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Clinical High-Risk for Psychosis (CHR-P) circa 2024: Synoptic analysis and synthesis of contemporary treatment guidelines

Michele Poletti [a], Lorenzo Pelizza [b], Antonio Preti [c], Andrea Raballo [d,e,*]

[a] Department of Mental Health and Pathological Addiction, Child and Adolescent Neuropsychiatry Service, Azienda USL-IRCCS di Reggio Emilia, Reggio Emilia, Italy
[b] Department of Biomedical and Neuromotor Sciences, Università di Bologna, Italy
[c] Department of Neuroscience, University of Turin, Turin, Italy
[d] Chair of Psychiatry, Faculty of Biomedical Sciences, University of Southern Switzerland, Lugano, Switzerland
[e] Cantonal Sociopsychiatric Organisation, Mendrisio, Switzerland

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ABSTRACT

The construct of Clinical-High Risk for Psychosis (CHR-P) identifies young help-seeking subjects in putative prodromal stages of psychosis and is a central component of the Early Intervention (EI) paradigm in Mental Health, aimed at facilitating rapid entry into appropriate care pathways to prevent the onset of psychosis or mitigate is biopsychosocial consequences. This approach, which promotes an innovative culture of care for early, at risk situations, is inspired by a clinical staging concept as a guide to optimal treatment. The objective of this article is to map the existing guidelines in the field of CHR-P treatment recommendations, examine overlaps and differences, and critically evaluate blind spots to be addressed in future guideline updated. The search identified 9 guidelines focused on CHR-P or schizophrenia and other psychotic conditions but containing a specific section on CHR-P or prodromal psychosis. All guidelines acknowledge that psychosis is preceded by more or less pronounced prodromal stages, and most detail CHR-P criteria. Among guidelines, 8 out of 9 indicate cognitive-behavioural therapy as the best psychotherapeutic option and 7 out of 9 suggest that antipsychotics can be prescribed as second option in case psychosocial and/or other pharmacological interventions prove insufficient or inadequate in reducing clinical severity and subjective suffering. Antidepressants, mood stabilizers, and benzodiazepines were considered for the treatment of comorbid disorders. Only the European Psychiatric Association Guidance paper distinguished treatment recommendations for adults and minors. Agreements in treatment guidelines were discussed in light of recent meta-analytical evidences on pharmacological and non-pharmacological treatments for CHR-P, suggesting the need to provide an updated, age-sensitive consensus on how to manage CHR-P individuals.

1. Introduction

Which criteria are most effective in identifying young individuals with non-specific symptoms who may be prone to developing a first psychotic episode? And then, which interventions are recommended for averting or delaying the transition from low-risk to high-risk states and enhancing outcomes?

In the last three decades, the construct of Clinical-High Risk for Psychosis (CHR-P) has offered a pragmatic answer to the first questions and inspired research on which interventions are best suited for CHR-P individuals (Mei et al., 2021; van der Gaag et al., 2013). CHR-P criteria, indeed, identify young help-seeking subjects in putative prodromal stages of psychosis (Yung and McGorry, 1996), therefore at enriched risk of imminent transition to full-blown psychosis (Fusar-Poli et al., 2013; Raballo and Larøi, 2009) (See Table 1). This has opened a new scenario for the treatment of these states, aimed at preventing or delaying possible negative consequences.

As research on treatments progressed and the global intellectual maturation of the field grew within the broader international debate on preventive interventions in mental health, a growing number of clinical and diagnostic-therapeutic guidelines were designed to summarize the evidence and address a specific question regarding the treatment of CHR-P. Current guidelines for CHR-P individuals, indeed, indicate a series of diagnostic criteria and assessment tools, including structured interviews, questionnaires, and psychopathological evaluations. These guidelines provide a diagnostic framework for identifying at-risk

* Correspondence to: Faculty of Biomedical Sciences, University of Lugano, Lugano, Switzerland.
E-mail address: andrea.raballo@usi.ch (A. Raballo).

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Table 1
Clinical High-Risk for Psychosis.

	Main characteristics	Associated characteristics
Prodromes of schizophrenia psychosis	Aspecific indicators of clinically relevant distress, such as anxiety, depression, changes in volition, perturbations of the sleep-wake cycle, or appetite. Mild or non-specific symptoms of psychosis, including neurocognitive deficits. Mild functional change or decline, social withdrawal.	Dysphoric symptoms or idiosyncratic behaviors often dominate the clinical presentation, with a duration that may vary from weeks to months. Often reconstructed in retrospect, this condition suffers an uncertain definition of the threshold according to the duration in time, frequency, and role of associated features (e.g., substance use or comorbid mental disorders).
At-risk mental state or Ultra-high risk for psychosis	Attenuated psychotic symptoms (APS) within the realm of schizotypy, such as ideas of reference; odd beliefs or magical thinking; undue grandiosity, suspicion, or diffidence; unusual perceptual experiences; odd behavior or speech. Brief limited intermittent psychotic symptom (BLIPS), i.e., full-displayed psychotic symptoms, such as hallucinations, delusions, or formal thought disorders, that are brief or limited in their intermittent recurrence. Genetic risk and functioning deterioration (GRFD) syndrome, corresponding to the presence of a genetic risk factor for psychosis, such as a first- or second-degree relative diagnosed with psychosis or having been diagnosed with schizotypal personality disorder, in association with a recent significant decline in psychosocial functioning during the last year.	Uncertain definition of the threshold according to the duration in time, frequency, role of associated features such as substance use, comorbid mental disorders, and current or past functioning; they may vary depending on the tool used to define the condition.
"Basic symptoms"	Subtle, subjectively experienced disturbances in elementary mental processes (thinking, speech, attention, perception, drive). Two major aggregations: Cognitive-perceptive basic symptoms (COPER) and Cognitive disturbances (COGDIS). COPER are identified through a rigorous application of the Schizophrenia Proneness Instrument (SPI), wherein one or more of ten fundamental thought or perceptual disturbances are detected. COGDIS, as well, are delineated by the Schizophrenia Proneness Instrument, pinpointing two or more of nine basic thought or perceptual disturbances, contingent upon attentional perturbations.	A specific threshold is required ($\geq$3) on the SPI and a time interval (occurrence within the last 3 months).
Attenuated Psychosis Syndrome (DSM−5 TR)	The patient displays psychotic-like symptoms that do not reach the threshold for full psychosis, i.e., they appear "attenuated" to a trained observer, have begun or worsened in the last year and persist for at least once per week over a month	Clinically relevant distress or functional impairment is present Symptoms are not entirely explained by a diagnosable disorder, illness, or the action of a substance

individuals and offer specific recommendations for clinical intervention once CHR-P has been detected, such as psychotherapy, symptom management, pharmacological intervention including low-dose antipsychotic medication, nutritional supplements like omega-3 polyunsaturated fatty acids (PUFAs), and psychoeducational education for the patient and their family. However, the implementation of these guidelines may vary across different clinical and cultural contexts (Stain et al., 2019), is obviously dependent on available specific resources (Meneghelli et al., 2023), and many questions remain unanswered. For example, the effectiveness of the proposed intervention strategies and the long-term prognosis of at-risk individuals require further research to consolidate scientific evidence and improve care.

The overarching aim of this critical overview is to identify existing guidelines on CHR-P and, specifically, examine overlaps and differences among their treatment recommendations in view of: 1) extracting harmonized and convergent indications, and, 2) signalling salient "knowledge-gaps" that warrant timely, evidence-based targeting. Through such comparison, our goal is to promote and guide the process of future unified indications. Published guidelines were detected in current databases such as Medline and through search in reference lists of guidelines themselves, being more recent guidelines progressively based on previous ones. Guidelines are chronologically presented starting by the first ones.

2. Methods

According to PRISMA guidelines (Page et al., 2021), we searched the main medical search engine, PubMed (https://pubmed.ncbi.nlm.nih.gov/), and two major scientific meta-search engines: Scopus (https://www.scopus.com) and Web of Science (https://www.webofscience.com). The following string was entered: (guideline OR guidelines) AND ("clinical high risk" OR "ultra high risk" AND psychosis). The search was done on January 12th, 2024.

We only looked at independent, published guidelines detailing recommendations for the treatment of CHR-P individuals. For each guidelines we extrapolated main treatment guidelines (Table 2) and we analysed thematic contents according to assessment of CHR-P as well as to emerging trends in literature according to prognosis (prognostic calculators and other outcomes than transition to psychosis) and prognostic modulators (pharmacological interventions) (Table 3).

3. Results

The search retrieved 77 items in PubMed, 106 in Scopus, and 126 in Web of Science. After the exclusion of duplicates and further elimination of articles unrelated to the topic, 15 records were fully read (Fig. 1).

In PubMed, four guidelines were retrieved: the NICE guidelines (and only indirectly, cited on a study on costs: Jin et al., 2021), the Canadian guidelines on CHR-P (Addington et al., 2017), the Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines (Galletly et al., 2016), and the EPA guidance on the early intervention in clinical high risk states of psychoses (Schmidt et al., 2015). Four guidelines were identified in Scopus (the NICE, the Canadian, the Royal Australian and New Zealand, and the EPA guidelines). Scopus also cited

Table 2
Treatment Guidelines on Clinical High-Risk for Psychosis (CHR-P).

Country/Society, Year	Guideline Official Name	Treatment indications
Italy, 2007	Sistema Nazionale Linee Guida. Linea guida del Sistema Nazionale Linee Guida. Gli interventi precoci nella schizophrenia. (Italian) Guidelines of the National Guideline System. Early interventions in schizophrenia. SNGS Document 14, 2007 (updated 2009).	Early interventions in individuals at risk or in the prodromal phase of schizophrenia (pag. 25, 26) • The use of pharmacological treatments in individuals at risk or in the prodromal phase of schizophrenia, with the aim of preventing the onset of the illness or improving its clinical course, is controversial. • The use of specific psychological treatments (cognitive-behavioral therapy) in individuals at risk or in the prodromal phase of schizophrenia is recommended to reduce symptoms, improve social skills, recognize dysfunctional thoughts, and lower levels of anxiety and depression often associated with distress experienced in the prodromal phase. However, there is insufficient evidence to recommend the use of specific psychological therapies in individuals at risk or in the prodromal phase of schizophrenia to prevent the onset of the illness or improve its clinical course.
Catalunya, 2009	Catalan Agency for Health Technology Assessment and Research. Clinical Practice Guideline for Schizophrenia and Incipient Psychotic Disorder. Roc Boronat, Barcelona, 2009	*Recommendations (page 116)* • Specific early intervention programs are recommended given that they can reduce and/or delay the transition to psychosis. • Specific early intervention programs are recommended to improve prepsychotic symptomatology and prevent social decline or stagnation. • It is recommended to carefully approach current symptomatology and suffering, both with the patient and with the family, with an empathetic and hopeful attitude • It is recommended to develop early intervention programs with comprehensive pharmacological (depending on symptomatology) and psychosocial (psychological treatment, family interventions and recovery support) interventions. • Antipsychotic medication should not be prescribed as standard procedure unless there is accelerated deterioration, a high risk of suicide, if treatment with any other antidepressant has not been effective or if increasing aggression and hostility endanger other people.
UK, 2014	National Institute for health and care Guidelines (NICE) Guidelines, 2014	*Treatment options to prevent psychosis (page 15)* If a person is considered to be at increased risk of developing psychosis • offer individual cognitive behavioural therapy (CBT) with or without family intervention • offer interventions recommended in NICE guidance for people with any of the anxiety disorders, depression, emerging personality disorder or substance misuse • Do not offer antipsychotic medication If, after treatment, the person continues to have symptoms, impaired functioning or is distressed, but a clear diagnosis of psychosis cannot be made, monitor the person regularly for changes in symptoms and functioning for up to 3 years using a structured and validated assessment tool. Determine the frequency and duration of monitoring by the severity and frequency of symptoms, level of

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Table 2 (*continued*)

Country/Society, Year	Guideline Official Name	Treatment indications
		impairment and/or distress and degree of family disruption or concern. If a person asks to be discharged from the service, offer follow-up appointments and the option to self-refer in the future. Ask the person's GP to continue monitoring changes in their mental state.
European Psychiatric Association. 2015	EPA guidance on the early intervention in clinical high risk states of psychoses (Schmidt et al. 2015)	*4.2.4. Recommendation 4 (grade of recommendation: D) (Page 399)* The EPA considers that in adult CHR patients a staged intervention model should be applied with the least restrictive service approach, i.e., CBT,.being offered as first choice. Where psychological interventions have proved ineffective, they should be complemented by low dose second-generation antipsychotics in adult CHR patients if severe and progressive CHR symptomatology (APS with only minimal or clearly declining insight, or BLIPS in higher or increasing frequency) is present and with the primary aim to achieve a degree of symptomatic stabilization that is required for psychological interventions to be effective. Thus, any long-term antipsychotic treatment with a primarily preventive purpose is not recommended. *4.2.5. Recommendation 5 (grade of recommendation: D)* The EPA considers that any intervention in CHR should also address current individual needs and other mental disorders present (co-morbidities), in particular depression and anxiety, according to their respective treatment guidelines. These disorders should be thoroughly assessed and monitored regularly by a specialist (psychiatrist, clinical psychologist, or equivalent mental health professional). *4.2.6. Recommendation 6 (grade of recommendation: A)* The EPA considers that the current evidence for the psychosis predictive value of CHR criteria and for the efficacy of psychological and pharmacological interventions in children and young adolescents is not sufficient to justify primarily preventive interventions. *4.2.7. Recommendation 7 (grade of recommendation: D)* The EPA considers that in children and adolescents, specific psychological interventions with the aim to improve functioning should be provided as part of an overall treatment plan and complemented by interventions for other psychosocial problems and co-morbid mental disorders according to their treatment guidelines. CHR symptoms should be carefully monitored and assessed for a potential progression over an extended period, and the treatment plan should be adapted according to their course.
Australia, 2016	Australian Clinical Guidelines for Early Psychosis	Recommendations (Page 52) 3.1.1 The possibility of psychotic disorder should be considered for anyone who is experiencing unexplained functional decline. 3.1.2 If subthreshold psychotic features combined with the onset of disability indicating ultra high risk are present, the individual and their relatives should be assessed and mental state and safety monitored regularly (every 2–4 weeks) in a context of ongoing support. CBT is the preferred intervention. 3.1.3 Information about the level of risk should be carefully provided taking into account social, educational and cultural factors. 3.1.4 Syndromes such as depression and substance use, and problem areas such as interpersonal, vocational and family stress, should be appropriately

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Table 2 (*continued*)

Country/Society, Year	Guideline Official Name	Treatment indications
		managed. 3.1.5 CBT may reduce psychotic symptomatology and prevent or delay transition to psychosis in the pre-onset phase. 3.1.6 CBT may improve social functioning in the pre-onset phase. 3.1.7 Supportive counselling alone may improve social functioning in the pre-onset phase. 3.1.8 Antipsychotic medications should not normally be prescribed unless at least 1 week of frank positive psychotic symptoms have been sustained. The exception may be where briefer or milder positive symptoms are directly associated with risk of self-harm or aggression. E.g. in substance-related psychotic disorder, or when subthreshold positive psychotic symptoms persist in the face of CBT and other psychosocial treatments and are causing distress and or disability. 3.1.9 Omega−3 fatty acids may delay or prevent transitions to psychosis.
Australia and New Zealand, 2016	Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the management of schizophrenia and related disorders (Galletly et al., 2016)	*Recommendations on the management of the pre-psychotic or prodromal phase (pag. 417)* The possibility of psychotic disorder should be considered for any young person who is experiencing unexplained functional decline. If subthreshold psychotic features combined with the onset of disability indicating ultra-high risk are present, the young person and their relatives should be assessed and mental state and safety monitored regularly (every 2–4 weeks), in a context of ongoing support, until recovery or transition. CBT is the preferred intervention. Syndromes such as depression and substance use, and problem areas such as interpersonal, vocational and family stress should be appropriately managed. Information about the level of risk should be provided carefully to the young person and their family, taking into account social, educational and cultural factors. Antipsychotic medicines should not normally be prescribed unless frank positive psychotic symptoms have been sustained for at least 1 week. The exception may be where briefer or milder positive symptoms are directly associated with risk of self-harm or aggression (e.g. in substance-related psychotic disorder), or when subthreshold positive psychotic symptoms persist despite CBT and other psychosocial treatments and are causing distress and/or disability.
Canada, 2017	Canadian Treatment Guidelines for Individuals at Clinical High Risk of Psychosis (Addington et al., 2017)	*Recommendation 3 (Page 659)* Offer individual cognitive-behavioural therapy (CBT) with or without family intervention. *Recommendation 4* Offer interventions recommended in NICE guidelines for the presenting problem, that is, current individual needs (anxiety, depression, emerging personality problems, or substance misuse). *Recommendation 5* Offer interventions to prevent the development or persistence of functional deficits (social, educational, or vocational). Functional impairments, defined by the presence of a decline in functioning and/or the presence of cognitive impairment, have been observed to be present before and often worsen until the onset of psychosis. These findings support the careful assessment of functioning and the use of psychosocial interventions such as social skills training that address the specific problems of the individual. *Recommendation 6* Psychological interventions, in particular CBT, as well as pharmacological

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Table 2 (*continued*)

Country/Society, Year	Guideline Official Name	Treatment indications
		interventions are able to prevent or at least postpone a first psychotic episode in adult CHR patients. *Recommendation 7* These treatments should be monitored by a psychiatrist, a clinical psychologist, or an equivalent mental health professional. In adult CHR patients, a staged intervention model should be applied with the least restrictive treatment approach (i.e., CBT) being offered as a first choice. Where psychological interventions have proved ineffective, and there are severe and progressive attenuated psychotic symptoms, they should be complemented by low-dose second-generation antipsychotics in adult CHR patients. Here the primary aim is to achieve a degree of symptomatic stabilisation. Any long term antipsychotic treatment with a primarily preventive purpose is not recommended. Staged intervention models have been advocated for interventions in the earlier and milder forms of specific mental disorders. Staging involves selecting treatments that may be simpler or less intrusive for the earlier stages of the disorder. For example, in those at clinical high risk who do not yet meet criteria for a psychotic illness, psychological interventions should be considered as first-line treatments and pharmacological interventions reserved for those who symptoms do not respond or are escalating. *Recommendation 9* If, after treatment, the person continues to have symptoms, impaired functioning, or is distressed but a clear diagnosis of psychosis cannot be made, monitor the person regularly for changes in symptoms and functioning for up to 3 years using structured and validated assessment tools. Determine the frequency and duration of monitoring by 1) the severity and frequency of symptoms, 2) the level of impairment and/or distress, and 3) the degree of family disruptions or concern. If a person asks to be discharged from the service, offer follow-up appointments and the option to self-refer in the future. Ask the person's family physician to continue monitoring changes in his or her mental state.
German Association for Psychiatry, Psychotherapy and Psychosomatics, 2019	German Association for Psychiatry, Psychotherapy and Psychosomatics, DGPPN S3 Guideline for Schizophrenia	*Recommendation 136 (pag. 71–73)* We recommend offering cognitive behavioural therapy (CBT; see Module 4b) to reduce the risk of or to delay transition to psychosis in people with an increased risk for psychosis (A). We recommend not to offer antipsychotics as the primary approach to prevent transition to full-blown psychosis (GCP). In cases in which CBT is insufficient and in which attenuated psychotic symptoms are occurring with increasing severity or brief psychotic episodes with increasing frequency, we suggest offering additional low-dose second-generation antipsychotics temporarily to reduce symptoms after a comprehensive risk-benefit evaluation
British Association for Psychopharmacology, 2020	Evidence-based guidelines for the pharmacological treatment of schizophrenia: Updated recommendations from the British Association for Psychopharmacology (Barnes et al. 2020)	*Recommendations for the at-risk mental state (page 4)* • Encourage a therapeutic relationship to allow for further assessment, review, 'watchful waiting' and monitoring of symptoms. • Assess the nature and impact of any substance use • If antipsychotic medication is considered for symptom relief: This should be treated as off-label prescribing. (S); the prescription should be treated as a

(*continued on next page*)

Table 2 (*continued*)

Country/Society, Year	Guideline Official Name	Treatment indications
		short-term, individual trial. • Very low doses should be used. • Symptom response should be monitored. • The nature and frequency of potential side effects should be explained before a patient starts medication and then side effects should be carefully monitored during treatment. • It should be prescribed by specialist psychiatric services, such as an early intervention team.
		• On the evidence available, individual CBT can be considered to be an acceptable alternative to pharmacological treatment.

the Croatian guidelines for the treatment of schizophrenia and other psychotic disorders, which also provide recommendations for the pharmacological treatment of patients with clinical high-risk and prodromal phases of a psychotic disorder (Ostojić, 2023). However, they were written in a language not accessible to us. Four guidelines were identified in Web of Science: the NICE, the Canadian, the Royal Australian and New Zealand, and the Italian guidelines (De Masi et al., 2008). Indeed, not all published guidelines are indexed in databases, thus we proceeded backwards, by checking the references of retrieved guidelines. We also decided to include recommendations from guidelines for schizophrenia if incorporating a specific section on the treatment of individuals at risk of psychosis.

Overall, the search identified 9 guidelines focused on CHR-P or containing a specific section on CHR-P or prodromal psychosis within the broader focus on schizophrenia and other psychotic conditions.

Specific treatment indications, extrapolated from each guideline, are synthetized in Table 2.

Overall, all treatment guidelines thematized multiple steps of bio-psycho-social interventions aligned with the severity of the clinical presentation, aiming at mitigating severity and averting negative outcomes. Furthermore, all retrieved guidelines highlighted the importance of an integrated and timely approach for the prevention and management of these conditions. Only EPA Guidelines (Schmidt et al., 2015) distinguished treatment recommendations for adults and minors, based on the available evidence at the time of publication. Treatment indications are presented distinguishing non-pharmacological and pharmacological interventions.

Table 3
Conceptual analysis of guidelines.

GL	Target age specified	Reference concept for early diagnosis	Diagnostic meta-system	Assessment explicitly thematized	Mention prognostic calculators	Conceptualize outcomes other than (psychometric) transition to psychosis	Stepped therapeutic interventions	Conceptualizes incident AP as equivalent of transition to psychosis in terms of need of care	Mention prognostic modulators other than CHR-P criteria (e.g. baseline pharmacotherapy)
1	/	*UHR*	/	*CAARMS SIPS BSABS*	/	/	/	/	/
2	/	*UHR*	/	/	/	/	*V*	/	/
3	/	/	/	/	/	/	*V*	/	/
4	*V*	*UHR BS*	/	*In the accompanying detection guidelines*	/	/	*V*	/	/
5	/	*UHR*	/	*CAARMS*	/	/	*V*	/	/
6	/	*UHR*	/	*CAARMS*	/	/	*V*	/	/
7	/	*UHR*	/	*CAARMS, SIPS*	/	/	*V*	/	/
8	/	/	*DSM 5*	*CAARMS, SIPS*	/	/	*V*	/	/
9	/	*UHR*	/	/	/	/	*V*	/	/

Legend: V = mentioned; / = not mentioned; AP = antipsychotics; BS = Basic Symptoms; BSABS = Bonn Scale for the Assessment of Basic Symptoms; CAARMS = Comprehensive Assessment of At Risk Mental States; CHR-P = Clinical High Risk for Psychosis; SIPS = Structured Interview for Prodromal Syndromes; UHR = Ultra High Risk

Guidelines:

1.Italy, 2007 Guidelines of the National Guideline System. Early interventions in schizophrenia. SNGS Document 14, 2007.

2.Catalunya, 2009 Catalan Agency for Health Technology Assessment and Research. Clinical Practice Guideline for Schizophrenia and Incipient Psychotic Disorder

3.UK, 2014 National Institute for health and care Guidelines (NICE) Guidelines, 2014

4.European Psychiatric Association. 2015 EPA guidance on the early intervention in clinical high risk states of psychoses

5.Australia, 2016 Australian Clinical Guidelines for Early Psychosis

6.Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the management of schizophrenia and related disorders (Galletly et al., 2016)

7.Canada, 2017 Canadian Treatment Guidelines for Individuals at Clinical High Risk of Psychosis (Addington et al., 2017)

8.German Association for Psychiatry, Psychotherapy and Psychosomatics, 2019 German Association for Psychiatry, Psychotherapy and Psychosomatics, DGPPNS3 Guideline for Schizophrenia

9.British Association for Psychopharmacology, 2020 Evidence-based guidelines for the pharmacological treatment of schizophrenia: Updated recommendations from the British Association for Psychopharmacology (Barnes et al., 2020)

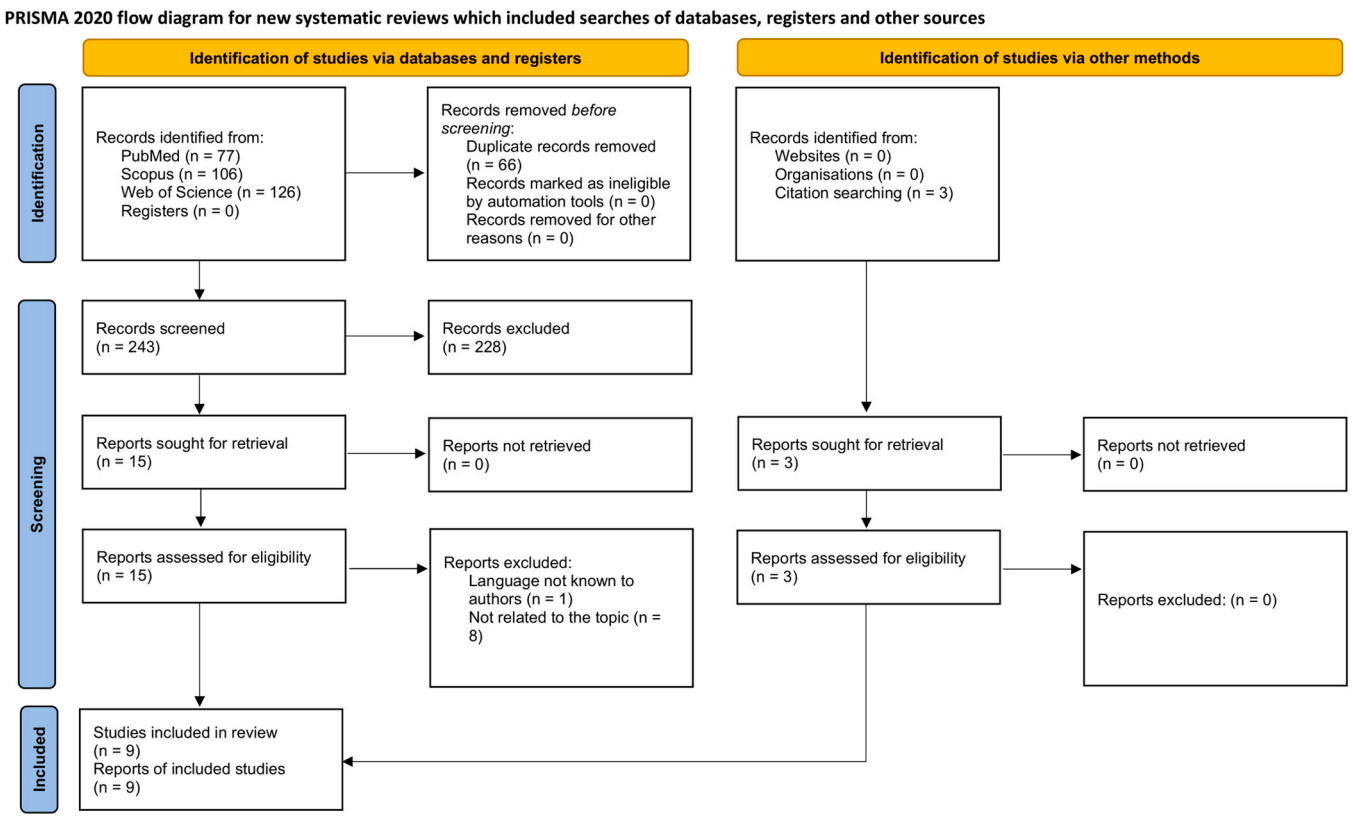

Fig. 1. Caption.

3.1. Definition of the construct of interest

In principle, a necessary precondition for the prescription of any treatment is the definition of the target construct for the treatment. Identified Guidelines, however, vary in the way they define the primary target of intervention in the phase that precedes the first episode of psychosis (FEP). There is a consensus that the FEP in schizophrenia is preceded by a prodromal phase, that typically manifests as a decline in personal functioning, marked by memory and concentration difficulties, unusual behaviors and thoughts, social withdrawal, and diminished interest in daily activities. Additionally, individuals may experience transient or attenuated psychotic symptoms alongside prevalent signs of apathy and anhedonia (negative symptoms). A more specific ultra-high risk or at-risk mental state is described in the Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines on schizophrenia (Galletly et al., 2016), in the Australian Clinical Guidelines for Early Psychosis of the (The National Centre of Excellence in Youth Mental Health, 2016), in the guidelines of the EPA (Schmidt et al., 2015), in those of the British Association for Psychopharmacology (BPA: Barnes et al., 2020), in the Canadian guidelines (Addington et al., 2017), in the Catalan guidelines (2009), and the Italian guidelines (2007). The EPA, Australian, and Catalan guidelines also pay attention to the "basic symptoms" model (Huber, 1983; Gross, 1989), which is briefly referred to in the Italian guidelines.

The importance of using a standardized assessment tool for diagnosing ultra-high risk or at-risk mental states is underscored by guidelines from Italy, Germany, Canada, Australia, and the EPA. These guidelines reference the Comprehensive Assessment of At Risk Mental States (CAARMS) (Yung et al., 2005) or the Structured Interview for Prodromal States (SIPS) (Miller et al., 2002).

Most guidelines recommend a staged intervention approach for earlier and mild psychosis, favouring less intrusive interventions in the initial stages. However, only the Australian guidelines delve into the stage model of schizophrenia while the German guidelines (2019) explicitly highlight that the stage of increased risk for psychosis is not a diagnostic category in ICD-10, ICD-11, or DSM-5 (p. 71).

4. Treatment indication synthesis

4.1. Non-pharmacological interventions

All guidelines emphasize the crucial role of psychological interventions in the treatment of CHR-P individuals as first therapeutic options. Among psychological interventions, with the exception of the Catalan Guidelines, all other guidelines indicate cognitive-behavioural therapy (CBT) as the first psychotherapeutic option, being focused on the recognition and management of prodromal symptoms as well as on dysfunctional thinking patterns and coping strategies (e.g. van der Gaag et al., 2012).

In particular, the Australian guidelines explicitly detailed the focus of CBT in this prodromal stages (see Box 1). Despite this early optimism on the effectiveness of CBT for CHR-P individuals, the theme has been recently debated and challenged (Bosnjak Kuharic et al., 2019; Davies et al., 2018; Zheng et al., 2022), suggesting a more cautious and sceptical position (Fusar-Poli et al., 2021; 2022) and the need of further empirical data on effectiveness for CBT as well as for other psychotherapeutic interventions.

4.2. Pharmacological interventions

Available guidelines generally distinguish between pharmacological interventions addressing positive psychotic symptoms (i.e. antipsychotics) and other symptoms domains (i.e. antidepressants, mood stabilizers, and benzodiazepines).

4.3. Antipsychotics

The Italian guidelines, published in 2007 and updated in 2009

simply state that the use of antipsychotics in CHR-P individuals is controversial, while NICE guidelines, published seven year later in 2014, do not recommend the use of antipsychotics for the treatment of CHR-P individuals.

Other guidelines suggest that antipsychotics can be prescribed:

- in case of accelerated deterioration, a high risk of suicide, if treatment with any other antidepressant has not been effective or if increasing aggression and hostility endanger other people (*Catalan guidelines*)
- in case of ineffectiveness of psychological interventions and progressive worsening of CHR-P symptomatology (APS with only minimal or clearly declining insight, or BLIPS in higher or increasing frequency) with the primary aim to achieve a degree of symptomatic stabilization; in this case low dose second-generation antipsychotics are indicated for CHR-P adults and for a short-term (*European guidelines* and *Canadian guidelines*)
- in case of at least 1 week of frank positive psychotic symptoms, associated with risk of self-harm or aggression (*Australian guidelines*)
- for symptom relief; in this case, antipsychotics should be used as off-label and short-term, individual trial, at a very low doses (*British Association for Psychopharmacology guidelines*)
- In cases in which CBT is insufficient and in which attenuated psychotic symptoms are occurring with increasing severity or brief psychotic episodes with increasing frequency, we suggest offering additional low-dose second-generation antipsychotics temporarily to reduce symptoms after a comprehensive risk-benefit evaluation (*German guidelines*).

Overall, this caution on the use of antipsychotic, is in line with recent meta-analyses indicating that baseline exposure to antipsychotics (AP) is associated with an increased risk of transition to psychosis in CHR-P individuals when compared to not exposed CHR-P (29 % vs. 16 %) (Raballo et al., 2020a), especially in the first two years since inception (Raballo et al., 2023c); this effects is not due to pre-test risk enrichment (Raballo et al., 2021a) and has been further confirmed in independent CHR-P cohorts (Pelizza et al., 2023; Zheng et al., 2022). Furthermore, emerging meta-analytical (Raballo et al., 2024a) and empirical evidence (Pelizza et al., 2024) revealed that such risk increase in risk of transition follows a dose-exposure pattern.

4.4. Other medications

In general, antidepressants, mood stabilizers, and benzodiazepines were considered for the treatment of comorbid disorders.

Antidepressants, in particular, were mentioned as potentially effective in at-risk mental states based on single observational studies in the EPA and the BPA guidelines. Recent meta-analytical evidence lends further rationale to such indications, showing that at least baseline prescription of antidepressants in CHR-P is associated to a lower risk of transition to psychosis (Raballo et al., 2023a).

With respect to benzodiazepines, both Catalan and BPA guidelines advised caution, although they are typically prescribed for agitation, anxiety, or insomnia, for the risk of abuse and reported increased mortality (Tiihonen et al., 2016). Furthermore emerging meta-analytical evidence indicates, that ongoing benzodiazepines exposure at inception in CHR-P individuals is associated to a higher risk of transition to psychosis at follow up (Raballo et al., 2023b).

Finally, a different class of medication, historically used to manage and treat hyperlipidemia (and thereby termed “antilipemic”), i.e. omega-3 polyunsaturated fatty acids (PUFAS), was described as an intervention under investigation in the EPA, BPA, and Australian guidelines. A recent meta-analysis, however, reported less favourable results than early randomized controlled trials (Devoe et al., 2019).

5. Discussion

The synoptic overview of available treatment guidelines for CHR-P reveals that there is substantial agreement on the topicality of timely detection of CHR-P and coherent deployment of psycho-social interventions (from simple monitoring and mental health literacy to psychotherapeutic intervention), with pharmacotherapy as a non-primary indication.

Nonetheless, salient issues remain to be optimized.

5.1. Age and developmentally-sensitive indications

Despite the original CHR-P concept was designed to cut across developmental years (i.e. childhood-adolescence) and early adulthood, and recent meta-analytical evidence confirms its prognostic value in help-seeking children and adolescents (Raballo et al., 2022), only EPA Guidelines (Schmidt et al., 2015) explicitly formulated distinct treatment recommendations for adults and minors. Surprisingly, although most guidelines recognize that prodromal stages of schizophrenia may manifest during childhood or adolescence or vaguely evoke a neurodevelopmental concept of schizophrenia, the treatment indications for children and adolescents at CHR-P typically focus on individuals with schizophrenia rather than adopting a stage-specific view of CHR-P. It is therefore imperative for future treatment guidelines to explicitly address distinct indications according to the developmental phase (childhood, adolescence, adulthood) of involved subjects.

5.2. Antipsychotic off-label prescription

Despite the shared caution and almost unanimous consensus that AP pharmacotherapy is not the first treatment of choice to prevent transition to psychosis in CHR-P (but rather it is conditional to the acute psycho-functional deterioration of the clinical presentation and/or the inadequate response to other, non-pharmacological interventions), this indication appears to be largely disattended in clinical practice. Indeed, the meta-analytic prevalence of baseline antipsychotic exposure in CHR-P is substantial, being documented in about one out of four (25 %) of enrolled individuals (Raballo and Poletti, 2022; Raballo et al., 2022a).

Does this suggest that in mental health services clinicians usually opt for off-label prescription of antipsychotics in defiance of guidelines? Or, on the contrary, that – at least in the specialized early detection centres where data collection for research is conducted – the quantitative pressure for boosting enrolment may favour more lenient inclusion criteria (i.e. also individuals already under antipsychotic treatment, therefore with a potential pharmacologically attenuated first episode psychosis, are ascribed to CHR-P is they fit below the psychometric threshold for psychosis)?

A study on community practitioners involved in child and adolescent psychiatry found that 72.1 % of all practitioners chose a psychopharmacological intervention and just 32 % individual psychotherapy after a vignette illustrating DSM-5-Attenuated Psychosis Syndrome (Yilmaz Kafali et al., 2022). This may suggest a widespread preference for the use of drugs by practitioners who are likely to be involved in the care of CHR-P help-seekers.

However, the off-label prescription of antipsychotics in real clinical practice may also derive from other factors. For example, the two most commonly used semi-structured interviews for the assessment of CHR-P have different positions on antipsychotics: the Comprehensive Assessment of At-Risk Mental States (CAARMS: Yung et al., 2003) excludes those with a history of more than minimal antipsychotic use from having a CHR-P diagnosis whereas the Structured Interview for Prodromal Syndromes (SIPS: Miller et al., 2003) does not. The pragmatic implications of this neglected issue emerge clearly in the ENIGMA-Clinical High Risk Working Group dataset (2024), where CHR-P individuals enrolled in sites using the SIPS have more than double risk of being under antipsychotic treatment compared to those enrolled in sites using the

CAARMS as assessment instrument (25.41 % baseline antipsychotic exposure vs. 11.98 %) (Raballo et al., 2024b). Incidentally, they also had almost double rates of transition to psychosis (i.e. 17.94 % vs 9.21 %), despite similar severity of positive symptoms (10.93 ± 4.66 vs. 10.37 ± 4.03).

A further, not mutually exclusive explanation for the off-label prescription of antipsychotics in CHR-P, may be that treating clinicians operate a therapeutic decision on the ground of the overall the severity of the clinical picture, going beyond the narrow focus of the psychometric severity of positive symptoms, which is nonetheless the central compass for current clinical staging of prodromal/CHR-P vs. first psychotic episode. Indeed, it is well known that in addition to positive psychotic symptoms (the severity/frequency of which determines the grading of psychosis risk in the CHR-P model), real-world help-seekers present other symptoms, such as negative, affective and cognitive ones. These symptom dimensions impact the overall clinical severity as well as subjective suffering and functional decline, and may lead to pharmacological prescription, including antipsychotics. The empirical fact that CHR-P individuals receiving antipsychotics are presumably those with the highest perceived clinical severity although still being psychometrically within the limits of CHR-P, is indirectly suggested by their higher risk of transitioning to psychosis over the long term as compared to antipsychotic-naïve CHR-P individuals (29 % vs. 16 %: risk ratio 1.47) (Raballo et al., 2020b). This suggests that antipsychotics may delay but not fully prevent the transition to psychosis in CHR-P individuals (see Preti and Cella, 2010; van der Gaag et al., 2013a; 2013b). Moreover, evidence from randomized controlled trials indicates that the prescription of antipsychotics to CHR-P was related to a high rate of attrition (McGorry et al., 2002; McGlashan et al., 2006), and might cause rapid weight gain (McGlashan et al., 2006).

5.3. *Comorbidity as a target*

Moreover, all guidelines univocally emphasize the importance of treating comorbid conditions in addition to prodromal psychotic symptoms. This indication is supported by recent meta-analytical evidence that baseline antidepressant exposure is associated with a lower rate of transition to psychosis (Raballo et al., 2023). Indeed, this positive prognostic effect might reflect the positive action of antidepressant on comorbid affective symptoms independently of their primary or secondary nature. Finally, no guidelines detailed risk factors and integrate them in prognostic calculators aimed at improving prognostic precision.

6. Conclusions

The integration of psychological therapies and, in some cases, targeted pharmacological interventions plays a crucial role in the management of CHR-P states and in the attempt to prevent or delay the transition to psychosis, i.e. modifying the natural longitudinal outcomes of such individuals.

This overview of existing guidelines provides valuable insights to enhance the care provision to individuals at risk for psychosis.

Two main indications emerge among guidelines, both challenged by accumulating empirical evidence, suggesting the need of revising and updating current guidelines, especially in consideration of the insertion of Attenuated Psychosis Syndrome in the DSM 5 (Zachar et al., 2020) and the lack of evidence supporting a preventive intervention over others (Davies et al., 2018).

The first indication from the guidelines concerns the non-pharmacological therapeutic options to be offered to CHR-P individuals, especially CBT; this suggestion has been recently challenged by doubts on its higher long-term superior effectiveness in comparison with other possible psychosocial interventions. In addition to CBT, psychoeducation for individuals and parents can improve long-term outcomes (Herrera et al., 2023), but no guideline explicitly indicates such intervention.

The second indication concerns the prescription of low-dose second generation antipsychotics in case of alarming clinical signals suggesting a worsening picture with possible risk of self-harm or aggression despite the implementation of psychotherapeutic interventions. This suggestion has been challenged by empirical data derived from real-word clinical settings showing that antipsychotics are more commonly prescribed than what expected according to guidelines. This misalignment could indicate that the clinical severity photographed with dedicated instruments such as CAARMS and SIPS, is not fully coherent with the global severity assessment of the whole clinical picture that guides therapeutic decision making in clinical practice (Raballo and Larøi, 2011). In other words, the clinical severity ascertained in clinical practice may differ from the stages of severity captured by CHR-P dedicated tools scales and related diagnostic algorithms, leading to more frequent antipsychotic prescription, in spite of formally recommendations contained in guidelines.

Finally, the Australian guidelines indicate the implementation of long-chain omega-3 fatty acid supplements as an alternative therapeutic option appearing effective in the prevention of psychosis in CHR-P individuals, an indication that deserves further and more solid empirical data (Susai et al., 2022).

Therefore, despite the clear recommendations provided by guidelines, further research is needed to refine the identification of at-risk individuals, to better estimate and rate their clinical severity and to consequently indicate appropriate treatments, evaluating along time their effectiveness of the proposed treatments.

In conclusion, according to collected evidence provided by guidelines on CHR-P, future, post-2024 guidelines on CHR-P should address:

1. Target age and developmentally-oriented risk assessment;
2. Specify the reference concept for early diagnosis (possibly combining CHR-P prospective staging and emerging neurodevelopmental evidences (Insel, 2010; Poletti and Raballo, 2020; Raballo and Larøi, 2009);
3. Offer updated and stratified indication for screening and confirmatory assessment;
4. Specify risk factors and integrate them in prognostic risk calculators (Sanfelici et al., 2020), possibly overcoming established limitations (Raballo et al., 2021).
5. Define a monitoring timeline to intercept also central outcomes other than transition to psychosis.
6. Better articulate the portfolio of evidence-based interventions along a continuum of intensity of need of care.

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Michele Poletti: Writing – review & editing, Writing – original draft, Visualization, Validation, Formal analysis, Data curation, Conceptualization. **Lorenzo Pelizza:** Writing – review & editing, Writing – original draft, Formal analysis, Conceptualization. **Antonio Preti:** Writing – review & editing, Writing – original draft, Supervision, Formal analysis, Data curation, Conceptualization. **Andrea Raballo:** Writing – review & editing, Writing – original draft, Supervision, Formal analysis, Data curation, Conceptualization.

Declaration of Competing Interest

None

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