BLIPS, late GRD and late basic symptoms such as COGDIS).

The validity of these risks groups as capable of accurately predicting a future psychotic disorder has been critiqued, in large part because of diminishing "transition rates" over the years since initial reports. For some authors the consideration is that if the majority of CHR patients do not transition to psychosis, diagnosis of CHR is not particularly valid and intervention is not justifiable (38, 88). However, the majority of CHR individuals in transition studies receive non-specific treatments (usually supportive care or needs-based interventions, which in therapy studies are often considered control conditions)(42). There are as yet no reliable studies of transition rates for CHR individuals receiving strictly no treatment, leaving open the question of the impact of non-specific treatment on transition rates. As such, the important apparent reduction of transition rates over 20 years, given that CHR criteria have remained relatively stable, may be indicative that CHR are being treated more effectively and therefore transitioning less, even if we don't yet have a clear idea of what treatment is helping (more on that below). While this would suggest that early detection and intervention is already preventing transition to psychosis in a portion of CHR patients presenting for care, the amplitude of this effect has yet to be determined.

Furthermore, the majority of CHR patients who do not transition to psychosis are usually not "spontaneously remitting". Up to 65% of them remain symptomatic at CHR stages at 2 years despite not transitioning further (89), or may develop or retain symptoms of other psychiatric disorders (usually anxiety and/or depression) (43).

Taken together, these observations do seem to validate the concept in that CHR detection allows help seeking individuals who are both impaired and at risk of developing more severe psychosis to be oriented to appropriate health care.

The current 3 UHR groups are potentially debatable. Particularly as the presentation and evolution appears different between groups, grouping them conceptually into the same risk category does not seem justified. The BLIPS group present apparently the highest risk of psychosis transition but is also "closest" to psychosis (depending on specific presentation a BLIPS diagnosis is often equivalent to a brief psychotic disorder) and perhaps should be treated as such. With accumulating data, the GRD group is first of all rarer, and risk to transition is not different from the general help seeking population of specialized centers (43). This questions the usefulness, particularly clinical, of this grouping. The focus of the DSM-5 on APS seems very warranted as the most promising group to focus on, in particular to improve treatment options for a less heterogeneous CHR group. Finally, the current comparative paucity of data for basic symptoms defined CHR does not strongly support using these criteria clinically. However, using basic symptoms to enhance risk estimation for the APS has shown interesting first results and could benefit from further research (32).

One striking observation concerning early detection of psychosis is that despite the widespread use of CHR detection in youth mental health services, the majority of first episode psychoses present without

ever having been detected as a CHR (between 88 to 95% of individuals with FEP have been reported to not have passed through detectable CHR stages (90)). Thus refining current categorization of CHR might not be sufficient. Defining new CHR criteria may be of interest, in particular if this could allow for the stratification of risk for developing psychosis. A recent meta-analysis (91) of risk factors in CHR predisposing to transition to psychosis confirmed that attenuated psychotic symptoms are as of yet the best predictor for ulterior development of psychosis. However this study also found that global functioning and negative symptoms show promise as usable risk factors for predicting transition. This could encourage a possibly more refined use of symptom domains not currently central to CHR definition, notably negative symptoms which historically were most associated with the concept of prodromes. Also promulgated strategy currently investigated to refine CHR precision and stratify risk is the development of biomarkers. Very promising results for neurostructural (92), neurophysiological (93) and neurochemical markers have been described, as well as possible genetic (polygenic risk score), to name a few. However as noted by Lieberman et al. (66), no currently investigated potential biomarker is yet sufficiently reliable to be clinically applied.

The CHR paradigm also appears to have enhanced our biological understanding of psychosis. In particular the staging system has shown merit, as biological processes altered in psychosis, such as striatal dopamine or cortical thinning can in many cases be shown to progress across stages. This can and will allow a more precise temporal localization of biological alterations unfolding during the psychotic process. Also it can allow for a more refined hypothesis driven development of risk factors, which combined with those already better studied (91), may further refine our possibilities to asses risk and stratify patients accordingly. A further potential benefit would be a better identification of biological treatment opportunities.

Finally, concerning treatment possibilities for CHR individuals, an initial assessment of the research to date could be seen as frustrating: Of the many treatment modalities explored, none seem to clearly show effectiveness, with some argument for CBT, and possibly omega-3 fatty acids (currently appreciated to be a long term protection against transition to psychosis). In response to this for future research, refining the CHR criteria (potentially with use of biomarkers), refining treatment modalities, and also being clear on treatment objectives (notably differentiation between aiming to lower transition rates or improve symptoms and function) may allow for more easily identifying effective treatments.

A final comment on treatment is that non-specific treatments offered in many early intervention services do seem to be working, if only based on the observation of decreasing transition rates. In particular a survey of English early intervention services discovered that current recommendations for treating CHR are not all that respected: Despite recommendations to favor CBT and avoid antipsychotics, CBT proposal is not widespread, whereas antipsychotic prescription is (94). Perhaps a better understanding of how effective current non-specific treatments offered are, and why, could refine therapeutic options.

To summarize, after more than 20 years, the CHR concept has arguably been very beneficial, both in detecting and treating individuals needing help and contributing significantly to our evolving understanding of psychosis. Future directions could include refining the concept and criteria based on evidence accumulated so far, but also enlarging the concept to other criteria (other symptom domains, biomarkers) once the research justifies it. A similar approach could be argued for investigating possible treatment by refining clinical criteria and treatment modalities, perhaps starting with the most promising strategies, but also investigating the effect of other non-specific approaches to get a better overall understanding of what is helping.

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